Science Vision

Hope and Hype

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"Virus in Stealth" to Help Kill Cancer Cells

In the current issue of the Journal of Virology, researchers have discovered a way to fight cancer by using parts of a virus found in tree shrews, small Southeast Asian mammals.[1] The researchers used the virus to create a camouflage for an engineered measles virus that enables it to sneak past the immune system. It kills cancer cells without harming healthy cells. The work is still experimental but it is a key step forward in the science of redirecting or retargeting a virus through genetic engineering. Retargeted measles virus can recognize surface molecules found only on cancerous cells, allowing selective killing. In this way, retargeted cancer-killing viruses help the body, rather than harming it as natural viruses do when they infect cells. The perspective was to exchange pieces on the viral coat, with the pieces from the coat of a related virus that has no known relatives that can infect humans. If parts of the Tupaia paramyxovirus (the shrew virus) got modified and inserted into the measles virus, then we have a virus in stealth.

While the stealth approach works, there is a problem. The disguise works only once because a healthy immune system makes antibodies against the modified viral coat immediately. But researchers are designing alternative disguises. That means the manufacturing of another coat to disguise it again and give the prospect of using the same retargeted measles virus with different coats. Researchers stress that multiple safeguards prevent the unintended creation of a super virus capable of causing a new human disease. There is an untapped resource in the form of animal viruses that can be used as a source of modules that can be combined with human viruses to evade the immune system. Springfeld et al indicate that their lab can do this safely because they have quite an elaborate safety system that block, interfere and provide an emergency brake to a virus' ability to spread in normal human cells and cause illness.

1. Springfeld C. Envelope targeting: hemagglutinin attachment specificity rather than fusion protein cleavage-activation restricts Tupaia Paramyxovirus Tropism. J. Virol 2005;79:10155-63.

Chronic Sinus Infection: a Tissue Issue?

Researchers[1] have found that the cause of chronic sinus infections, or rhinosinusitis, lie in the nasal mucus and not in the nasal and sinus tissue targeted by standard treatment. This strikingly contradicts the notion that inflammatory cells break down, releasing toxic proteins into the diseased airway tissue. Instead, this study shows that these toxic proteins are released into the mucus, and not in the tissue. Therefore, scientists might need to take not only the tissue but also the mucus into account when trying to understand what causes chronic sinus infections and probably other airway diseases. This suggests a beneficial effect in treatments

that target primarily the underlying and presumably damage-inflicting nasal and sinus membrane inflammation, instead of the secondary bacterial infection that has been the primary target of treatments for the disease. Also, some surgeons have already started to change the way they do surgery for patients with chronic sinus infections, focusing now on removing the mucus, which is loaded with toxins from the inflammatory cells, rather than the tissue during surgery. Leaving the mucus behind might predispose patients for early recurrence of the chronic sinus infection.

The team found that in patients with rhinosinusitis, activated white blood cells (eosinophils) cluster in the nasal and sinus mucus and scatter a toxic protein (major basic protein) onto the nasal and sinus membrane. While major basic protein was not distributed in the nasal and sinus tissue, the level of this protein in the mucus of chronic sinus infection patients far exceeded that needed to damage the nasal and sinus membranes and make them more susceptible to infections such as chronic sinus infection. Chronic sinus infection produces nose and sinus problems characterized by stuffy nose, loss of sense of smell, postnasal drip, nasal discharge, and head and face pain lasting three months or longer.

1. Ponikau JU. Striking deposition of toxic eosinophil major basic protein in mucus: implications for chronic rhinosinusitis. J Allergy Clin Immunology 2005;116:362-9.

Researchers use Ultrasound to describe Subtle Heart Muscle Motions

By using sound waves, researchers have described subtle changes in the motion of the heart that are measurable by ultrasound and may improve understanding of heart function, and possibly be a noninvasive aid in predicting impending heart damage, including heart attacks. The study[1] could also contribute to optimal adjustment of cardiac pacemakers or perhaps better design of artificial hearts. The findings, published in the current issue of the Journal of Applied Physiology, are based on "snapshots" of the mechanical transitions that occur between the main relaxation and contraction phases of the adult pig heartbeat. During these split-second transitions, the heart muscle "shifts gears" or prepares for the upcoming phase. These methods could improve our chances in predicting cardiac events, so that preventive measures could be taken. And in patients with an existing heart condition, a detailed analysis of cardiac function could contribute to therapeutic optimization of heart performance. Researchers studied the mechanical, biochemical and electrical aspects of these transitions which occur between phases of relaxation when the heart ventricles fill with a volume of blood and contraction when the heart ejects most of the blood volume into body circulation. Recently advanced, high-resolution ultrasound tissue Doppler imaging allowed them to experimentally measure these transitional tissue deformations, which last only milliseconds and are unnoticeable to the human eye. The technology allows slow-motion comparisons of these events separately between the inner and outer layers of the cardiac left ventricle. The results demonstrate how a rapid succession of motions occurring within tissue of the ventricular wall can appear chaotic if not observed closely and with high temporal resolution. The data also show how these transitions "reorganize" the ventricle to best perform its cycles of filling and ejection.

Until recently, it was thought to be sufficient to study the function of the heart muscle during the relaxation and ejection phases of the heartbeat. Now, technological improvements in imaging have allowed studies of the heart muscle condition during the transitional phases. These short-lived mechanical transitions are successfully accomplished and prepare the heart for the next beat optimally only if the mechanical, biochemical and electrical events in the cardiac muscle work in concert and delivery of nutrients and oxygen are uninterrupted. Understanding these rapid transitional events not only improves fundamental understanding of heart functioning, but their dependence on various conditions makes these events vulnerable. Using pigs as a very close model to human heart function, researchers established benchmarks for measuring normal and abnormal transitions in heart muscle layers. Accurate analyses of motion, deformation (strain), electrical impulses and other parameters characterize the transitional events between the phases of cardiac filling and ejection.

1. Sengupta PP, Khandheria BJ, Korinek J, Wang J, Belohlavek M. Biphasic Tissue Doppler waveforms during isovolumic phases are associated with asynchronous deformation of subendocardial and subepicardial layers. J Appl Physiol 2005;99:1104-11.

Surgery gives fresh start to Patients with Thickened Hearts

Patients who have surgery for hypertrophic cardiomyopathy (HCM), a leading cause of sudden cardiac death in young people, do not just get symptom relief; their mortality rates match those of the general population, according to findings of a study published in Journal of the American College of Cardiology.[1]

HCM is an abnormal thickening of the heart, and surprisingly it is more common than better-known conditions such as Crohn's disease, Multiple Sclerosis and Anorexia Nervosa. HCM involves thickening particularly of the septum, and can affect blood flow into and out of the heart, leading to symptoms such as shortness of breath, chest pain, dizziness, palpitations, or fainting after exertion.

HCM can cause sudden death by sending the heart into a dangerous electrical rhythm pattern and is the most common cause of death during athletic competition. The primary cause of HCM seems to be genetic. About half of HCM patients have a close relative with the disease. Treatments may include medications such as beta-blockers to slow the heart's contractions, and placement of an internal defibrillator to shock the heart back into normal rhythm. For patients with severe obstructions of blood flow whose symptoms do not respond to medications, myectomy, which involves removing a portion of the thickened muscle wall, provides excellent symptom relief.

This new study suggests that for younger HCM patients, whose average age was 45 years at the time of surgery, the operation gave them the same life expectancy as someone who had never had the disease. The mortality rate for myectomy patients was statistically the same as that for the patients with non-obstructive HCM or for persons in the general population, matched for age and sex. Patients with severe symptoms related to HCM can now be counseled that surgical myectomy, a time-proven operation with low complication rates, can be expected to markedly improve symptoms and result in normal longevity.

1. Ommen SR. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.

Malaria parasite's 'secret handshake' revealed

Scientists have identified the structure of a protein that malaria parasites use to invade human erythrocytes. This could help efforts to develop vaccines against the disease. The team, led by Leemor Joshua-Tor at US-based Cold Spring Harbor Laboratory, New York, published their results in the prestigious journal Cell. The researchers found that two 'arms' of a protein called EBA-175 on the outer surface of the parasite join together in "a molecular handshake". This structure grabs hold of a protein on the surface of human erythrocytes, allowing the parasite to invade them. Parasites that do not manage to enter erythrocytes soon die. Thus, stopping the parasite from entering the cells could prevent the disease. Joshua-Tor's team says drugs that stop the two arms joining, or stop the joined arms holding on to the red blood cell protein, might prevent malaria. Alternatively, a vaccine could work by stimulating our immune system to recognise and attack the parasite protein EBA-175. Malaria kills between one and three million people every year. Nearly 80 per cent of these are children under five years old in sub-Saharan Africa.

1. Tolia NH, Enemark EJ, Sim BK, Joshua-Tor L. Structural basis for the EBA-175 Erythrocyte Invasion Pathway of the malaria parasite plasmodium falciparum. Cell 2005;122:183-93.

Hope for Hepatitis B treatment

Scientists have harnessed remarkable novel genetic technology to develop a potentially potent treatment for hepatitis B. The work has been published in Nature Biotechnology and paves the way for the development of safe and highly effective treatment options.

The efficacy of lipid-encapsulated, chemically modified short interfering RNA (siRNA) targeted to hepatitis B virus (HBV) was examined in an in vivo mouse model of HBV replication. The researchers incorporated the key molecules called small interfering RNAs (siRNAs) into fat-like particles that protect them from attack by digestive enzymes in the blood. These enzymes normally degrade RNA molecules in cells or the circulation. Not only did this increase the stability when injected into mice, it also reduced the dose needed for therapeutic effect.

Lipid-encapsulated siRNA was administered by intravenous injection three times daily into mice carrying replicating HBV, at a dose of 3 mg/kg/day. This treatment reduced viral load in mice by upto 90%. The reduction in HBV DNA was specific, dose-dependent and lasted for up to 7 days after dosing. Furthermore, reductions were seen in serum HBV DNA for up to 6 weeks with weekly dosing. These spectacular advances demonstrate that siRNA is a clinically viable therapeutic approach. The scientists plan to test the treatment in human subjects early next year.

1. Morrissey DV. Potent and persistent in vivo anti-HBV activity of chemically modified siRNAs. Nat Biotechnol 2005;23:1002-7.