http://medicalxpress.com/news/2012-01-drug-induced-liver-injury.html

Researchers find novel way to prevent drug-induced liver injury

Massachusetts General Hospital (MGH) investigators have developed a novel strategy to protect the liver from drug-induced injury and improve associated drug safety.

In their report receiving advance online publication in the journal Nature Biotechnology, the team reports that inhibition of a type of cell-to-cell communication can protect against the damage caused by liver-toxic drugs such as acetaminophen.

"Our findings suggest that this therapy could be a clinically viable strategy for treating patients with drug-induced liver injury," says Suraj Patel, PhD, of the MGH Department of Surgery, the paper's lead author. "This work also has the potential to change the way drugs are developed and formulated, which could improve drug safety by providing medications with reduced risk of liver toxicity."

Developing, approving and prescribing a drug requires that the therapeutic benefits be weighed against any potential toxicities. Liver toxicity limits the development of many therapeutic compounds and presents major challenges to both clinical medicine and to the pharmaceutical industry. Drug-induced liver injury is the most common cause of acute liver failure in the U.S. and is also the most frequent reason for abandoning drugs early in development or withdrawing them from the market. Since no pharmaceutical strategies currently exist for preventing drug-induced liver injury, treatment options are limited to discontinuing the offending drug, supportive care and transplantation for end-stage liver failure.

Gap junctions are hollow channels that connect neighboring cells and allow direct intercellular communication between coupled cells. In the heart, gap junctions are known to propagate the electrical activity required for contraction, but their role in the liver is poorly defined. Recent work by the MGH team and others has shown that assemblies of intercellular gap junctions spread immune signals from injured liver cells to surrounding undamaged cells, amplifying overall inflammation and injury. The current study was designed to discover the potential of targeting liver-specific gap junctions to limit drug-induced liver injury.

The researchers first used a strain of genetically mutated mice that lack a particular liver-specific gap junction. The mice were administered various liver-toxic drugs, such as the commonly used medicine acetaminophen. Overdoses of acetaminophen, which is best known under the brand name Tylenol, are the most frequent cause of drug-induced liver injury. Compared to normal mice, those lacking liver gap junctions were protected against liver damage, inflammation and death caused by administration of liver-toxic drugs.

The team then identified a small-molecule inhibitor of liver gap junctions that, when given with or even after the toxic drugs, protected the livers of normal mice against any injury and prevented their death. Additionally, cell culture experiments indicated that blocking gap junctions limited the spread through liver cells of damaging free radicals and oxidative stress, suggesting a possible mechanism for the observed protection.

"This finding is very exciting and potentially very powerful from a number of basic science and clinical application standpoints, which we are continuing to explore," says Martin Yarmush, MD, PhD, director of the MGH Center for Engineering in Medicine and senior author of the study. "However, before we can think about applying this approach to patients, we need to know more about any off-target effects of these gap junction inhibitors and better understand the long-term ramifications of temporarily blocking liver-specific gap junction channels."

A patent related to the work has been filed by Partners Healthcare, and an early stage biotechnology company, Heprotech Inc., was recently established to develop this new technology further. "The findings from this work suggest a novel drug development strategy in which therapeutically effective but potentially liver-toxic compounds could be co-formulated with selective gap junction inhibitors to improve their safety," explains Patel, a co-founder of Heprotech along with Yarmush. "We look forward to helping commercialize this new technology, with the ultimate goal of developing liver-safe pharmaceuticals and better treatments for drug-induced liver injury." *Provided by Massachusetts General Hospital*

http://www.bbc.co.uk/news/magazine-16536598

Twenty top predictions for life 100 years from now

Last week we asked readers for their predictions of life in 100 years time. Inspired by ten 100-year predictions made by American civil engineer John Elfreth Watkins in 1900, many of you wrote in with your vision of the world in 2112.

Many of the "strange, almost impossible" predictions made by Watkins came true. Here is what futurologists Ian Pearson (IP) and Patrick Tucker (PT) think of your ideas.

1. Oceans will be extensively farmed and not just for fish (Jim 300)

IP: Likelihood 10/10. We will need to feed 10 billion people and nature can't keep up with demand, so we will need much more ocean farming for fish. But algae farming is also on the way for renewable energy, and maybe even for growth of feedstock (raw materials) or resource extraction via GM seaweed or algae.
PT: Good chance. According to Dennis Bushnell, chief scientist at the Nasa Langley Research Center, saltwater algae that's been genetically modified to absorb more nitrogen from the air than conventional algae could free up to 68% of the fresh water that is now tied up in conventional agriculture. This water could go to thirsty populations.

2. We will have the ability to communicate through thought transmission (Dev 2)

IP: Likelihood 10/10. Transmission will be just as easy as other forms of brain augmentation. Picking up thoughts and relaying them to another brain will not be much harder than storing them on the net.
PT: Good chance. Synthetic telepathy sounds like something out of Hollywood but it is absolutely possible, so long as "communication" is understood to be electrical signals rather than words.

3. Thanks to DNA and robotic engineering, we will have created incredibly intelligent humans who are immortal (game_over)

IP: Likelihood 9/10. It is more likely that direct brain links using electronics will achieve this, but GM will help a lot by increasing longevity - keeping people alive until electronic immortality technology is freely available at reasonable cost.
PT: Good chance. The idea that breakthroughs in the field of genetics, biotechnology and artificial intelligence will expand human intelligence and allow our species to essentially defeat death is sometimes called the Singularity.

4. We will be able to control the weather (mariebee_)

IP: Likelihood 8/10. There is already some weather control technology for mediating tornadoes, making it rain and so on, and thanks to climate change concerns, a huge amount of knowledge is being gleaned on how weather works. We will probably have technology to be able to control weather when we need to. It won't necessarily be cheap enough to use routinely and is more likely to be used to avoid severe damage in key areas.
PT: Good chance. We will certainly attempt to. A majority of scientists in the US support a federal programme to explore methods for engineering the Earth's climate (otherwise known as geoengineering). These technologies aim to protect against the worst effects of manmade climate change.

5. Antarctica will be "open for business" (Dev 2)

IP: Likelihood 8/10. The area seems worth keeping as a natural wilderness so I am hesitant here, but I do expect that pressure will eventually mean that some large areas will be used commercially for resources. It should be possible to do so without damaging nature there if the technology is good enough, and this will probably be a condition of exploration rights.
PT: Pretty close. Before there is a rush to develop Antarctica we will most likely see a full-scale rush to develop the Arctic. Whether the Arctic states tighten control over the region's resources, or find equitable and sustainable ways to share them will be a major political challenge in the decades ahead. Successful (if not necessarily sustainable) development of the Arctic portends well for the development of Antarctica.

6. One single worldwide currency (from Kennys_Heroes)

IP: Likelihood 8/10. This is very plausible. We are already seeing electronic currency that can be used anywhere, and this trend will continue. It is quite likely that there will be only a few regional currencies by the middle of the century and worldwide acceptance of a global electronic currency. This will gradually mean the others fall out of use and only one will left by the end of the century.
PT: Great try! The trend on this is actually more in the opposite direction. The internet is enabling new forms of bartering and value exchange. Local currencies are also now used by several hundred communities across the US and Europe. In other words, look for many more types of currency and exchange not fewer, in the coming decades.

7. We will all be wired to computers to make our brains work faster (Dev 2)

IP: Likelihood 10/10. We can expect this as soon as 2050 for many people. By 2075 most people in the developed world will use machine augmentation of some sort for their brains and, by the end of the century, pretty much everyone will. If someone else does this you will have to compete.

8. Nanorobots will flow around our body fixing cells, and will be able to record our memories (Alister Brown)

PT: Good chance. Right now, medical nanorobots exist only in theory and nanotechnology is mostly a materials science. But it's a rapidly growing field. Nanorobots exist within the realm of possibility, but the question of when they will arrive is another matter

IP: Likelihood: 7/10.

9. We will have sussed nuclear fusion (Kennys_Heroes)

IP: Likelihood 10/10. This is likely by 2045-2050 and almost certain by 2100. It's widely predicted that we will achieve this. What difference it makes will depend on what other energy technologies we have. We might also see a growth in shale gas or massive solar energy facilities. I don't think that wind power will be around.

10. There will only be three languages in the world - English, Spanish and Mandarin (Bill Walker)

IP: Likelihood 8/10. This does look like a powerful trend, other languages don't stand a lot of chance. Minor languages are dying at a huge rate already and the other major ones are mostly in areas where everyone educated speaks at least one of the other three. Time frame could be this century.

11. Eighty per cent of the world will have gay marriage (Paul)

IP: Likelihood 8/10. This seems inevitable to those of us in the West and is likely to mean different kinds of marriages being available to everyone. Gay people might pick different options from heterosexual people, but everyone will be allowed any option. Some regions will be highly resistant though because of strong religious influences, so it isn't certain.

12. California will lead the break-up of the US (Dev 2)

IP: Likelihood 8/10. There are some indications already that California wants to split off and such pressures tend to build over time. It is hard to see this waiting until the end of the century. Maybe an East Coast cluster will want to break off too. Pressures come from the enormous differences in wealth generation capability, and people not wanting to fund others if they can avoid it.

13. Space elevators will make space travel cheap and easy (Ahdok)

IP: Likelihood 8/10. First space elevators will certainly be around, and although "cheap" is a relative term, it will certainly be a lot cheaper than conventional space development. It will create a strong acceleration in space development and tourism will be one important area, but I doubt the costs will be low enough for most people to try.

14. Women will be routinely impregnated by artificial insemination rather than by a man (krozier 93)

PT: Pretty close. At the very least, more couples are choosing advanced fertility techniques over old-fashioned conception. Pre-implantation genetic diagnosis, in which an artificially inseminated embryo is carefully selected among other inseminated embryos for desirability, is becoming increasingly common in fertility clinics. Using this technique, it's now possible to screen an embryo for about half of all congenital illnesses. Within the next decade, researchers will be able to screen for almost all congenital illnesses prior to embryo implantation.
IP: Likelihood 5/10.

15. There will be museums for almost every aspect of nature, as so much of the world's natural habitat will have been destroyed (LowMaintenanceLifestyles)

PT: Pretty close. I cannot comment on the museums but the Earth is on the verge of a significant species extinction event. Protecting biodiversity in a time of increased resource consumption, overpopulation, and environmental degradation will require continued sacrifice on the part of local, often impoverished communities. Experts contend that incorporating local communities' economic interests into conservation plans will be essential to species protection in the next century.
IP: Likelihood 2/10.

16. Deserts will become tropical forests (jim300)

IP: Likelihood 7/10. Desert greening is progressing so this is just about possible.

17. Marriage will be replaced by an annual contract (holierthanthou)

IP: Likelihood 6/10. I think we will certainly see some weaker forms of marriage that are designed to last a decade or two rather than a whole lifetime, but traditional marriage will still be an option. Increasing longevity is the key - if you marry at 20 and live to well over 100, that is far too long a commitment. People will want marriages that aren't necessarily forever, but don't bankrupt them when they end.

18. Sovereign nation states will cease to exist and there will be one world government (krozier93)

PT: Great try! However, I think that the trend is in the direction of more sovereign nations rather than fewer. In the coming years, corporations or wealthy private citizens will attempt to use earth-moving technologies to build their own semi-sovereign entities in international waters.
IP: Likelihood 2/10.

19. War by the West will be fought totally by remote control (LowMaintenanceLifestyles)

IP: Likelihood 5/10.

20. Britain will have had a revolution (holierthanthou)

IP: Likelihood 7/10. Well, possible, but not as likely as some other trends.

http://medicalxpress.com/news/2012-01-fluorescent-dye-tiniest-oesophageal-cancer.html

Fluorescent dye pinpoints tiniest signs of oesophageal cancer

A fluorescent dye that can be sprayed onto the oesophagus - the food pipe - could be used to detect oesophageal cancer earlier and spare patients unnecessary treatment, according to research published today (Sunday) in Nature Medicine.

Medical Xpress - When sprayed onto the oesophagus the dye attaches to normal, healthy, cells but is unable to stick to cancer cells or those in the early stages of turning cancerous. This gives doctors a clear signpost to where the disease is developing.

The researchers, funded by the Medical Research Council (MRC) and Cancer Research UK, studied samples of a particular type of oesophageal cancer called adenocarcinoma, cases of which are soaring. Before this disease develops there is a detectable pre-cancerous stage called Barrett's oesophagus, which can be easily treated successfully.

The fluorescent dye works by attaching to glycans - molecules on the surface of cells in the oesophagus. When the cells begin to turn cancerous the glycan structures change, meaning that the dye no longer sticks to the surface of these cells. This gives an early warning of where the cancer is developing.

At this point the cancer can be treated with radiofrequency ablation - an electrical current applied to the affected area to kill the cancer cells.

Dr Rebecca Fitzgerald, lead author based at the MRC Cancer Cell Unit in Cambridge, said: "Current methods to screen for oesophageal cancer are controversial - they are costly, uncomfortable for the patient and are not completely accurate. Our technique highlights the exact position of a developing oesophageal cancer, and how advanced it is, giving a more accurate picture. This could spare patients radical surgery to remove the oesophagus that can result in having to eat much smaller more regular meals and worse acid-reflux."

After pilot studies on large numbers of biopsies the researchers used four patients having removal of early cancer to show how the spray could be used. In two of the cases, pre-cancerous areas were not detected using conventional imaging, but the spray clearly highlighted an area that needed treating.

In another patient, their entire oesophagus had been removed because a small pre-cancerous area had been identified. Using current techniques it had been impossible to determine how developed the cancer was, but using the fluorescent spray, the researchers found the affected area was small and could have been treated with a less radical procedure.

Professor Kevin Brindle, one of the researchers based at Cancer Research UK's Cambridge Research Institute, said: "The benefit of using this dye is that it is specific, relatively cheap and is found in our normal diets so unlikely to cause any unwanted effects at the levels we use. We now need to test our technique in newly diagnosed patients, but it has great potential to be used with current imaging techniques to help improve treatment for oesophageal cancer."

Oesophageal cancer is the ninth most common cancer in the UK. Each year around 8,000 people are diagnosed with oesophageal cancer and the incidence of the disease in men has risen by more than 50 per cent in a generation.

Dr Julie Sharp, senior science information manager at Cancer Research UK, said: "Oesophageal cancer is one of the most difficult cancers to detect and treat, with only eight per cent of people with the disease surviving at least five years. We urgently need new ways to detect the cancer earlier, and this dye offers a great opportunity to treat the cancer more promptly and more successfully, potentially saving many lives a year."

More information: Bird-Lieberman, E.L., et al Molecular imaging using fluorescent lectins permits rapid endoscopic identification of dysplasia in Barrett's esophagus. Nature Medicine (2012) DOI: 10.1038/nm.2616

Provided by Cancer Research UK

http://www.eurekalert.org/pub_releases/2012-01/uoia-pds011312.php

Powerful drug's surprising, simple method could lead to better treatments

With one simple experiment, University of Illinois chemists have debunked a widely held misconception about an often-prescribed drug.

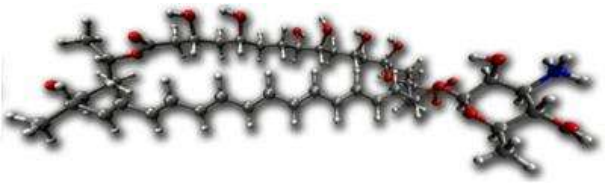
CHAMPAIGN, Ill. - Led by chemistry professor and Howard Hughes Medical Institute early career scientist Martin Burke, the researchers demonstrated that the top drug for treating systemic fungal infections works by simply binding to a lipid molecule essential to yeast's physiology, a finding that could change the direction of drug development endeavors and could lead to better treatment not only for microbial infections but also for diseases caused by ion channel deficiencies.

"Dr. Burke's elegant approach to synthesizing amphotericin B, which has been used extensively as an antifungal for more than 50 years, has now allowed him to expose its elusive mode of action," said Miles

Fabian, who oversees medicinal chemistry research grants at the National Institute of General Medical Sciences. The institute is part of the National Institutes of Health, which supported the work. "This work opens up avenues for improving upon current antifungals and developing novel approaches for the discovery of new agents."

Systemic fungal infections are a problem worldwide and affect patients whose immune systems have been compromised, such as the elderly, patients treated with chemotherapy or dialysis, and those with HIV or other immune disorders. A drug called amphotericin (pronounced AM-foe-TARE-uh-sin) has been medicine's best defense against fungal infections since its discovery in the 1950s. It effectively kills a broad spectrum of pathogenic fungi and yeast, and has eluded the resistance that has dogged other antibiotics despite its long history of use. The downside? Amphotericin is highly toxic.

"When I was in my medical rotations, we called it 'ampho-terrible,' because it's an awful medicine for patients," said Burke, who has an M.D. in addition to a Ph.D. "But its capacity to form ion channels is fascinating. So my group asked, could we make it a better drug by making a derivative that's less toxic but still powerful? And what could it teach us about avoiding resistance in clinical medicine and possibly even replacing missing ion channels with small molecules? All of this depends upon understanding how it works, but up until now, it's been very enigmatic."



This is a model of amphotericin, the most relied-upon drug for treating fungal infections, despite its toxicity. **Martin Burke**

While amphotericin's efficacy is clear, the reasons for its remarkable infection-fighting ability remained uncertain. Doctors and researchers do know that amphotericin creates ion channels that permeate the cell membrane. Physicians have long assumed that this was the mechanism that killed the infection, and possibly the patient's cells as well. This widely accepted dogma appears in many scientific publications and textbooks.

However, several studies have shown that channel formation alone may not be the killing stroke. In fact, as Burke's group discovered, the mechanism is much simpler.

Amphotericin binds to a lipid molecule called ergosterol, prevalent in fungus and yeast cells, as the first step in forming the complexes that make ion channels. But Burke's group found that, to kill a cell, the drug doesn't need to create ion channels at all - it simply needs to bind up the cell's ergosterol.

Burke's group produced a derivative of amphotericin using a molecule synthesis method Burke pioneered called iterative cross-coupling (ICC), a way of building designer molecules using simple chemical "building blocks" called MIDA boronates joined together by one simple reaction. They created a derivative that could bind ergosterol but could not form ion channels, and tested it against the original amphotericin.

If the widely accepted model was true, and ion channel formation was the drug's primary antifungal action, then the derivative would not be able to wipe out a yeast colony. But the ergosterol-binding, non-channel-forming derivative was almost equally potent to natural amphotericin against both of the yeast cell lines the researchers tested, once of which is highly pathogenic in humans. The researchers detailed their findings in the journal Proceedings of the National Academy of Sciences.

"The results are all consistent with the same conclusion: In contrast to half a century of prior study and the textbook-classic model, amphotericin kills yeast by simply binding ergosterol," Burke said.

"The beauty is, because we now know this is the key mechanism, we can focus squarely on that goal. Now we can start to think about drug discovery programs targeting lipid binding."

The researchers currently are working to synthesize a derivative that will bind to ergosterol in yeast cells, but will not bind to cholesterol in human cells, to see if that could kill an infection without harming the patient. They also hope to explore other derivatives that would target lipids in fungi, bacteria and other microbes that are not present in human cells. Attacking these lipids could be a therapeutic strategy that may defy resistance.

In addition to exploiting amphotericin's lipid-binding properties for antimicrobial drugs, Burke and his group hope to harness its channel-creating ability to develop treatments for conditions caused by ion-channel deficiencies; for example, cystic fibrosis. These new findings suggest that the ion-channel mechanism could be decoupled from the cell-killing mechanism, thus enabling development of derivatives that could serve as "molecular prosthetics," replacing missing proteins in cell membranes with small-molecule surrogates.

"Now we have a road map to take ampho-terrible and turn it into ampho-terrific," Burke said.

The paper, "Amphotericin Primarily Kills Yeast by Simply Binding Ergosterol," is available from the News Bureau or PNAS.

http://medicalxpress.com/news/2012-01-blood-human-mad-cow-disease.html

Blood test for human form of mad cow disease developed

A blood test has been developed that can identify the prion involved, which until now has only been identifiable via brain autopsies, or sometimes through tonsil biopsies

Medical Xpress - Mad cow disease is serious business in the U.K., the human form, known as Creutzfeldt-Jakob after Hans Gerhard Creutzfeldt and Alfons Maria Jakob (CJD), who independently first described its existence in humans, (more commonly known as variant CJD, or vCJD), has killed 176 people in that country since 1995, and worse, authorities suspect that thousands more may have it right now. Fortunately, it appears that a blood test has been developed that can identify the prion involved, which until now has only been identifiable via brain autopsies, or sometimes through tonsil biopsies. Currently, there is no cure for vCJD. Those infected lose proper brain function and eventually die within a few months to a couple of years after onset of symptoms. After death, the victims brains appear sponge-like due to the holes left behind as clumps of tissue die. The disease is neither viral nor bacterial and is instead, caused by a prion, which is an infectious type of protein.

Because normal cleansing and cooking processes don't kill the prions, the disease has spread undetected. Antibacterial processes used on surgical implements for performing tonsillectomies for example, don't eliminate the prions, and because those very same prions are associated with tonsils, it is believed many people have been infected when undergoing such procedures.

What's more alarming however is the lack of knowledge regarding blood supplies used for transfusions. Without a test, it's been impossible to know which samples are safe and which aren't. Now however, it appears researchers in Britain have come up with a blood test. Though no official announcement has been made, various sources say the country's NHS National Prion Clinic, has sent out messages to neurologists across the country indicating that a new blood test is now available. One local news outlet has reportedly spoken with Professor John Collinge, a member of the team that developed the blood test and says that he reports that thus far, no false-positives have occurred.

The next phase of testing will apparently be done on 5,000 blood samples obtained from the United States where the disease is far less common. Such a test should show how often false-positives occur. Sadly, if too many occur, the research team will have to start over.

Because there is no cure, it's not likely that many people will likely opt to be tested if the new test pans out unless they develop symptoms, but it would be used either for all blood donors, or at the least on the blood that is donated, thus sparing countless people from contracting a disease that by all accounts is a truly awful way to go.

http://www.sciencedaily.com/releases/2012/01/120116112610.htm

Revolutionary Surgical Technique for Perforations of the Eardrum

A revolutionary surgical technique for treating perforations of the tympanic membrane (eardrum) in children and adults has been developed at the Sainte-Justine University Hospital Centre, an affiliate of the Université de Montreal, by Dr. Issam Saliba.

ScienceDaily - The new technique, which is as effective as traditional surgery and far less expensive, can be performed in 20 minutes at an outpatient clinic during a routine visit to an ENT specialist. The result is a therapeutic treatment that will be much easier for patients and parents, making surgery more readily available and substantially reducing clogged waiting lists.

"In the past five years, I've operated on 132 young patients in the outpatient clinic at the Sainte-Justine UHC using this technique, as well as on 286 adults at the University of Montreal Hospital Centre (CHUM) outpatient clinic," says Dr. Saliba. "Regardless of the size of the perforation, the results are as good as those obtained using traditional techniques, with the incomparable advantage that parents don't have to lose an entire working day, or 10 days or more off school in the case of children."

The technique, which Dr. Saliba has designated "HAFGM" (Hyaluronic Acid Fat Graft Myringoplasty), requires only basic materials: a scalpel, forceps, a probe, a small container of hyaluronic acid, a small amount of fat taken from behind the ear and a local anesthetic. The operation, which is performed through the ear canal, allows the body by itself to rebuild the entire tympanic membrane after about two months on average, allowing patients to recover their hearing completely and preventing recurring cases of ear infection (otitis). Because it requires no general anesthetic, operating theatre or hospitalization, the technique makes surgery much more readily available, particularly outside large hospital centres, and at considerably lower cost.

"With the traditional techniques, you have to be on the waiting list for up to a year and a half in order to be operated on. Myringoplasty (reconstruction of the eardrum) using the HAFGM technique reduces waiting times,

cost of the procedure and time lost by parents and children. What's more, it will help clear the backlogs on waiting lists," Dr. Saliba says.

Perforations of the eardrum

Myringoplasty is surgical procedures to repair the tympanic membrane or eardrum when it has been perforated or punctured as the result of infection, trauma or dislodgement of a myringotomy tube (also known as a pressure equalization tube). Surgical repair of the perforation will allow the patient to recover his or her hearing and prevent repeated ear infections, particularly after swimming or shower. Traditionally, these procedures are performed using what are known as overlay and underlay techniques, which require hospitalization for at least one day, and 10 to 15 days off work. Every year in Quebec, some 750 myringoplasties are performed on adult or child patients.

Details of the study

This world premiere of a new form of eardrum surgery is based on results of a four-year prospective cohort study of 208 children and adolescents, 73 of whom were treated using the new HAFGM technique. This study was published on December 16, 2011 in the scientific journal Archives of Otolaryngology -- Head and Neck Surgery by Dr. Issam Saliba, otolaryngologist (ear, nose and throat or ENT specialist), surgeon and researcher at the Sainte-Justine University Hospital Centre affiliated with the Université de Montréal, where he is also professor of otology and neuro-otology. Dr. Saliba is also a surgeon and researcher at the CHUM, where he conducted a similar study, applying the same HAFGM technique to cohorts of adult patients between 2007 and 2010, with publication in the August 20, 2008 issue of the scientific journal Clinical Otolaryngology and subsequently in the February 12, 2011 issue of The Laryngoscope. The University of Montreal and Sainte-Justine University Hospital Centre are known officially as Université de Montréal and Centre hospitalier universitaire Sainte-Justine, respectively.

Journal Reference:

I. Saliba, P. Froehlich. Hyaluronic Acid Fat Graft Myringoplasty: An Office-Based Technique Adapted to Children. Archives of Otolaryngology - Head and Neck Surgery, 2011; 137 (12): 1203 DOI: 10.1001/archoto.2011.188

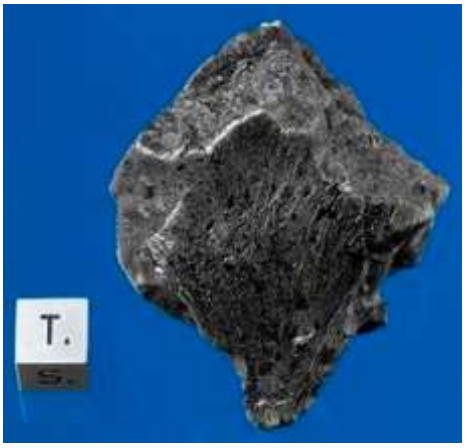
http://www.physorg.com/news/2012-01-mars-fell-africa-july.html

Scientists confirm rocks fell from Mars (Update)

Mars rocks fell in Africa last July

They came from Mars, not in peace, but in pieces. Scientists are confirming that 15 pounds of rock collected recently in Morocco fell to Earth from Mars during a meteorite shower last July.

This is only the fifth time in history scientists have chemically confirmed Martian meteorites that people witnessed falling. The fireball was spotted in the sky six months ago, but the rocks weren't discovered on the ground in North Africa until the end of December. This is an important and unique opportunity for scientists trying to learn about Mars' potential for life. So far, no NASA or Russian spacecraft has returned bits of Mars, so the only samples scientists can examine are those that come here in a meteorite shower.



Scientists and collectors are ecstatic, and already the rocks are fetching big bucks because they are among the rarest things on Earth - rarer even than gold. The biggest rock weighs over 2 pounds.

"It's Christmas in January," said former NASA sciences chief Alan Stern, director of the Florida Space Institute at the University of Central Florida. "It's nice to have Mars sending samples to Earth, particularly when our pockets are too empty to go get them ourselves."

This handout photo provided by Darryl Pitt of the Macovich Collection shows an external view of a Martian meteorite recovered in December 2011 near Foumzgit, Morocco following a meteorite shower believed to have occurred in July 2011. Scientists are confirming a recent and rare invasion from Mars - meteorite chunks that fell from the red planet over Morocco last summer. Meteorites from Mars are more than 1 million times rarer than gold. And this is only the fifth time experts have chemically confirmed fresh Martian rocks fell to Earth. The last time was in 1962. Scientists believe this meteorite fell last July because there were sightings of it. **(AP Photo/Darryl Pitt, Macovich Collection)**

A special committee Tuesday of meteorite experts, including some NASA scientists, confirmed test results that showed the rocks came from Mars, based on their age and chemical signature.

Astronomers think millions of years ago something big smashed into Mars and sent rocks hurtling through the solar system. After a long journey through space, one of those rocks plunged through Earth's atmosphere, breaking into smaller pieces. Most other Martian meteorite samples sat around on Earth for millions of years -

or at the very least, decades - before they were discovered, which makes them tainted with Earth materials and life. These new rocks, while still probably contaminated because they have been on Earth for months, are purer.

The last time a Martian meteorite fell and was found fresh was in 1962. All the known Martian rocks on Earth add up to less than 240 pounds.

The new samples were scooped up by dealers from those who found them. Even before the official certification, scientists at NASA, museums and universities scrambled to buy or trade these meteorites.

"It's incredibly fresh. It's highly valuable for that reason," said Carl Agee, director of the Institute of Meteoritics and curator at the University of New Mexico. "This is a beauty. It's gorgeous."

Meteorite dealer Darryl Pitt said he is charging $11,000 to $22,500 an ounce and has sold most of his supply already. At that price, the Martian rock costs about 10 times as much as gold.

One of the key decisions the scientists made Tuesday was to officially connect these rocks to the fiery plunge witnessed by people and captured on video last summer. The announcement and the naming of these meteorites - called Tissint - came from the International Society for Meteoritics and Planetary Science, which is the official group of 950 scientists that confirms and names meteorites.

Tony Irving of the University of Washington did the scientific analysis on the rocks and said there is no doubt they are from the red planet. Several of the world's top experts in meteorites told The Associated Press that they, too, are convinced.

Scientists can tell when meteorites are from Mars because they know what the Martian atmosphere is made of, thanks to numerous probes sent there. The chemical signature of the rocks and the Martian air match, Irving said. Another clue is that because Mars is geologically active, its rocks tend to be much younger - millions of years old instead of hundreds of millions or more - than those from the moon or asteroids.

Most of the known Martian rocks on Earth have been around for centuries or longer and have been found in Antarctica or the desert. They look so similar to dark Earth rocks that if they fell in other places, such as Maryland, they would blend right in and never be discovered.

Because known Martian meteorite falls happen only once every 50 years or so - 1815 in France, 1865 in India, 1911 in Egypt and 1962 in Nigeria - this is a once-in-a-career or even a once-in-a-lifetime event.

Jeff Grossman, a NASA scientist who is the meteorite society's database editor, said there is a higher probability of finding "something interesting" from Mars on these rocks because they fell so recently. However, six months is a long time for Earthly contamination to occur, he said.

University of Alberta meteorite expert Chris Herd, who heads the committee that certified the discovery, said the first thing he would do with the rocks would be to rinse them with solvents to try to get rid of earthly contamination and see what carbon-based compounds are left.

But Cornell University astronomer Steve Squyres, who is the principal investigator for NASA's Mars Exploration Rover Program and the space agency's go-to guy on Mars, said unfortunately this type of rock isn't the kind scientists are most hoping for. This find is igneous, or volcanic, rock. A softer kind of rock that could hold water or life would be better, but that type is unlikely to survive a fiery re-entry through Earth's atmosphere, he said.

Scientists are hoping NASA and the European Space Agency team up in 2018 to send robotic spaceships to Mars that can bring back samples of rock and dirt. Just this past weekend, a Russian probe that was going to try to bring samples back from a Martian moon came plummeting back to Earth in failure.

A Martian meteorite that was buried in Antarctica made news in 1996. NASA scientists theorized the rock showed traces of life from Mars. Even the White House declared it the first sign of life outside of Earth. Years of study since then have led much of the astronomy world to conclude there was insufficient evidence to support the claim. *More information: The Meteoritical Society: http://bit.ly/xDh6zz*
Tony Irving's list of Martian meteorites: http://bit.ly/yl7jBD

http://www.eurekalert.org/pub_releases/2012-01/bmj-eot011612.php

Effects of Tamiflu still uncertain, warn experts, as Roche continues to withhold key trial data

2 years after pharmaceutical giant Roche promised the BMJ it would release key Tamiflu trial data for independent scrutiny, the safety and effectiveness of this anti-influenza drug remains uncertain, warn experts today

Two years after pharmaceutical giant Roche promised the BMJ it would release key Tamiflu trial data for independent scrutiny, the safety and effectiveness of this anti-influenza drug remains uncertain, warn experts today. A new report by the Cochrane Collaboration says Roche's refusal to provide full access to all its data leaves critical questions about how well the drug works unresolved.

A BMJ investigation, published to coincide with today's report, also raises serious concerns about access to drug data, the use of ghost writers in drug trials, and the drug approval process. Meanwhile, Tamiflu has become the mainstay of influenza treatment in the UK. It has also made it onto the World Health Organisation's list of Essential Medicines and Roche's claims continue to be supported by influential health agencies.

The Cochrane researchers set out to test Roche's claim that Tamiflu prevented complications and reduced the number of people needing hospital treatment. But their investigation was hampered by Roche's refusal to provide all of its trial data for analysis. The team obtained some clinical study reports from the European Medicines Agency (EMA), but found inconsistencies with published reports and possible under-reporting of side effects. When previously questioned by the BMJ, Roche also admitted that some of the published papers had been ghost written.

The BMJ investigation reveals how different regulators took different approaches to the data submitted to them, leading to conflicting messages about it effectiveness. For example, the EMA released a proportion of the clinical study reports relating to the Tamiflu trials to Cochrane, but it admits that it did not ask for the remainder from the manufacturer, although it was legally entitled to do so. The EMA has since told the BMJ that it plans to start publishing reports for all drugs submitted for approval in the next few years.

Dr Fiona Godlee, BMJ Editor-in-Chief says: "We hope very much that the EMA will indeed take this important step in making the full study reports available. But we are still a long way away from having a full trial history for all drugs in clinical use. Public safety and the proper use of public money demands that we should stop at nothing less than this."

Meanwhile, the US Food and Drug Administration (FDA), which has reviewed the Tamiflu trial programme in perhaps more detail than anyone outside of Roche, chose not to review the largest ever trial of Tamiflu when considering the drug for approval. It states that "Tamiflu has not been shown to prevent such complications [serious bacterial infections]."

However, the US Centers for Disease Control and Prevention (CDC) continue to cite key published trials of Tamiflu, claiming a reduced risk of influenza complications, even after Roche admitted that some of these trials have been ghost written.

Dr Godlee says: "The discrepancies between the conclusions reached by different regulators around the world highlights the absurd situation we find ourselves in. In a globalised world, regulators should cooperate and pool their limited resources. Otherwise we will continue to waste money and risk people's health on drugs that don't work."

The investigation also raises questions about Tamiflu's clinical effects. After careful evaluation of trial data, the Cochrane group say that Tamiflu appears to affect antibody production - a claim that Roche refutes. This is important, say Cochrane, because influenza vaccination relies on an antibody response to be effective. But when asked by the BMJ, Roche refused to explain how the drug works.

As such, the Cochrane group say that "until more is known about the mode of action of neuraminidase inhibitors, health professionals, patients and other decision makers need to reflect on the findings of this review before making any decision about the use of the drug."

Cochrane also argue that Tamiflu's ability to prevent the spread of influenza has not been demonstrated in trials. Yet this is one of the main reasons governments around the world have spent billions of dollars stockpiling Tamiflu in case of a pandemic.

Roche maintain they provided the Cochrane team with enough information to conduct their evaluation, but the Cochrane team say this is not the case. Dr Peter Doshi from Johns Hopkins University School of Medicine says: "In the BMJ in December 2009, Roche promised full study reports to any legitimate investigators. They have not provided a single full study report to Cochrane, despite our repeated requests."

http://www.eurekalert.org/pub_releases/2012-01/bidm-sft011112.php

Study finds that tumor cells can prevent cancer spread

Paradoxical discovery finds that a group of cells known as pericytes help prevent metastasis

BOSTON - A new study finds that a group of little-explored cells in the tumor microenvironment likely serve as important gatekeepers against cancer progression and metastasis. Published in the January 17 issue of Cancer Cell, these findings suggest that anti-angiogenic therapies - which shrink cancer by cutting off tumors' blood supply - may inadvertently be making tumors more aggressive and likely to spread.

One approach to treating cancer targets angiogenesis, or blood vessel growth. In this new investigation, senior author Raghu Kalluri, MD, PhD, Chief of the Division of Matrix Biology at Beth Israel Deaconess Medical Center (BIDMC) and Professor of Medicine at Harvard Medical School (HMS), wanted to find out if targeting a specific cell type, the pericyte, could inhibit tumor growth in the same way that other antiangiogenic

drugs do. Pericytes are an important part of tissue vasculature, covering blood vessels and supporting their growth.

Kalluri and his colleagues began by creating mice genetically engineered to support drug-induced depletion of pericytes in growing tumors. They then deleted pericytes in implanted mouse breast cancer tumors, decreasing pericyte numbers by 60 percent. Compared with wild-type controls, they saw a 30 percent decrease in tumor volumes over 25 days. However, contrary to conventional clinical wisdom, the investigators found that the number of secondary lung tumors in the engineered mice had increased threefold compared to the control mice, indicating that the tumors had metastasized.

"If you just looked at tumor growth, the results were good," says Kalluri. "But when you looked at the whole picture, inhibiting tumor vessels was not controlling cancer progression. The cancer was, in fact, spreading."

To understand the mechanism behind this increased metastasis, Kalluri and his team examined the tumor's microenvironment to find out what changes were taking place at the molecular level. They found a fivefold percentage increase in hypoxic areas in tumors lacking pericytes. "This suggested to us that without supportive pericytes, the vasculature inside the tumor was becoming weak and leaky - even more so than it already is inside most tumors - and this was reducing the flow of oxygen to the tumor," explains Kalluri.

"Cancer cells respond to hypoxia by launching genetic survival programs," he adds. To that end, the investigators found evidence of epithelial-to-mesenchymal transition (EMT), a change that makes the cells more mobile, so they can travel through those leaky vessels to new locations, and makes them behave more like stem cells, so they are better able to survive. Experiments that demonstrated fivefold increases in protein markers of EMT showed that the cells had undergone the change. The team also found a fivefold increase in activation of Met, a receptor molecule that promotes cell migration and growth.

Importantly, the team found that these molecular changes occurred inside the smaller, pericyte-depleted tumors that had increased incidences of secondary tumors in the lungs in the mouse models. "This suggested that smaller tumors are shedding more cancer cells into the blood and causing more metastasis," says Kalluri. "We showed that a big tumor with good pericyte coverage is less metastatic than a smaller tumor of the same type with less pericyte coverage."

Because cancer therapies such as Imatinib, Sunitinib and others have been shown to decrease pericytes in tumors, the researchers' next step was to perform the same experiments in mice with primary tumors, only this time, using Imatinib and Sunitinib rather than genetic programs to decrease pericyte numbers. And while both Imatinib and Sunitinib caused a 70 percent pericyte depletion, the end results, stayed the same: metastasis increased threefold. "We showed that a big tumor with good pericyte coverage is less metastatic than a smaller tumor of the same type with less pericyte coverage," says Kalluri, who corroborated these findings in multiple types of cancer by repeating these same experiments with implanted renal cell carcinoma and melanoma tumors.

Additional experiments showed that combining pericyte-depleting drugs with the Met-inhibiting drug helped suppress EMT and metastasis.

Finally, to determine if the findings were relevant to patients, the scientists examined 130 breast cancer tumor samples of varying cancer stages and tumor sizes and compared pericyte levels with prognosis. They found that samples with low numbers of pericytes in tumor vasculature and high levels of Met expression correlated with the most deeply invasive cancers, distant metastasis and 5- and 10- year survival rates lower than 20 percent.

"These results are quite provocative and will influence clinical programs designed to target tumor angiogenesis," says Ronald A. DePinho, president of the University of Texas MD Anderson Cancer Center. "These impressive studies will inform and refine potential therapeutic approaches for many cancers."

Meanwhile, for Kalluri, the work suggests that certain assumptions about cancer must be revisited. "We must go back and audit the tumor and find out which cells play a protective role versus which cells promote growth and aggression," says Kalluri. "Not everything is black and white. There are some cells inside a tumor that are actually good in certain contexts."

Collaborators in this study include BIDMC investigators Vesselina Cooke and Valerie LeBleu (co-first authors) Doruk Keskin, Zainab Khan, Joyce O'Connell, Yingqi Teng, Michael Duncan, Liang Xie, Genta Maeda, Sylvia Vong, and Hikaru Sugimoto. Additional investigators Rafael Rocha, Aline Damascena, and Ricardo Brentani collaborated from Hospital A. C. Camargo in the National Institute of Oncogenomics of Brazil.

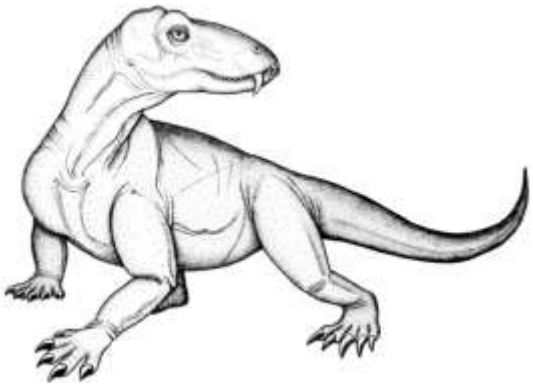
This study was supported by the National Institutes of Health (NIH). Kalluri is a Champalimaud investigator funded by the Champalimaud metastasis programme. Cooke is funded by a Ruth Kirschstein Post-doctoral fellowship. LeBleu is funded by an NIH training grant in gastroenterology. Duncan is funded by an NIH training grant in cancer biology, an NIH supplemental grant to support diversity, and a United Negro College Fund-Merck Postdoctoral Science Research Fellowship. Sugimoto is funded by an NIH research training grant in cardiovascular medicine. O'Connell is funded by the Department of Defense Breast Cancer Predoctoral Traineeship Award.

http://www.wired.com/wiredscience/2012/01/how-the-terrible-heads-became-world-travelers/

How the 'Terrible Heads' Became World Travelers

Earlier this week, paleontologists described another of our distant, ancient cousins.

By Brian Switek Email Author



Earlier this week, paleontologists described another of our distant, ancient cousins. This was no hominin, early primate, or even archaic mammal, but a much, much older variety of creature that would superficially seem to have more in common with terrible primeval reptiles than with us. Named Pampaphoneus biccai, this knobby-headed, 260-million-year-old predator is a clue to one of life's major events in the time before the dinosaurs. There is no common name for the peculiar group of animals Pampaphoneus belonged to. Researchers and science writers alike used to call such creatures "mammal-like reptiles", but that title has been tossed. The old phrase no longer makes any sense.

Top Image: Pampaphoneus strikes a pose. Image from Cisneros et al., 2012.

At a broad level, Pampaphoneus was a synapsid - a member of the major vertebrate group that includes mammals and all creatures more closely related to mammals than to diapsids (the group which contains lizards, dinosaurs, snakes, and other reptiles). The position and arrangement of openings at the back of the skull are a quick and dirty way to tell the difference between the two lineages. Synapsids (including us) have a single opening, while diapsids have two (or at least did ancestrally).

The very first synapsids looked very much like lizards. During the early part of the Permian period, however, these archaic forms were adapted into a wider variety of creatures, including the famous sail-backed synapsids Dimetrodon and Edaphosaurus. These were some of the world's first large carnivores and herbivores, but, by about 260 million years ago, this particular flavor of synapsid had virtually disappeared. (Late last year, paleontologist Sean Modesto and colleagues described the last known member of the archaic synapsid dynasty - a roughly 260 million year old creature known as a varanopid, found in the strata of South Africa.

But one lineage of these early varieties was adapted into swifter, more specialized forms. These animals, which replaced the likes of Dimetrodon and the varanopids, were called therapsids. Pampaphoneus was one of them.

So far, all we know of Pampaphoneus is the skull. The foot-long fossil has been briefly described by paleontologist Juan Carlos Cisneros and co-authors in PNAS. At the front of the long, oval-shaped skull were a set of pointed, interlocking incisors, followed by prominent canines and a set of eight smaller, serrated teeth. This appears to be the dental toolkit of an omnivore, if not a dedicated carnivore, and makes Pampaphoneus the first large predator found in the Middle Permian deposits of Brazil.

Pampaphoneus was also a relatively well-ornamented hunter. The animal's skull features small ridges which extend from the eye socket to the upper jaw, and the region around the eyes is decorated with a midline ridge and prominent bosses of bone over the eyes. This ornamentation is consistent with the particular group of therapsid to which Pampaphoneus belongs - the Dinocephalia, or "terrible heads." In many of these animals, the skull was thickened to create lumps of reinforced bone or strange ornamentation. You have probably seen at least one of these creatures - Estemmenosuchus, a tubby animal with weird, antler-like flanges of bone projecting out of its skull - in museum displays and on book covers. More specifically, Pampaphoneus belonged to a subset of this bizarre group called the anteosaurids, and that conclusion may be a clue to how these animals dispersed through the ancient supercontinent Pangea.

The significance of Pampaphoneus isn't how weird the animal was, or, as played up to hyperbolic levels by Discovery News, how vicious a killer it might have been. What the discovery of Pampaphoneus indicates is that the particular group of animals to which it belonged quickly spread through Pangea shortly after their origin. The previous discovery of similar dinocephalians in Russia, China, and South Africa - all of which were stuck together in a giant landmass around 260 million years ago - supports the hypothesis that animal lineages spread all over the world to create a cosmopolitan fauna. If you could visit prehistoric South Africa, Brazil, Russia, and China, you would see the same sorts of creatures. There must have been some central connection which allowed the animals to spread between the areas of the continent which would later split and drift to become Asia, Africa, and South America. Pampaphoneus wasn't the first creature of its kind to be discovered, nor was it the weirdest, but its existence at a critical time and place may help paleontologists figure out how our distant synapsid cousins took over the world.

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Modesto, S., Smith, R., Campione, N., & Reisz, R. (2011). The last "pelycosaur": a varanopid synapsid from the Pristerognathus Assemblage Zone, Middle Permian of South Africa Naturwissenschaften, 98 (12), 1027-1034 DOI: 10.1007/s00114-011-0856-2

http://bit.ly/xDFYth

Researchers evolve a multicellular yeast in the lab in 2 months

When we think of life on Earth, most of us think of multicellular organisms, like large mammals or massive trees.

By John Timmer | Published 3 days ago

But we're only aware of three groups of complex, multicellular organisms, which suggested it might be a major hurdle. Now, a new study describes how researchers evolved a multicellular form of yeast (the same species that contributes to bread and beer), and were able to see specialized cell behaviors and reproduction in as little as 60 days.

The authors lay out the problem very simply in their introduction, stating that, "Multicellularity was one of the most significant innovations in the history of life, but its initial evolution remains poorly understood." There is some evidence that it can be a favorable trait - research shows that clusters of cells evolve when a single-celled organism is kept in culture with a predator that can only swallow one cell at a time.

But that's about as far as these experiments went. It wasn't clear how these clusters of cells formed, whether they were genetically related, or whether they engaged in any sort of specialized behavior. More significantly, it wasn't obvious whether these clusters took a sort of "every cell for itself" approach to reproduction. So, although this work showed a multicellular lifestyle could be selected for, the researchers didn't look into how far down the road towards specialization those cells would go.

The new study attempts to follow more the behavior of simple multicellular groups more closely. It uses baker's yeast (Saccharomyces cerevisiae), an organism that normally grows as single cells. The authors grew these in culture and, once a day, transferred them in a way that favored multicellular growth.

Their method was pretty simple. Normally, yeast are grown in a culture that's shaken, and the single cells will only slowly settle to the bottom when that's stopped. The authors only transferred the cells at the bottom of the culture to fresh food, so that they selected for those cells that settled to the bottom quickly. This favors large clusters of cells, instead of single ones.

With only 60 daily transfers, all of their experimental populations were dominated by yeast cells that grew as clusters, which the authors describe as "roughly spherical snowflake-like." These were formed because, instead of separating after they divided, cells would remain attached, expanding the cluster with each division. Although this comes at a cost compared to individual cells - the authors calculate that individual cells in the cluster are 10 percent less fit than their single-celled relatives when they're not selecting for things on the bottom. But, with the selection in place, the clusters had a huge advantage. But the clusters didn't simply keep growing indefinitely. Instead, the yeast quickly evolved a form of reproduction by splitting off what the authors call "propagules," or smaller clusters that break off and go on to develop on their own.

With more generations, this form of reproduction began to include specialized cell behavior. A small percentage of cells in the cluster would start committing suicide through a process called apoptosis. This death would allow the propagule to split off cleanly at the site of the dead cell, improving the efficiency of reproduction. Normally, there's no evolutionary advantage to a cell ending up dead but, since the cells in the propagule are genetically identical, this behavior can be selected for.

This new form of growth and reproduction is still a long way off from the complex, specialized tissues found in most multicellular organisms. But the ease with which this behavior evolved suggests that the foundations of multicellularity may evolve very easily, and don't present the barrier to complexity that many people have assumed it was. *PNAS, 2012. DOI: 10.1073/pnas.1115323109 (About DOIs).*

http://medicalxpress.com/news/2012-01-effective-prompting-people-stairs-elevator.html

Signs prove effective in prompting people to use stairs instead of elevator

Signs that read, "Burn Calories, Not Electricity" posted in lobbies of New York City buildings, motivated more people to take the stairs and continue to use them even months later.

A new study, which appears online in the February issue of the American Journal of Preventive Medicine, observed and analyzed people making 18,462 trips up and down stairs at three sites. The signs immediately increased stair use between 9.2 and 34.7 percent at all locations.

"The gains in physical activity continued to be observed nine months after the signs were first placed," noted Karen K Lee, M.D., author of the study at New York City Department of Health and Mental Hygiene. "We found that placing stair prompts at the point of decision is effective."

The study is among the first to assess the effects of stair prompts on stair climbing as well as descent in different types of buildings over many months. Prompts were posted in a three-story health clinic, a 10-story affordable housing building, and an 8-story academic site and studied over several months.

"Human-made environments in everyday life offer numerous opportunities for maintaining health, controlling weight and preventing disease," Lee said. "One of those health opportunities is stair climbing, a vigorous activity which can burn more calories than jogging."

Patrick Remington, M.D., associate dean for public health in the University of Wisconsin School of Medicine & Public Health said, "For decades, we've known this type of intervention works, but few, if any, places actually have these signs."

Instead of removing the signage after the study was completed, the prompts were purposely left in place. New York City continues to promote the health benefits of stair climbing by distributing free stair signs to owners and managers of public and private buildings who request them.

"So far, we've distributed over 26,000 signs to owners and managers of about 1,000 buildings including residential, worksites, hospitals and academic centers," said Lee.

Remington sees opportunities for widespread use of prompts. "For example, a zoning law could be enacted that requires buildings to have stair prompts …like they require signs for exits." Remington added, "Overall, this is a great study, showing how for almost no investment we can improve health."

More information: Lee, K.K. et al. (2012). Promoting Routine Stair Use Evaluating the Impact of a Stair Prompt Across Buildings. American Journal of Preventive Medicine. Provided by Health Behavior News Service

http://www.eurekalert.org/pub_releases/2012-01/mu-stm011812.php

Solving the mystery of an old diabetes drug that may reduce cancer risk

Research opens exciting new avenues in cancer prevention

In 2005, news first broke that researchers in Scotland found unexpectedly low rates of cancer among diabetics taking metformin, a drug commonly prescribed to patients with Type II diabetes. Many follow-up studies reported similar findings, some suggesting as much as a 50-per-cent reduction in risk. How could this anti-diabetic drug reduce the risk of developing cancer and what were the mechanisms involved?

In a paper published today in the journal Cancer Prevention Research, researchers from McGill University and the University of Montreal reported an unexpected finding: they learned that exposure to metformin reduces the cellular mutation rate and the accumulation of DNA damage. It is well known that such mutations are directly involved in carcinogenesis, but lowering cancer risk by inhibiting the mutation rate has never been shown to be feasible.

"It is remarkable that metformin, an inexpensive, off-patent, safe and widely used drug, has several biological actions that may result in reduced cancer risk – these latest findings suggest that it reduces mutation rate in somatic cells, providing an additional mechanism by which it could prevent cancer, explained Dr. Michael Pollak, professor in McGill's Departments of Medicine and Oncology, researcher at the Lady Davis Institute for Medical Research at the Jewish General Hospital and the study's director.

The study, carried out in collaboration with the laboratory of Dr. Gerardo Ferbeyre at Université de Montréal's Department of Biochemistry, suggests that metformin reduces DNA damage by reducing levels of reactive oxygen species (ROS). ROS are known to be DNA-damaging agents produced as by-products when cells generate energy from nutrients. This action appears to take place in mitochondria, the cellular organelles that produce energy in cells by "burning" nutrients. Past studies have identified the mitochondria as a site of action for metformin related to its anti-diabetic function, but those studies had not considered that the drug also acted here to reduce ROS production, thereby reducing the rate at which DNA damage accumulates. "We found that metformin did not act as a classic antioxidant," said Ferbeyre. "The drug seems to selectively prevent ROS production from altered mitochondria such as those found in cells with oncogenic mutations."

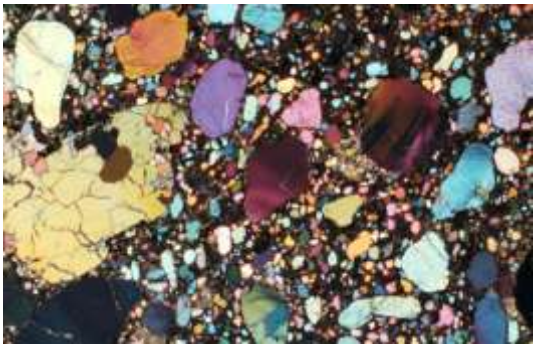
"This study opens an exciting new direction in cancer-prevention research," said Pollak. "This doesn't imply, however, that metformin is now ready to be widely used for cancer prevention. We do not yet know if the drug accumulates to sufficient concentrations in human tissues at risk for cancer, such as breast or colon, when taken at the usual doses used for diabetes treatment, nor do we know if the findings from the original studies showing reduced cancer risk, which were carried out in diabetics, also apply to people without diabetes. But the possibility of protecting DNA from oxidative damage by the use of a well-tolerated drug was not expected, and this topic now needs further study at many levels."

http://www.sciencenews.org/view/generic/id/337737/title/Carbonation_brings_diamonds_to_surface

Carbonation brings diamonds to surface

Chemical reactions deep inside the Earth fuel magma's gem-laden upward journey

By Alexandra Witze



Drop a Mentos candy in a bottle of Diet Coke, and carbon dioxide will bubble violently out of the soda. Similar chemical reactions may send certain kinds of magma frothing up from deep within the Earth, carrying diamonds along the way.

The discovery, reported in the Jan. 19 Nature, solves several mysteries about why and how diamond-bearing rocks appear where they do. As gem-laden magma rises, the theory goes, it gobbles a mineral called orthopyroxene, changing the magma's chemical composition and belching carbon dioxide gas that drives its continued ascent.

This thin slice of a kimberlite rock from northern Canada, seen through a microscope and in polarized light, shows colorful minerals caught up in magma that rose from deep within the Earth. **Lucy Porritt**

"We've provided a simple, chemically reasonable process to have dissolved gas at depth," says Kelly Russell, lead author of the new paper and a volcanologist at the University of British Columbia in Vancouver.

Diamond mines tap volcanic rocks called kimberlites, which contain many kinds of crystals that must have formed at high pressures 150 kilometers or more deep, in the planetary layer known as the mantle. How those mantle crystals make it to the surface has been a puzzle, since magma gets denser the more crystals it picks up. Most geologists have assumed that the magma must bubble gases to keep it moving up, but no one has been able to explain exactly how.

Russell and his colleagues realized that gas could do the trick if the magma starts out relatively poor in silicon dioxide, a major component of the Earth's crust also known as silica. As magma rises through cracks it begins to dissolve the surrounding rock - especially that containing lots of orthopyroxene, a mineral rich in magnesium, iron and silica. The orthopyroxene releases its silica into the magma, and as the silica content rises the magma's ability to hold dissolved carbon dioxide drops. The gas bubbles out and by the time the kimberlite gets to the surface, it erupts at supersonic speeds.

Working in a high-temperature laboratory at the University of Munich, Russell melted sodium carbonate as a stand-in for silica-poor magma. He then added orthopyroxene and watched as the mixture furiously bubbled carbon dioxide.

The research could explain why the gem-laden kimberlites appear only in ancient parts of continents, known as cratons, like those in northwestern Canada and southern Africa. Cratons contain lots of orthopyroxene, allowing the magma to gobble it and ascend. "We've always wondered, how do the kimberlites find the craton?" Russell says. "They don't. Their passage through the craton converts them."

Lionel Wilson, an earth scientist at Lancaster University in England, says the study fits with other ideas about how kimberlites rise. In 2007, he and James Head of Brown University proposed that diamond-bearing magma moved upward by shattering rocks above it (SN: 6/30/07, p. 412). But their calculations showed it slowing down in shallower depths. The chemistry proposed by Russell's team would give the magma enough oomph to continue all the way to the surface. "So I see this as a really important contribution," Wilson says.

Russell's team is now working to see how quickly orthopyroxene and other minerals dissolve in the magma, to better estimate the speeds at which kimberlites rise.

http://medicalxpress.com/news/2012-01-game-prevalent-teens-texas.html

Choking game prevalent among teens in Texas

Nearly one out of seven college students surveyed at a Texas university has participated in the Choking Game, a dangerous behavior where blood flow is deliberately cut off to the brain in order to achieve a high

Nearly one out of seven college students surveyed at a Texas university has participated in the Choking Game, a dangerous behavior where blood flow is deliberately cut off to the brain in order to achieve a high, according to a study by The Crime Victims' Institute at Sam Houston State University.

The Choking Game, also known as the Fainting Game, Pass Out, or Space Monkey, is played individually or in groups and involves manually choking oneself or others, applying a ligature around the neck or a plastic bag over the head, placing heavy objects on the chest, or hyperventilating to attain a euphoric feeling. This practice has led to several suffocation deaths in Texas and across the country.

"This study was undertaken to determine who is playing the game, in what context, and how they learned about it," said Dr. Glen Kercher, director of the Crime Victims' Institute. "It is our hope that these findings will inform efforts by parents, schools, and community agencies to warn young people about the dangers of participating in the Choking Game."

The study was based on a survey completed by 837 students at a Texas university. Among the findings were:

16% percent of students reported having played the game; 72% reportedly played the game more than once
Males were more likely to have played than females
The average age when students first played the game was 14
90% of those who played the game first heard about it from peers
Most students reported that others were present when they first played the game
Curiosity about the effects of the Choking Game was a primary motivation for playing the game

Learning about the potential dangers in engaging in this activity served as a deterrent for the majority of non-participants.

"Even though awareness of the Choking Game is growing, it should be noted that encouragement for parents to discuss this activity with their children should still be stressed," said Brittany Longino Smith, who co-authored the study "The Choking Game" with Dr. Kercher and Dr. Leana Bouffard, an Associate Professor at SHSU.

A similar study on the Choking Game found that 90 percent of parents would support incorporating information on the behavior in health and drug prevention classes.

While preventative programs have increased to help warn adolescents of the use of illegal substances, the Choking Game is another method of achieving similar effects that has been introduced to this age group. "This 'game,' as it is often called, does not require obtaining any drugs or alcohol, is free, and can go undetected by many parents, teachers, physicians, and other authority figures. Most importantly, many of those who engage in this activity, do not understand that the practice can be just as deadly as the illegal substances youth have been warned against," the study found. *Provided by Sam Houston State University*

http://www.sciencedaily.com/releases/2012/01/120118155338.htm

Saving Dogs With Spinal Cord Injuries

Dogs with spinal cord injuries may soon benefit from an experimental drug

ScienceDaily - Dogs with spinal cord injuries may soon benefit from an experimental drug being tested by researchers at the University of California, San Francisco (UCSF) and Texas A&M College of Veterinary Medicine & Biomedical Sciences -- work that they hope will one day help people with similar injuries.

Funded through a three-year, $750,000 grant from the U.S. Department of Defense, the drug to mitigate damage has already proven effective in mice at UCSF. Now the Texas team will test how it works in previously injured short-legged, long torso breeds of dog like dachshunds, beagles and corgis, who often suffer injuries when a disk in their back spontaneously ruptures, damaging the underlying spinal cord.

About 120 dogs a year that develop sudden onset hind limb paralysis after such injuries are brought to the Small Animal Hospital of Texas A&M University, where they receive surgical and medical treatment similar to that for human spinal cord injury. Now, researchers will test whether the new treatment works on some of these dogs, with their owners' consent.

Dog in medical device **Credit: UCSF**

"It would be phenomenal if it works," said Linda J. Noble-Haeusslein, PhD, a professor in the UCSF departments of Neurological Surgery and Physical Therapy and Rehabilitation Science who designed the intervention. "We are in a unique position of being able to treat a dog population where there are simply no current therapies that could effectively improve their hind limb function."

The new treatment does not seek to regrow injured pathways in the spinal cord. Instead, it aims to mitigate damage secondary to the spinal cord injury. Most spinal cord injuries trigger a cascade of chemical reactions in the spinal cord that collectively damage nearby cells and pathways, contributing to functional deficits including hind limb function.

A few years ago, Noble and her UCSF colleague Zena Werb, PhD, showed how blocking the action of one protein found in the spinal cord of mammals can help mice recover from spinal cord injuries. This protein, called matrix metalloproteinase-9, can degrade pathways within the cord and cause local inflammation, leading to cell death.

The injured dogs offer a great opportunity to take the next step on this treatment because their injuries more closely mimic spontaneous human spinal cord injury and, as is the case with humans, no existing treatment has substantially reduced paralysis.

Noble's co-investigator on the new study, Jonathan Levine, DVM, an assistant professor in neurology at Texas A&M University, will treat the dogs through injections of a protein-blocking drug. He will then help the dogs through rehabilitation and assess their recovery. Ongoing studies at UCSF focus on further refining delivery of the drug so as to optimize recovery.

Other researchers have shown that movement can be preserved if as little as 18 percent to 20 percent of the nerve fiber tracts in the spinal cord remain intact.

If successful, the trials in injured dogs may lead to the development of similar treatments for people who suffer spinal cord injuries, Noble said. These are among the most expensive injuries: every person with an injured spinal cord costs the health care system millions of dollars over his or her lifetime.

Such costs often are overshadowed by the tragic and devastating personal price of the injuries, which dramatically alter lives and most often occur in younger people, with long lives in front of them. According to the National Spinal Cord Injury Statistical Center, based at the University of Alabama, Birmingham, most of the 12,000 Americans who suffer spinal cord injuries are between the ages of 16 and 30.

As of this year, some 265,000 people in the United States are living with such injuries, according to the national center. This includes many wounded soldiers who have returned home from war zones.

UCSF is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care.

www.physorg.com/news/2012-01-cognitive-scientists-problem-human-language.html

Cognitive scientists develop new take on old problem

Why human language has so many words with multiple meanings

Why did language evolve? While the answer might seem obvious -- as a way for individuals to exchange information -- linguists and other students of communication have debated this question for years. Many prominent linguists, including MIT's Noam Chomsky, have argued that language is, in fact, poorly designed for communication. Such a use, they say, is merely a byproduct of a system that probably evolved for other reasons -- perhaps for structuring our own private thoughts.

As evidence, these linguists point to the existence of ambiguity: In a system optimized for conveying information between a speaker and a listener, they argue, each word would have just one meaning, eliminating any chance of confusion or misunderstanding. Now, a group of MIT cognitive scientists has turned this idea on its head. In a new theory, they claim that ambiguity actually makes language more efficient, by allowing for the reuse of short, efficient sounds that listeners can easily disambiguate with the help of context.

"Various people have said that ambiguity is a problem for communication," says Ted Gibson, an MIT professor of cognitive science and senior author of a paper describing the research to appear in the journal Cognition. "But once we understand that context disambiguates, then ambiguity is not a problem — it's something you can take advantage of, because you can reuse easy [words] in different contexts over and over again."

Lead author of the paper is Steven Piantadosi PhD '11; Harry Tily, a postdoc in the Department of Brain and Cognitive Sciences, is another co-author.

What do you 'mean'?

For a somewhat ironic example of ambiguity, consider the word "mean." It can mean, of course, to indicate or signify, but it can also refer to an intention or purpose ("I meant to go to the store"); something offensive or nasty; or the mathematical average of a set of numbers. Adding an 's' introduces even more potential definitions: an instrument or method ("a means to an end"), or financial resources ("to live within one's means").

But virtually no speaker of English gets confused when he or she hears the word "mean." That's because the different senses of the word occur in such different contexts as to allow listeners to infer its meaning nearly automatically.

Given the disambiguating power of context, the researchers hypothesized that languages might harness ambiguity to reuse words - most likely, the easiest words for language processing systems. Building on observation and previous studies, they posited that words with fewer syllables, high frequency and the simplest pronunciations should have the most meanings.

To test this prediction, Piantadosi, Tily and Gibson carried out corpus studies of English, Dutch and German. (In linguistics, a corpus is a large body of samples of language as it is used naturally, which can be used to

search for word frequencies or patterns.) By comparing certain properties of words to their numbers of meanings, the researchers confirmed their suspicion that shorter, more frequent words, as well as those that conform to the language's typical sound patterns, are most likely to be ambiguous - trends that were statistically significant in all three languages.

To understand why ambiguity makes a language more efficient rather than less so, think about the competing desires of the speaker and the listener. The speaker is interested in conveying as much as possible with the fewest possible words, while the listener is aiming to get a complete and specific understanding of what the speaker is trying to say. But as the researchers write, it is "cognitively cheaper" to have the listener infer certain things from the context than to have the speaker spend time on longer and more complicated utterances. The result is a system that skews toward ambiguity, reusing the "easiest" words. Once context is considered, it's clear that "ambiguity is actually something you would want in the communication system," Piantadosi says.

Tom Wasow, a professor of linguistics and philosophy at Stanford University, calls the paper "important and insightful."

"You would expect that since languages are constantly changing, they would evolve to get rid of ambiguity," Wasow says. "But if you look at natural languages, they are massively ambiguous: Words have multiple meanings, there are multiple ways to parse strings of words. … This paper presents a really rigorous argument as to why that kind of ambiguity is actually functional for communicative purposes, rather than dysfunctional."

Implications for computer science

The researchers say the statistical nature of their paper reflects a trend in the field of linguistics, which is coming to rely more heavily on information theory and quantitative methods.

"The influence of computer science in linguistics right now is very high," Gibson says, adding that natural language processing (NLP) is a major goal of those operating at the intersection of the two fields.

Piantadosi points out that ambiguity in natural language poses immense challenges for NLP developers. "Ambiguity is only good for us [as humans] because we have these really sophisticated cognitive mechanisms for disambiguating," he says. "It's really difficult to work out the details of what those are, or even some sort of approximation that you could get a computer to use."

But, as Gibson says, computer scientists have long been aware of this problem. The new study provides a better theoretical and evolutionary explanation of why ambiguity exists, but the same message holds: "Basically, if you have any human language in your input or output, you are stuck with needing context to disambiguate," he says. *Provided by Massachusetts Institute of Technology*

http://www.physorg.com/news/2012-01-salt-free-primordial-soup.html

A salt-free primordial soup?

In his book, First Life, David Deamer provides an overview of research into life's beginnings.

Most scientists who study the origin of life assume that it occurred in the ocean. But a minority view is that ions in seawater may interfere with prebiotic chemistry, making a freshwater environment more likely.

The saltiness of our blood is often cited as evidence that life originated in the ocean. However, some researchers contend that the first chemical steps toward biology would have been easier in freshwater rather than saltwater.

The exact location for the origin of life is still a wide open question, but many scientists have assumed that it happened somewhere in the ocean.

"The main argument for a marine origin is that there is so much seawater," says David Deamer of UC Santa Cruz. Roughly 98% of the Earth's water bodies are salty, and this percentage was likely much higher 4 billion years ago when we think the first life-forms made their appearance.

But Deamer doesn't think quantity is a substitute for quality. Seawater, in his estimation, is too reactive with certain biomolecules to have served as the "broth" for the primordial soup.

A freshwater origin seems to have been what Charles Darwin was proposing when he imagined the spontaneous formation of biomolecules in "some warm little pond."

Deamer and his colleagues are testing Darwin's idea, but with the temperature turned up. They have gone to several geothermally heated "ponds" around the world to see if they can't cook up some of the more complex molecules of life in these freshwater environments. Deamer recounts these adventures in a new book called "First Life: Discovering the Connections between Stars, Cells, and How Life Began."

His critics might say the work could use a pinch of salt.

The ocean in your veins

It's no accident that our blood is about a quarter as salty as the ocean. This level is tightly regulated by the kidneys. Our cells will die if the salt level in blood and other fluids goes too high or too low.

The normal salt that we are familiar with is sodium chloride (NaCl). In solution, the salt breaks up into ions: specifically positively-charged sodium ions and negatively charged chloride ions. All cells – human and otherwise – spend a great deal of time shuffling these and other ions around. This shuffling is necessary to maintain the fluid pressure inside the cell, but it also creates electric potentials that provide a kind of "battery" for performing certain cellular functions.

"This sort of bioenergy is common to all life forms," says Shiladitya DasSarma of the University of Maryland Biotechnology Institute.

The ubiquity of ion-mediated potentials in cells may be telling us something about where life got started.

"I wouldn't think ions could play such an important role unless they were around in the beginning," he says.

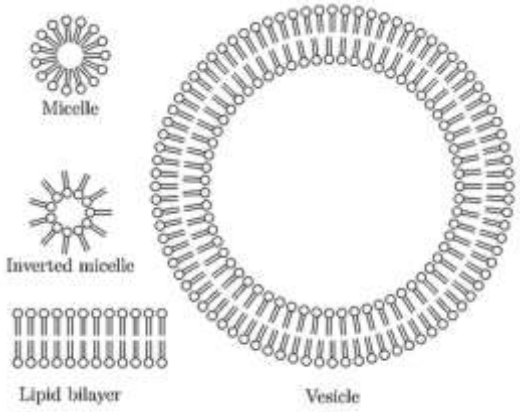
DasSarma believes that the first organisms arose in salt water that was perhaps extremely salty. The early ocean was perhaps twice as salty as it is today. Moreover, the ingredients of life may have been concentrated by evaporation in a seaside pool or lagoon, which would have concentrated the salt as well.

Bursting life's bubble

The problem with seawater, according to Deamer, isn't the salt, per se. Seawater also contains other ions, like those of magnesium and calcium, which carry a charge of +2. These so-called divalent ions react unfavorably with certain building blocks of life.

Lipid molecules will spontaneously form layers and vesicles. Credit: Henrik Skov Midtiby

For example, calcium ions readily bind with phosphate, thus making this molecule unavailable for important biological functions, such as energy transfer (in the case of adenosine triphosphate, or ATP) and genetic coding (as part of the backbone of DNA and RNA).



Lipid molecules will spontaneously form layers and vesicles. **Credit: Henrik Skov Midtiby**

Deamer is especially concerned with the effect that divalent ions have on simple fatty acids. These "soapy" molecules – generically called lipids – line up together to form closed vesicles. Several scientists have theorized that self-forming "bubbles" of this sort might have served as a kind of rudimentary cell membrane for the very first organisms.

However, the simple vesicles can't form in seawater because the divalent ions react with the fatty acids. People with mineral-rich "hard" water in their homes are familiar with this chemistry. Soap products don't lather as well with hard water, which has high concentrations of calcium and magnesium ions that react with the soap molecules to form a solid that we call soap scum.

"Seawater would definitely precipitate fatty acids, preventing membrane formation," says Jack Szostak of Harvard University. "So I agree with Dave Deamer that primitive cells had to live in a fresh water environment."

Throwing the catalyst out with the seawater

The challenge for Deamer is that those divalent ions are far from a nuisance when it comes to other aspects of biochemistry. DasSarma points out that divalent magnesium ions are needed for important phosphate chemistry, and calcium ions play a vital role in cellular signaling.

Moreover, "some of those divalent ions are transition metals, which I think of as being involved with ligands in pre-macromolecular catalysis," says Harold Morowitz of George Mason University.

A three-dimensional view of a model protocell approximately 100 nanometers in diameter. Credit: Janet Iwasa, Szostak Laboratory, Harvard Medical School and Massachusetts General Hospital

Transition metals are elements (like iron, manganese and nickel) that occupy the middle of the Periodic Table. They trade electrons fairly easily, which makes them good catalysts for driving chemical reactions.

When transition metals combine with small organic molecules called "ligands," they can drive important chemical reactions. Nowadays, this catalysis is done by proteins, but these large molecules are so complex that it's hard to imagine them being around at the dawn of life. Morowitz believes transition metals were necessary to get the biological ball rolling.

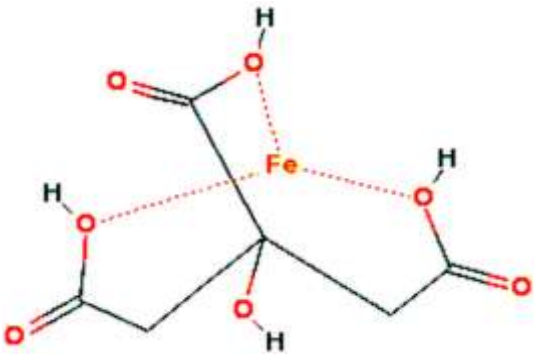
Michael Russell from the Jet Propulsion Lab seems to agree: "It is the inorganic elements that bring organic chemistry to life." And he goes on to stress that these elements can only stay in solution in saltwater (with its abundant chloride ions), otherwise they tend to precipitate into solids where they no longer can play their biological roles.

Contrary to Deamer's position, Russell doesn't believe life necessarily needed a lipid vesicle in the beginning. He thinks the prebiotic chemistry could have begun inside tiny pores of rocks. Here, proteins and DNA could

have assembled in a closed environment. "It's the proteins that do the work," Russell says. "The lipids are merely the castle wall."

Membranes-first

Deamer doesn't deny that some of the first biological steps may have occurred inside pores or on the surface of clay minerals. But eventually, organisms freed themselves from these fixed structures and ventured out into open water. And that's when they would need a good "container." "At some point during its origin, life started using membranes," Deamer says.



Ferric citrate is a structure formed from the transition metal iron and citrate, a compound produced by plants, algae, and many bacteria. Morowitz and his colleagues propose that structures like this could have catalyzed the formation of molecular building blocks, leading ultimately to the formation of complex molecules essential for the origin of life. Credit: Marine Biological Laboratory

Ferric citrate is a structure formed from the transition metal iron and citrate, a compound produced by plants, algae, and many bacteria. Morowitz and his colleagues propose that structures like this could have catalyzed the formation of molecular building blocks, leading ultimately to the formation of complex molecules essential for the origin of life.

Credit: Marine Biological Laboratory

As any fish will tell you, there are ways to make membranes that are "salt-proof," but these are complicated structures that need to be synthesized by enzymes or something similar, says Deamer. The far easier route is to use spontaneously forming membranes that work great in freshwater. Even though divalent ions would be scarce in this environment, the first proto-cells could still probably scavenge some if needed.

"I certainly would not claim that life began in distilled water," Deamer says. He believes life would need some ions to get going. "It's just that seawater is too much of a good thing."

So where might early life have found a nice freshwater launching pad? The Earth had no continents 4 billion years ago, as the planet was essentially one big ocean. But geologists believe that there were volcanic islands, like Hawaii and Iceland, which could have trapped fresh rain water in ponds or lakes.

Szostak believes these freshwater bodies could accumulate useful organic molecules (in contrast to the ocean where everything tends to get diluted). Being near volcanoes could have provided heat for creating wet-dry cycles. Experiments have shown that these cycles can concentrate lipid molecules to help them organize into membranes.

Deamer has witnessed first-hand these wet-dry cycles in ponds next to modern-day volcanoes in Kamchatka, Hawaii and California. He and his colleagues went so far as to dump lipid molecules into the ponds to see if they might form membranes "in the wild." The answer was no. The organic material attached itself to clay minerals at the bottom of the ponds (something that wouldn't have likely been a problem on the early Earth).

But these field tests haven't deterred Deamer. "I've learned from visiting these places what to do to simulate these environments in the lab," he says.

His team has built a "hot pond" simulator. Little vials with freshwater and the basic ingredients of life are heated to above 60 degrees Celsius and routinely re-wetted with "rain water" from a syringe. Recent results have shown that membrane-forming lipids not only form vesicles, but they may help drive DNA replication -- something that modern cells need protein enzymes to do.

All the simulations have so far used freshwater, but Deamer says they plan to test saltwater to see how the results change. The salt habit is hard to break. *Source: Astrobio.net*

http://www.eurekalert.org/pub_releases/2012-01/tum-aor011912.php

Avalanche of reactions at the origin of life

Mechanism of evolution of the primordial metabolism discovered

Volcanic-hydrothermal flow channels offer a chemically unique environment, which at first glance appears hostile to life. It is defined by cracks in the crust of the earth, through which water flows, laden with volcanic gases are contacting a diversity of minerals. And yet – it is precisely this extreme environment, where the two mechanisms could have emerged, which are at the root of all life: The multiplication of biomolecules (reproduction) and the emergence of new biomolecules on the basis of previously formed biomolecules (evolution).

At the outset of this concatenation of reactions that led eventually to the formation of cellular forms of life there are only a few amino acids, which are formed from volcanic gases by mineral catalysis. Akin to a domino

stone that triggers a whole avalanche, these first biomolecules stimulate not only their own further synthesis but also the production of wholly new biomolecules. "In this manner life begins by necessity in accordance with pre-established laws of chemistry and in a pre-determined direction", declares Günter Wächtershäuser, honorary professor for evolutionary biochemistry at the University of Regensburg. He developed the mechanism of a self-generating metabolism – theoretically, alas, an experimental demonstration has been lacking so far.

Now, scientists around Claudia Huber and Wolfgang Eisenreich, at the Chair of Biochemistry in the Department of Chemistry at the TUM in close cooperation with Wächtershäuser, managed for the first time to demonstrate experimentally the possibility of such a self-stimulating mechanism. A catalyst consisting of compounds of the transition metals nickel, cobalt or iron has the lead role in these reactions. It provides not only for the formation of the first biomolecules, but it also initiates the concatenation of reactions. The reason: The biomolecules just newly formed from the volcanic gases engage the center of the transition metal catalyst to enable further chemical reactions bringing forth wholly new biomolecules. "This coupling between the catalyst and an organic reaction product is the first step", explains Wächtershäuser. "Life arises, if subsequently a whole cascade of further couplings takes place, and this primordial life leads eventually to the formation of genetic material and of the first cells".

The scientists simulated in their experiments the conditions of volcanic-hydrothermal flow channels and established an aqueous-organometallic system that produces a whole suite of different biomolecules, among them the amino acids glycin and alanin. Here the carbon source was provided by a cyano compound and the reducing agent by carbon monoxide. Nickel compounds turned out to be the most effective catalysts in these experiments. The scientists then added the products glycin and alanin to another system, that generated again two new biomolecules. The result: The two amino acids increased the productivity oft he second system by a factor of five.

In future experiments the scientists intend to recreate more precisely the conditions of volcanic-hydrothermal systems, wherein life could have arisen billions of years ago. "For this purpose we simulate first certain stages in the development of a volcanic-hydrothermal flow system in order to determine essential parameters", explains Wächtershäuser. "Only thereafter we may engage in a rational construction of a flow reactor".

The results of the scientists around Wächtershäuser and Eisenreich show that an origin and evolution of life in hot water of volcanic flow ducts is feasible. The results reveal advantages of the theory compared to other approaches. Within the flow ducts temperature, pressure and pH change along the flow path, and thereby a graded spectrum of conditions is offered that is appropriate for all stages of early evolution up to the formation of genetic material (RNA/DNA).

The most important property of the system is its autonomy: As opposed to the notion of a cool prebiotic both, the first metabolism was not dependent on accidental events or an accumulation of essential components over thousands of years. As soon as the first domino stone is toppled, the others will follow automatically. The origin of life proceeds along definite trajectories, pre-established by the rules of chemistry – a chemically determined process giving rise to the tree of all forms of life.

Original publication: *Elements of metabolic evolution. C. Huber, F. Kraus, M. Hanzlik, W. Eisenreich, G. Wächtershäuser, Chemistry – A European Journal, advanced online publication: 13 Jan 2012 – DOI: 10.1002/chem.201102914*

http://www.eurekalert.org/pub_releases/2012-01/uoc--tao012012.php

Tiny amounts of alcohol dramatically extend a worm's life, but why?

Minuscule amounts of ethanol can more than double the life span of a tiny worm

Minuscule amounts of ethanol, the type of alcohol found in alcoholic beverages, can more than double the life span of a tiny worm known as Caenorhabditis elegans, which is used frequently as a model in aging studies, UCLA biochemists report. The scientists said they find their discovery difficult to explain.

"This finding floored us — it's shocking," said Steven Clarke, a UCLA professor of chemistry and biochemistry and the senior author of the study, published Jan. 18 in the online journal PLoS ONE, a publication of the Public Library of Science.

In humans, alcohol consumption is generally harmful, Clarke said, and if the worms are given much higher concentrations of ethanol, they experience harmful neurological effects and die, other research has shown.

"We used far lower levels, where it may be beneficial," said Clarke, who studies the biochemistry of aging.

The worms, which grow from an egg to an adult in just a few days, are found throughout the world in soil, where they eat bacteria. Clarke's research team — Paola Castro, Shilpi Khare and Brian Young — studied thousands of these worms during the first hours of their lives, while they were still in a larval stage. The worms normally live for about 15 days and can survive with nothing to eat for roughly 10 to 12 days.

"Our finding is that tiny amounts of ethanol can make them survive 20 to 40 days," Clarke said.

Initially, Clarke's laboratory intended to test the effect of cholesterol on the worms. "Cholesterol is crucial for humans," Clarke said. "We need it in our membranes, but it can be dangerous in our bloodstream."

The scientists fed the worms cholesterol, and the worms lived longer, apparently due to the cholesterol. They had dissolved the cholesterol in ethanol, often used as a solvent, which they diluted 1,000-fold.

"It's just a solvent, but it turns out the solvent was having the longevity effect," Clarke said. "The cholesterol did nothing. We found that not only does ethanol work at a 1-to-1,000 dilution, it works at a 1-to-20,000 dilution. That tiny bit shouldn't have made any difference, but it turns out it can be so beneficial."

How little ethanol is that?

"The concentrations correspond to a tablespoon of ethanol in a bathtub full of water or the alcohol in one beer diluted into a hundred gallons of water," Clarke said.

Why would such little ethanol have such an effect on longevity?

"We don't know all the answers," Clarke acknowledged. "It's possible there is a trivial explanation, but I don't think that's the case. We know that if we increase the ethanol concentration, they do not live longer. This extremely low level is the maximum that is beneficial for them."

The scientists found that when they raised the ethanol level by a factor of 80, it did not increase the life span of the worms.

The research raises, but does not answer, the question of whether tiny amounts of ethanol can be helpful for human health. Whether this mechanism has something in common with findings that moderate alcohol consumption in humans may have a cardiovascular health benefit is unknown, but Clarke said the possibilities are intriguing. In follow-up research, Clarke's laboratory is trying to identify the mechanism that extends the worms' life span.

About half the genes in the worms have human counterparts, Clarke said, so if the researchers can identify a gene that extends the life of the worm, that may have implications for human aging.

"It is important for other scientists to know that such a low concentration of the widely used solvent ethanol can have such a big effect in C. elegans," said lead author Paola Castro, who conducted the research as an undergraduate in Clarke's laboratory before earning a bachelor's degree in biochemistry from UCLA in 2010 and joining the Ph.D. program in bioengineering at UC Santa Cruz. "What is even more interesting is the fact that the worms are in a stressed developmental stage. At high magnifications under the microscope, it was amazing to see how the worms given a little ethanol looked significantly more robust than worms not given ethanol."

"While the physiological effects of high alcohol consumption have been established to be detrimental in humans, current research shows that low to moderate alcohol consumption, equivalent to one or two glasses of wine or beer a day, results in a reduction in cardiovascular disease and increased longevity," said co-author Shilpi Khare, a former Ph.D. student in UCLA's biochemistry and molecular biology program who is now a postdoctoral fellow at the Genomics Institute of the Novartis Research Foundation in San Diego. "While these benefits are fascinating, our understanding of the underlying biochemistry involved in these processes remains in its infancy.

"We show that very low doses of ethanol can be a worm 'lifesaver' under starvation stress conditions," Khare added. "While the mechanism of action is still not clearly understood, our evidence indicates that these 1 millimeter–long roundworms could be utilizing ethanol directly as a precursor for biosynthesis of high-energy metabolic intermediates or indirectly as a signal to extend life span. These findings could potentially aid researchers in determining how human physiology is altered to induce cardio-protective and other beneficial effects in response to low alcohol consumption."

Clarke's laboratory identified the first protein-repair enzyme in the early 1980s, and his research has shown that repairing proteins is important to cells. In the current study, the biochemists reported that life span is significantly reduced under stress conditions in larval worms that lack this repair enzyme. (More than 150 enzymes are involved in repairing DNA damage, and about a dozen protein-repair enzymes have been identified.)

"Our molecules live for only weeks or months," Clarke said. "If we want to live long lives, we have to outlive our molecules. The way we do that is with enzymes that repair our DNA — and with proteins, a combination of replacement and repair."

Researcher Brian Young, now an M.D./Ph.D. student at the David Geffen School of Medicine at UCLA, is a co-author on the research.

The research was federally funded by the National Institutes of Health's National Institute of General Medical Sciences.

http://medicalxpress.com/news/2012-01-brain-cells-die-alzheimer-disease.html

Study identifies a new way brain cells die in Alzheimer's disease

A new study challenges conventional thinking about how brain cells die in Alzheimer's disease.

Medical Xpress - The findings demonstrate a previously unknown mechanism by which the cells die and will help lead researchers in new directions for treating the degenerative brain disease. The study by scientists at the University of Calgary's Hotchkiss Brain Institute is published this week in the prestigious journal Proceedings of the National Academy of Sciences (PNAS).

At the cellular level, our brains require a delicate balance of chemicals and molecules in order to function properly. The cells 'talk to each other' using chemicals called neurotransmitters, which activate specialized receptors. But as this study by Gerald Zamponi, PhD, and Dr. Peter Stys shows, the cells of Alzheimer's patients are dying because the key receptor responsible for memory and learning, called the NMDA receptor, is malfunctioning.

It has previously been shown that Alzheimer's patients have a malformed protein called Ab42 present in their brains. With this research, Stys, Professor in the Department of Clinical Neurosciences and Zamponi, Head of the Department of Physiology and Pharmacology, show in animal models a completely new mechanism of how this protein kills brain cells.

They found that the NMDA receptor is strongly regulated by copper. If copper is prevented from regulating this key receptor, such as in Alzheimer's disease, brain cells become over stimulated; with time they become sick and ultimately die. "We cannot underestimate the importance of copper for proper brain cell functioning," says Zamponi, "For example, there are several diseases where copper levels are altered, and this leads to the same NMDA receptor deficiency and neurodegeneration." When the Ab42 steals the copper away from the NMDA receptor, the receptor gets over-activated, which kills the brain cell. "This particular mechanism was previously unknown and could have fundamentally important therapeutic implications," says Zamponi.

Co-senior author Stys adds, "Ultimately we are seeing an underlying deficiency in copper, but at a subcellular level. Unfortunately because of the way that the body regulates copper, we can't simply eat more of a certain kind of food or take a copper supplement to compensate. What we are looking at now is the development of a drug that acts on the NMDA receptor to mimic the effect of copper in the brain, therefore restoring normal NMDA receptor function and protecting brain cells."

Alzheimer's disease destroys brain cells and results in memory loss, changes in mood and behavior and difficulty with day-to-day tasks. Most commonly diagnosed in adults over the age of 65, more than 100,000 new cases of this progressive and eventually fatal disease are diagnosed each year.

Bill Gaudette, CEO, Alzheimer Society of Alberta & Northwest Territories, noted, "Our Society, and the people we work with, welcome the research being conducted by Drs. Zamponi and Stys at the Hotchkiss Brain Institute. The promising therapeutic implications of this work could potentially be a 'game changer' for everyone involved with dementia research and care." *Provided by University of Calgary*

http://medicalxpress.com/news/2012-01-turkish-hospital-limb-transplants.html

Turkish hospital performs triple limb transplant

A hospital in southern Turkey on Saturday was attempting the world's first triple limb transplant, attaching two arms and one leg to a 34-year-old man, the country's state-run news agency reported.

AP - A team of doctors at Akdeniz University Hospital, in the Mediterranean coastal city of Antalya, was at the same time transplanting the face of the same donor onto another patient - a 19-year-old man. It would be Turkey's first face transplant. "Today could be a day of many firsts for the medical world," the Anadolu Agency quoted Dr. Zafer Aydin as saying. "We are hoping that the operation is a success and that it is a world first," said Aydin, who heads the organ transplant unit at the hospital in western Turkey where the donor's limbs were removed. "Two arms and a leg have never been transplanted on one patient until today."

The hospital in Antalya said an announcement would be made after the surgery.

Anadolu said Atilla Kavdir, the 34-year-old receiving the limbs, lost his arms and right leg when he was 11 after he hit power lines outside his home with an iron rod to scare away pigeons and received an electric shock.

The teenage face transplant recipient was burned in a house fire when he was a baby. The limbs and the face became available early on Saturday and the hospital began the operation at 3:15 a.m., Anadolu said.

The world's first double arm transplant was in Germany in 2008, while the first double leg transplant took place in Spain in July 2011.More than a dozen face transplants have been carried out around the world, starting in November 2005 with a French woman who was mauled by her dog. The first face transplant in the U.S. was in December 2008.

http://www.sciencedaily.com/releases/2012/01/120120182729.htm

Chemical in Personal Care Products (Phthalates) May Contribute to Child Obesity

Researchers from have found an association between exposure to phthalates and obesity in young children - including increased body mass index and waist circumference

ScienceDaily - Researchers from the Children's Environmental Health Center at The Mount Sinai Medical Center in New York have found an association between exposure to the chemical group known as phthalates and obesity in young children -- including increased body mass index (BMI) and waist circumference.

Phthalates are human-made, endocrine-disrupting chemicals that can mimic the body's natural hormones. They are commonly used in plastic flooring and wall coverings, food processing materials, medical devices, and personal-care products. While poor nutrition and physical inactivity are known to contribute to obesity, a growing body of research suggests that environmental chemicals -- including phthalates -- could play a role in rising childhood obesity rates.

This study was the first to examine the relationship between phthalate exposure and measurements used to identify obesity in children.

Mount Sinai researchers measured phthalate concentrations in the urine of 387 black and Hispanic children in New York City, and recorded body measurements including BMI, height, and waist circumference one year later. The urine tests revealed that greater than 97 percent of study participants had been exposed to phthalates typically found in personal care products such as perfume, lotions, and cosmetics; varnishes; and medication or nutritional supplement coatings. The phthalates included monoethyl phthalate (MEP) and other low molecular-weight phthalates. The team also found an association between concentrations of these phthalates with BMI and waist circumference among overweight children. For example, BMI in overweight girls with the highest exposure to MEP was 10 percent higher than those with the lowest MEP exposure.

"Research has shown that exposure to these everyday chemicals may impair childhood neurodevelopment, but this is the first evidence demonstrating that they may contribute to childhood obesity," said the study's lead author Susan Teitelbaum, PhD, Associate Professor in the Department of Preventive Medicine at Mount Sinai School of Medicine. "This study also further emphasizes the importance of reducing exposure to these chemicals where possible."

The percentage of obese children ages six to 11 in the United States has grown from seven percent in 1980 to more than 40 percent in 2008, according to the U.S. Centers for Disease Control and Prevention. More than 15 percent of American children between the ages six and 19 are characterized as obese. In New York City, more than one in five children in public schools are obese.

Dr. Teitelbaum and the team at the Children's Environmental Health Center plan to further evaluate the impact of these chemicals on childhood obesity. "While the data are significant, more research is needed to definitively determine whether phthalate exposure causes increases in body size," she said.

The paper is available online in the journal Environmental Research. The project was funded by the National Institute for Environmental Health Sciences, the National Cancer Institute, and the U.S. Environmental Protection Agency.

www.sciencedaily.com/releases/2012/01/120120182914.htm

Why Do Smells Make Some People Sick?

Do you get a headache from the perfume of the lady next to you at the table?

ScienceDaily - Do you get a headache from the perfume of the lady next to you at the table? Do cleaning solutions at work make your nose itch? If you have symptoms prompted by everyday smells, it does not necessarily mean you are allergic but rather that you suffer from chemical intolerance. According to Linus Andersson at Umeå University, this hypersensitivity can be the result of an inability to get used to smells.

Normally your smell perceptions diminish rapidly, as when you enter a friend's apartment. Even though you clearly notice smells just inside the door, you don't think about them for long. For people with chemical intolerance, on the other hand, smells seem always to be present. Psychology researcher Linus Andersson has exposed both intolerant and non-intolerant individuals to smells and compared their reactions.

"The hypersensitive individuals felt that the smell was getting stronger even though its concentration had not changed. Their brain activity images also differed from those in the other group," he says.

The results were observed using methods based on both electroencephalography (EEG) and functional brain imaging technology (fMRI). The EEG method involved placing electrodes on the heads of trial subjects and registering the minute changes in tension in the brain that arise following exposure to smells. Unlike the people in the normal group, Linus Andersson explains, the intolerant people did not evince a lessening of brain activity

during the period of more than an hour they were exposed to a smell. The inability to grow accustomed to smells is thus matched by unchanging brain activity over time.

"These individuals also have a different pattern in the blood flow in their brains, compared with those who perceive that a smell diminishes. A similar change can be found in patients with pain disorders, for example."

Sensitivity to smell impacts the entire body A further finding in the dissertation is that chemical intolerant people also react strongly to substances that irritate the mucous linings of their nose and mouth. People who cough more when they inhale capsaicin, the hot compound in chili peppers, also have heightened reactions in the brain to other smells. Besides the fact that intolerant individuals perceive that smells grow stronger, effects are also seen in mucous linings and in the brain.

"In other words we can see indications that this intolerance affects both the body and the mind, and that it's important not to blindly focus on just one of these aspects," says Linus Andersson.

Chemical intolerance is surprisingly common -- up to ten percent of the Swedish population report they are bothered by everyday smells, whereas roughly two percent experience severe symptoms. Yet, in contrast to the situation regarding allergies and asthma, there is very little research about what causes this condition. Linus Andersson maintains that if it were possible to identify what characterizes this hypersensitivity then it would be possible to develop methods for diagnosis and treatment. But research can also provide new knowledge about how we should think about our work and everyday environments.

"Some co-workers are bothered more than others by the smell of the printer -- what should we do to make our working conditions acceptable to as many people as possible?" ***Dissertation.***

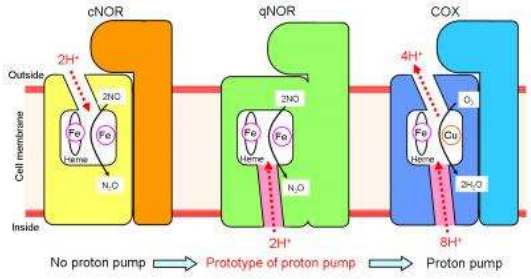
http://www.eurekalert.org/pub_releases/2012-01/r-nss012012.php

New study sheds light on evolutionary origin of oxygen-based cellular respiration

Researchers have clarified the crystal structure of a bacterial enzyme that offers clues on the origins of our earliest oxygen-breathing ancestors

Researchers at the RIKEN SPring-8 Center in Harima, Japan have clarified the crystal structure of quinol dependent nitric oxide reductase (qNOR), a bacterial enzyme that offers clues on the origins of our earliest oxygen-breathing ancestors. In addition to their importance to fundamental science, the findings provide key insights into the production of nitrogen oxide, an ozone-depleting and greenhouse gas hundreds of times more potent than carbon dioxide.

As the central process by which cells capture and store the chemical energy they need to survive, cellular respiration is essential to all life on this planet. While most of us are familiar with one form of respiration, whereby oxygen is used to transform nutrients into molecules of adenosine triphosphate (ATP) for use as energy ("aerobic respiration"), many of the world's organisms breathe in a different way. At the bottom of the ocean and in other places with no oxygen, organisms get their energy instead using substances such as nitrate or sulfur to synthesize ATP, much the way organisms did many billions of years ago ("anaerobic respiration").



This is a schematic representation of the proton transfer pathways for the NO reduction reaction in cNOR and qNOR, and the proton pumping pathway in COX. The direction of the proton transfer is denoted by red dotted arrows. cNOR has a proton transfer pathway from the outside of the cell to the catalytic site for the NO reduction reaction. In sharp contrast to this, there is no proton transfer pathway from the outside of the cell in qNOR. Unexpectedly, however, we identified a proton transfer pathway from the inside of the cell to the catalytic site in qNOR. In COX, protons are pumped from the inside to the outside of the cell through the catalytic site. The location of the proton transfer pathway we identified in qNOR (pink color) is similar to a part of the proton pumping pathway in COX. **RIKEN**

While less well-known, this latter type of cellular respiration is no less important, fuelling the production of most of the world's nitrous oxide (N2O), an ozone depleting and greenhouse gas 310 times more potent than carbon dioxide. As the enzyme responsible for catalyzing the reactions underlying anaerobic respiration, nitric oxide reductase (NOR) has attracted increasing attention in environmental circles. The mystery of NOR's catalyzing mechanism, however – which accounts for a staggering 70% of the planet's N2O production – remains largely unsolved.

With their latest research, the team sought an answer to this mystery in the origin of an evolutionary innovation known as the "proton pump". To accelerate ATP-synthesis, aerobic organisms harness the potential of an electrochemical concentration gradient across the cell, created by "pumping" protons out using energy

from an oxygen reduction reaction. The enzyme powering this mechanism, cytochrome oxidase (COX), is genetically and structurally similar to NOR, suggesting a common ancestor. No evidence of any "pump", however, has been detected in anaerobic organisms.

That is, until now. Using radiation from the RIKEN SPring-8 facility in Harima, Japan, the world's largest synchrotron radiation facility, the researchers probed the 3D structure of qNOR and discovered a channel acting as a proton transfer pathway for a key catalytic reaction. While not itself a proton pump, the position and function of this pathway suggest it is an ancestor of the proton pump found in COX. The finding thus establishes first-ever evidence for a proton pump in anaerobic organisms, shedding light onto the mysterious mechanisms governing the production of nitrogen oxide and the evolutionary path that led to their emergence.

http://www.eurekalert.org/pub_releases/2012-01/bc-pfl012012.php

Plant flavonoid luteolin blocks cell signaling pathways in colon cancer cells

New research shows that luteolin is able to inhibit the activity of cell signaling pathways important for the growth of cancer in colon cancer cells

Luteolin is a flavonoid commonly found in fruit and vegetables. This compound has been shown in laboratory conditions to have anti-inflammatory, anti-oxidant and anti-cancer properties but results from epidemiological studies have been less certain. New research published in BioMed Central's open access journal BMC Gastroenterology shows that luteolin is able to inhibit the activity of cell signaling pathways (IGF and PI3K) important for the growth of cancer in colon cancer cells.

Colon cancer is the second most frequent cause of cancer-related death in the Western World. Colon cancer cells have elevated levels of IGF-II compared to normal colon tissues. It is thought that this is part of the mechanism driving uncontrolled cell division and cancer growth. Researchers from Korea showed that luteolin was able to block the secretion of IGF-II by colon cancer cells and within two hours decreased the amount of receptor (IGF-IR) precursor protein. Luteolin also reduced the amount of active receptor (measured by IGF-I dependent phosphorylation).

Luteolin inhibited the growth stimulatory effect of IGF-I and the team led by Prof Jung Han Yoon Park found that luteolin affected cell signaling pathways which are activated by IGF-I in cancer. Prof Jung Han Yoon Park explained, "Luteolin reduced IGF-I-dependent activation of the cell signaling pathways PI3K, Akt, and ERK1/2 and CDC25c. Blocking these pathways stops cancer cells from dividing and leads to cell death."

Prof Jung Park continued, "Our study, showing that luteolin interferes with cell signaling in colon cancer cells, is a step forward in understanding how this flavonoid works. A fuller understanding of the in vivo results is essential to determine how it might be developed into an effective chemopreventive agent."

Notes to Editors

1. Luteolin decreases IGF-II production and downregulates insulin-like growth factor-I receptor signaling in HT-29 human colon cancer cells. Do Young Lim, Han Jin Cho, Jongdai Kim, Chu Won Nho, Ki Won Lee and Jung Han Yoon Park. BMC Gastroenterology (in press)