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WEIZMANN INSTITUTE OF SCIENCE

Science Tips

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Interfering with Interferon

Virus-killing molecules may need all their skills, including inflammation, to fight HIV infection

Using the body's natural virus killers to prevent and treat HIV infection has been problematic until now because of the strong inflammatory response these molecules can arouse as they get rid of the invaders. Now, collaborative research conducted by scientists at the Weizmann Institute and the National Institutes of Health (NIH) have demonstrated how suppressing the activity of these molecules – interferons – around the time of infection could have long-term implications for the course of the disease. Their research appeared in *Nature*.

Interferons, named for their ability to "interfere" with viral replication, protect us against disease, but they are also the source of inflammation when we are sick. Today, interferons are used to treat such viral diseases as hepatitis. But in HIV, it has been thought that the inflammation and other side effects could be too harmful and the danger of a "runaway" immune response too great. Prof. Gideon Schreiber of the Weizmann Institute's Biological Chemistry Department and team, including postdoctoral fellow Dr. Doron Levin and former postdoc Dr. Ganit Yarden, had, in previous research, designed an antagonist molecule that is able to block some of the activities of interferons while still allowing them to proceed to act against viruses.

Their original motivation, says Schreiber, was to better understand the mechanisms of different versions of the interferon molecule. This research revealed that the activity of each interferon is tuned to specific cells and viruses. The molecule they had created, says Schreiber, "was not a true 'antagonist' in the biological sense: Instead of blocking all IFN activity, it was able to target the mechanisms leading to the prevention of replication and modulation of the immune system, leaving the antiviral activity mostly intact."

Next, Schreiber and his group teamed up with Dr. Netanya Sandler and Prof. Daniel Douek at the NIH to understand what happens when full-out interferon activity is tampered with in HIV. The research was done on simian immunodeficiency virus (SIV) – the animal equivalent to HIV. Their results show that the actions blocked by the molecule may have important functions, even if they appear to be "detrimental." The team administered an antagonist, blocking a particular interferon known as Type 1 IFN for the first four weeks after infection. Even after this short period, they found that the natural immune system activities did not recover and compensate to the level they otherwise would have; and this led to a progression of the disease.

Schreiber: "These results clearly demonstrate the importance of an early, general IFN response in fighting HIV infection, and removing the 'harmful' IFN functions even for just a short period at the onset of infection can have devastating and permanent consequences in shaping the course of disease." Taken together, these findings suggest that not only the type of treatment, but also the timing of IFN administration needs to be considered in the management and prevention of disease. ❙

Prof. Gideon Schreiber's research is supported by the Dana and Yossie Hollander Center for Structural Proteomics, which he heads; and the R Baby Foundation.

Mutations from Venus, Mutations from Mars

Some 15% of adults suffer from fertility problems, many of these due to genetic factors. This is something of a paradox: We might expect such genes, which reduce an individual's ability to reproduce, to disappear from the population. Research at the Weizmann Institute of Science that recently appeared in *Nature Communications* may now have solved this riddle. Not only can it explain the high rates of male fertility problems, it may open new avenues in understanding the causes of genetic diseases and their treatment.

Various theories explain the survival of harmful mutations: A gene that today causes obesity, for example may have once granted an evolutionary advantage; or a

disease-causing gene may persist because it is passed on in a small, relatively isolated population.

Dr. Moran Gershoni, a post-doctoral fellow in the group of Prof. Shmuel Pietrokovski of the Molecular Genetics Department, decided to investigate another approach – one based on differences between males and females. Although males and females carry nearly identical sets of genes, many are activated differently in each sex. So natural selection works differently on the same genes in males and females.

Take, for example, a mutation that impairs breast milk. It will undergo negative selection only in women. Conversely, a hypothetical gene variant that benefits women but is harmful to men could spread in a population, as it undergoes positive selection in half that population. Gershoni and Pietrokovski created a mathematical model for harmful mutations that affect only half the population; their model showed that these mutations should occur twice as often as those that affect males and females equally.

To test the model, the researchers searched in a computational analysis of the activities of all the human genes that appear in public databases, identifying 95 genes that are exclusively active in the testes. Most of these genes are vital for procreation; and damage to them leads, in many cases, to male sterility.

The researchers then looked at these 95 genes in people whose genomes had been made available through the 1000 Genomes Project, which gave them a broad cross-section of human populations. Their analysis revealed that genes that are active only in the testes have double the harmful mutation rate of those that are active in both sexes – right in line with the mathematical model. Pietrokovski and his team are now conducting follow-up experiments to see whether the mutations they identified do, indeed, play a role in these problems and whether the "sex-difference" approach can explain their survival.

This new understanding of the persistence of genetic mutations could yield insights into other diseases with genetic components, especially those that affect the sexes asymmetrically, including schizophrenia and Parkinson's, which are more likely to affect men, and depression and autoimmune diseases, which affect more women. And, say Gershoni and Pietrokovski, these findings highlight the need to fit even common medical treatments to the gender of the patient. ❙

Prof. Shmuel Pietrokovski is the incumbent of the Herman and Lilly Schilling Foundation Professorial Chair.

Measuring the Smallest Magnets

Imagine trying to measure a tennis ball that bounces wildly, every time to a distance a million times its own size. The bouncing obviously creates enormous "background noise" that interferes with the measurement. But if you attach the ball directly to a measuring device, so they bounce together, you can eliminate the noise problem.

As reported recently in *Nature*, physicists at the Weizmann Institute of Science used a similar trick to measure the interaction between the smallest possible magnets – two single electrons – after neutralizing magnetic noise that was a million times stronger than the signal they needed to detect.

Dr. Roee Ozeri of the Institute's Physics of Complex Systems Department says: "The electron has spin, a form of orientation involving two opposing magnetic poles. In fact, it's a tiny bar magnet." The question is whether pairs of electrons act like regular bar magnets in which the opposite poles attract one another.

Dr. Shlomi Kotler performed the study while a graduate student under Dr. Ozeri's guidance, with Drs. Nitzan Akerman, Nir Navon and Yinnon Glickman. Detecting the magnetic interaction of two electrons poses an enormous challenge: When the electrons are at a close range – as they normally are in an atomic orbit – forces other than the magnetic one prevail. On the other hand, if the electrons are pulled apart, the magnetic force becomes dominant, but so weak in absolute terms that it's easily drowned out by ambient magnetic noise emanating from power lines, lab equipment and the earth's magnetic field.

The scientists overcame the problem by borrowing a trick from quantum computing that protects quantum information from outside interference. This technique binds two electrons together so that their spins point in opposite directions. Thus, like the bouncing tennis ball attached to the measuring device, the combination of equal but opposite spins makes the electron pair impervious to magnetic noise.

The Weizmann scientists built an electric trap in which two electrons are bound to two strontium ions that are cooled close to absolute zero and separated by 2 micrometers (millionths of a meter). At this distance, which is astronomic by the standards of the quantum world, the magnetic interaction is very weak. But because the electron pairs were not affected by external magnetic noise, the interactions between them could be measured with great precision. The measurement lasted for 15 seconds – tens of thousands of times longer than the milliseconds during which scientists have until now been able to preserve quantum data.

The measurements showed that the electrons interacted magnetically just as two large magnets do: Their north poles repelled one another, rotating on their axes until their unlike poles drew near. This is in line with the predictions of the Standard Model, the currently accepted theory of matter. Also as predicted, the magnetic interaction weakened as a function of the distance between them to the power of three.

In addition to revealing a fundamental principle of particle physics, the measurement approach may prove useful in such areas as the development of atomic clocks or the study of quantum systems in a noisy environment. ❙

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