

For Immediate Release
May 8, 2003

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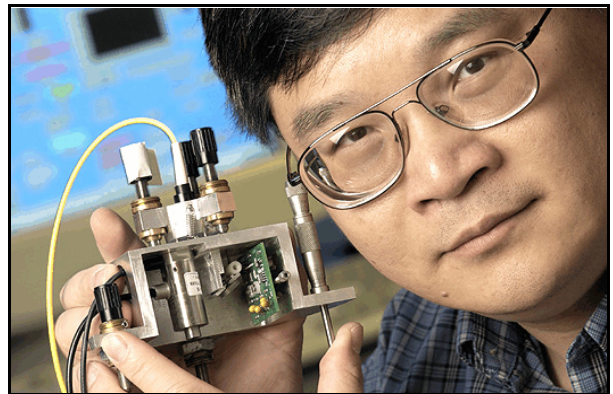
CONTROLLING CELL ADHESION: RESEARCHERS PROVIDE FIRST EXPERIMENTAL EVIDENCE OF "CATCH BONDS" REGULATING CELLS UNDER STRESS

An article published this week in the journal *Nature* provides the first experimental evidence for an unusual molecular bonding mechanism that could explain how certain cells adhere to surfaces such as blood vessel walls under conditions of mechanical stress.

Known as "catch bonds," the adhesion mechanism displays surprising behavior, prolonging rather than shortening the lifetimes of bonds between specific molecules as increasing force is applied. Proposed theoretically nearly 15 years ago, catch bonds could help explain how the body regulates the activity of white blood cells, which must flow freely through blood vessels -- yet bond to injury sites despite blood flow forces.

Understanding how catch bonds work could offer drug designers a new target for anti-inflammatory and anti-thrombosis compounds, and potentially provide a new approach to controlling the metastasis process that cancers use to spread.

"Before the experimental demonstration of catch bonds, we tended to think that force could regulate biochemical reactions only in one direction," said Cheng Zhu, a professor in the Woodruff School of Mechanical Engineering at the Georgia Institute of Technology. "This work



Cheng Zhu, a professor in Georgia Tech's Woodruff School of Mechanical Engineering, shows atomic force microscopy equipment used to study catch bonds.

demonstrates that force can alter the rate in the other direction, depending on the type of interaction. In this post-genome era, we need to know more about how proteins interact with one another and with DNA. This work illustrates a new regulatory mechanism for how proteins -- which from a mechanical engineer's perspective are nanomachines -- operate."

Supported by the National Institutes of Health (NIH), the research involves two teams of scientists, one at Georgia Tech and Emory University in Atlanta, and the other at the Oklahoma Medical Research Foundation and University of Oklahoma Health Sciences Center in Oklahoma City. A paper describing the work was published in the May 8 issue of the journal *Nature*.

The researchers studied the activity of selectin molecules, a family of proteins that helps control the adhesion of white blood cells -- leukocytes -- used by the body to fight infection and repair injuries. Before they can respond to injury or infection, leukocytes must first tether to and then roll along the wall of a blood vessel.

While tethered, the cells receive signals instructing them to enter underlying tissue to fight pathogens or repair injuries. The selectins control the first stage of that process, causing the leukocytes to drop out of the bloodstream and begin attaching to blood vessel walls.

In two separate but complementary experiments, the researchers found evidence of catch bonds operating within the complex of P-selectin and its ligand PSGL-1.

Using a custom-built atomic force microscope, researcher Bryan Marshall applied piconewton-scale forces to a junction connecting P-selectin and PSGL-1 molecules. Despite the difficulty of measuring such small forces, he was able to demonstrate that increasing the force extends the lifetime of the bonds under certain conditions.

"In one range, when we are increasing the force, we actually see the lifetimes of the bonds increase," he said. "Once you get past a certain point, the bonds behave like you would expect -- when you apply a larger force, things come apart faster."

In making the measurements, Marshall carefully picked up only the effects of the interaction between P-selectin and PSGL-1 and shielded the instrument from thermal fluctuations that produce forces greater than those he was trying to measure. In several hundred measurements, Marshall applied forces of less than 10 piconewtons -- comparable to the force exerted by a beam of photons leaving a laser pointer. He measured bond lifetimes as short as a few thousandths of a second and as long as a few seconds.

The second experiment involved flow chamber tests designed to simulate blood flow in the body. Oklahoma researchers perfused cells into the chamber while controlling flow rates and shear forces. This allowed them to study how

adhesive bonds form and dissociate under the rolling interactions.

"We found that one range of forces, applied by increasing wall shear stress, actually increased the lifetimes of adhesive bonds between the cell adhesion molecule P-selectin and its ligand PSGL-1," said Dr. Rodger McEver, Fred Jones Distinguished Scientist at the Oklahoma Medical Research Foundation and adjunct professor of Biochemistry and Molecular Biology at the University of Oklahoma Health Sciences Center. "These observations confirmed the atomic force microscopy results and reinforced their physiological relevance in an experimental design that recapitulates cell interactions in the circulation."

Understanding the phenomenon is important, McEver noted, because the lifetimes of the adhesive bonds determine whether the white blood cells form the rolling interactions with blood vessel walls that are necessary for them to reach the point of inflammation.

The mechanism may play a vital role in allowing the leukocytes to do their job without creating problems elsewhere in the body.

"Catch bonds may play a role in preventing the accumulation of white blood cells in low-flow regions," said Marshall. "You really want the adhesion to be very specific to where they are needed. If you had really strong adhesion all the time, white blood cells would accumulate in regions where they shouldn't. Catch bonds may be the body's way of preventing white blood cells from lingering in stagnant backwaters in the bloodstream where there is little flow."

While the existence of catch bonds has so far been confirmed in selectin molecules, Zhu believes the phenomenon applies other instances in which adhesive molecules interact in the presence of mechanical stress caused by liquid flows. The adhesion of bacterial cells to the gastrointestinal tract, for instance, may also rely on the mechanism to regulate when cells should attach -- and when they should not.

"One of our goals now is to demonstrate that catch bonds are universal to at least several classes of molecules," added Zhu, who also holds

a faculty appointment in the Coulter Department of Biomedical Engineering operated by Georgia Tech and Emory University. "At the atomic level, we want to understand what makes these interactions behave as catch bonds."

In addition to the researchers already mentioned, the team included Mian Long and James Piper of Georgia Tech and Tadayuki Yago of the Oklahoma Medical Research Foundation.

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URL:

gtresearchnews.gatech.edu/newsrelease/catchbond.htm