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"I see this synapse as the center of the world

AIDS Uses Trojan Horse Attack

In the battle against AIDS, the virus that causes it has proved a stealthy foe. The ability of HIV to evade the body's defenses and lurk in unknown recesses has long baffled scientists and stymied their efforts to develop effective drugs and vaccines.

New findings from collaborating researchers at Vanderbilt University Medical Center, the University of Illinois, Chicago, and the National Cancer Institute provide evidence of a Trojan horse-like mechanism whereby HIV infiltrates the immune system undetected and then exploits the system to promote its own survival.

The study, published online in *Science*, describes how the transmission of HIV is facilitated through a critical "infectious synapse," created by concentrating virus, receptor and co-receptor at the tight junction that forms between two specialized immune cells.

"I see this synapse as the center of the world for the immune response," says Dr. Derya Unutmaz, assistant professor of microbiology and immunology. "That's where all the decisions are made … whether you will have a useful immune response, a harmful immune response, or a useless immune response."

With HIV, the response falls somewhere between useful and useless. The immune system does mount an initially strong response, Unutmaz says, but something happens that causes the defense to fall short of the goal of total extinction.

It's all about subterfuge, really. To gain a foothold in the body, HIV enters the system through specialized immune cells called dendritic cells, which serve as scouts in the defense system, scanning mucosal tissues and mopping up any encountered bacteria and viruses.

Normally, once a virus is engulfed, enzymes within the dendritic cell chop it up and use the pieces to alert other soldier immune cells—the T cells—that an invader has been captured. In the case of HIV, dendritic cells capture it just as they would any other virus, but HIV remains somehow invisible to enzymatic destruction. Scientists have learned that the virus can hide there, unharmed, for days before the dendritic cell links up with a T cell.

What happens next is the subject of the current study. Using remarkable time-lapse microscopy, the researchers found that the "cloaked" virus particles rapidly stream toward the surface of the dendritic cell at the point of interaction with a T cell. At that same point of contact, the T cell concentrates HIV entry receptors, including CD4, CCR5 and CXCR4, which allow the virus to slip undetected across the junction, into the T cell.

Passing from the dendritic cell to the T cell is not sufficient for the virus to launch a productive infection, however. The T cell must be activated, which means that molecular signals passing between the two cells across this "infectious synapse" must trigger the T cell to begin the process of dividing and proliferating into an army of clones, which would be the normal response to battle an invading pathogen.

Once HIV moves inside the T cell, however, the cell doesn't have time to begin its proliferation. The virus takes over the cellular machinery, turning it into a factory for its own reproduction. Eventually, the T cell is killed, releasing viral progeny and furthering HIV infection. "So in a way what we have is a two-punch model," says Unutmaz, "where the virus exploits both its capture and presentation to a T cell, and at the same time utilizes dendritic cells to

Unutmaz

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for the immune response ... where all the decisions are made. —DERYA UNUTMAZ

activate the T cell, making a perfect environment for its own benefit."

Unutmaz and his collaborators believe their model opens up a number of possibilities in the way of drug or vaccine design, from preventing capture of the virus to interfering with the ability of the virus to become "cloaked" to preventing transport across the cell junction.

"If we come to understand these mechanisms precisely, and how the virus utilizes these mechanisms to exploit the immune system, we could come up with ways to plug the weak points and ways to potentiate the response against the virus," he says.

Understanding HIV infection also sheds light on normal immune function, adds Unutmaz. "I always say that HIV knows more about immunology than I do," he laughs. "Understanding how it utilizes these mechanisms, we learn more about how dendritic cells talk to T cells. And that, of course, has a wider range of implications in designing vaccines against a variety of pathogens, not just HIV."

Recent studies have implicated the same dendritic cell receptor that captures HIV in Ebola virus, hepatitis C, and cytomegalovirus, among others.

Molecular Fingerprinting and Cancer Therapy

2 In the future, many cancer scientists and physicians believe a "molecular fingerprint" of an individual's cancer may be used to diagnose that patient's disease and to tailor his or her therapy.

Researchers at Vanderbilt have moved a step closer to that scenario with the identification of a distinct pattern of expression of 15 proteins in lung cancers that can predict a poor prognosis or a good prognosis. All patients in the poor prognosis group had died one year after diagnosis, while all patients in the good prognosis group were still alive. Median survival, the point at which half the patients were still alive, was six months for the poor prognosis group, compared to 33 months for the good prognosis group.

"If this pattern is confirmed in larger studies, its prognostic power exceeds that of virtually any previously published standard molecular marker," the authors write in the Aug. 9 issue of *The Lancet*.

The scientists also demonstrate that protein profiles obtained from a tiny amount of tumor tissue—only 1 millimeter in diameter and 1/1000th of a millimeter in thickness—can be used to predict risk that the cancer has spread to nearby lymph nodes.

STEVEN HUNT/PHOTOGRAPHERS CHOICE

"Involvement of lymph nodes is one of the most important factors in determining treatment strategies, so the clinical implications of these data could be significant," says Dr. David P. Carbone, Ingram Professor of Cancer Research and professor of medicine and cancer biology. "Being able to use molecular markers to divide patients into high- or low-risk groups would also be very useful in determining treatment strategy."

Such a predictor could help patients and families, with their physicians, in deciding the most appropriate action, which could range from more aggressive therapy at the outset to the avoiding of therapies that are more likely to hurt quality of life for the patient than to extend that life.

The research involved investigators from the Vanderbilt-Ingram Cancer Center; Vanderbilt School of Medi-

cine's departments of medicine, preventive medicine, molecular physiology and biophysics, cardiac and thoracic surgery, and pathology; and Vanderbilt's Mass Spectrometry Research Center. The project is part of Vanderbilt's Specialized Program of Research Excellence (SPORE) in lung cancer, a major initiative funded by the National Cancer Institute.

Now that the human genome has been defined, proteomics—the study of the proteins that carry out the work of cells at the instruction of the genes—is widely considered the next frontier in biomedical research. Vanderbilt has one of the strongest programs in the world in proteomics research, with the sophisticated equipment, informatics power and statistical expertise required to analyze comprehensively the activity of thousands of proteins at once.

The investigators used mass spectrometry and customized software to analyze samples from 79 lung tumors and 14 samples of normal lung tissue. The investigators were able, based on differences in patterns of protein expression, to distinguish with 100 percent accuracy: lung tumor from normal lung; primary non-small-cell lung cancer (NSCLC) from normal lung; primary NSCLC from cancer that had spread to the lungs from other organs; and adenocarcinomas from squamous cell carcinomas, squamous cell carcinomas from large-cell carcinomas. Predictions based on protein profiles were confirmed by pathological evaluation under a microscope.

In one case, a large-cell carcinoma may have been misclassified based on protein patterns as an adenocarcinoma, but investigators report that this tumor may actually be an adenocarcinoma that is too poorly differentiated to identify as such under the microscope.

The investigators note that using protein profiles to make distinctions that are already apparent under the microscope offers little use in clinical care, although the approach is potentially useful in identifying novel therapeutic targets.

However, the ability to use protein profiles to predict node involvement or to identify patients as high or low risk could have great implications for treatment strategies, Carbone says.

"Because such small tissue samples are needed, it would be of great interest to analyze protein expression patterns of tissue samples from needle aspirations or from different cell subtypes within the lung," says Carbone. "It also would be interesting to look for patterns associated with response to specific therapies, with smoking exposure, or with preneoplasia and the progression to cancer. If these data are confirmed using larger numbers of patients, this technology could have significant implications for the clinical management of non-small-cell lung cancer."


Carbone

DEAN DIXON

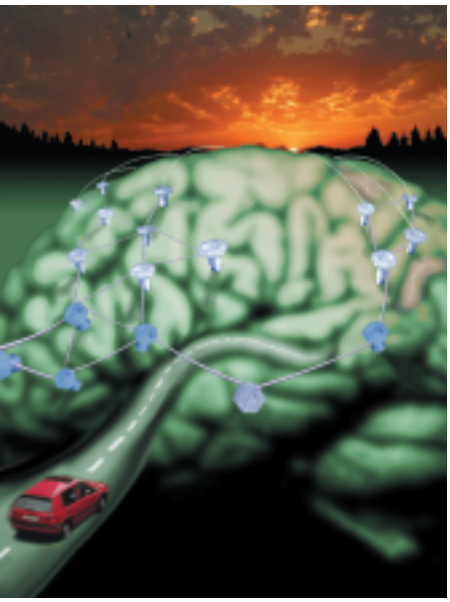
Perceptual Traffic Jams

3 Not only may automobile aficionados treat their cars as if they are people, but it now appears they recognize their cars with the special part of the brain that is also used to identify faces. And when they try to identify cars and faces at the same time, they are likely to experience a kind of perceptual traffic jam.

Those are the implications of research conducted at Vanderbilt University and the University of Colorado at Boulder. Researchers there compared how the brains of auto experts and novices process pictures of cars and faces. They found that viewing cars elicits signals from the brains of car experts that are just like the signals evoked by viewing faces in other brains. Moreover, the experts' skill interfered with their ability to identify faces when they were forced to process cars and faces simultaneously.

The findings, reported online on March 10 in the journal *Nature Neuroscience,* directly challenge the widely held view that a small, specialized area in the brain is specially hardwired to recognize faces. When confronted with a novel object, people use different parts of the brain to identify it by breaking it down into pieces. By contrast, the special facial recognition area appears to recognize faces holistically, all at one time, and does so more quickly than the piecemeal approach.

For more information



Some researchers, including Isabel Gauthier, assistant professor of psychology at Vanderbilt who co-authored the current paper, have argued that faces are not recognized in a special-purpose module but rather by a general-purpose visual processor that can be trained to identify other objects holistically, not just faces.

Three years ago Gauthier published a study that showed car fanciers and bird watchers both used the facial recognition area in the brain to identify the objects of their interest. Last year she published work showing that as people are trained as experts on identifying novel, computer-generated objects, they begin to recognize them holistically.

But these studies left unanswered the question of whether the same neural circuitry was involved in processing faces, birds and automobiles or whether the faces and objects were processed by different neural networks that are intermingled in the same small area in the brain. So Gauthier, working with Tim Curran, assistant professor of psychology at CU Boulder, designed a study to address this issue.

"With this study, we show that the holistic identification process takes place very early in the sequence of visual processing and that at least some of the same neural circuitry must be involved in identifying faces and other objects of extreme interest," says Gauthier.

The researchers recruited 40 men for the study—20 car fanciers and 20 car novices. They had the subjects view alternating sequences of faces and cars and asked them to compare each car to the previous car they saw, and each face to the previous face they saw. In this fashion, the person had an image of a car in his mind when he was looking at the faces. A trick the researchers used was to cut both the images of the faces and cars in half and ask the subjects to ignore the top parts of the images. By modifying the top halves of the images, they were able to measure whether the subjects looked at both the cars and faces in a holistic or piecemeal fashion.

Gauthier and Curran found that individuals with the greatest degree of car savvy recognized the cars in a holistic fashion, but this came at a cost. It reduced their ability to process faces holistically at the same time. By contrast, auto novices used the piecemeal approach to identify the cars, which did not interfere with their ability to recognize faces holistically.

"This indicates that the two holistic processes are not independent," Gauthier maintains.

In order to determine the timing of the interference between holistic car and face recognition, the researchers had their subjects wear a net intermeshed with electric sensors that measured their brain waves. They took the readings from all the subjects and averaged them together to reduce individual variability using a technique called event-related potential (ERP). This allowed them to identify the timing and general location of the processing associated with both car and face recognition.

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Gauthier

The ERP analysis found the difference in a brain wave labeled N170, which has been associated with facial recognition in previous studies. It also established that the conflict between face and car recognition in the auto experts takes place shortly after a person views an image. "This indicates that it is a basic perceptual process, not something that happens because auto experts attend to, or reason about, cars in a different way," says Gauthier.

The analysis also located this activity in the right hemisphere in the same area where functional MRI brain scans have located the facial recognition area, known as the fusiform face area. The fMRI brain-scanning technique provides higher-resolution mapping of brain activity than ERP, but does not provide information about how this activity varies over the short time periods involved in visual processing.

"The ERP results indicate that holistic processing of faces and cars by experts both involve fast-acting visual recognition processes that occur less than one-fifth of a second after faces or cars are seen," Curran explains.

The researchers argue that if the brain's holistic processing capability can be applied to automobiles, which are about as visually distinct from faces as possible, then it should be possible to train it to identify almost any type of object.

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