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TINY CELLS INSIDE BLOOD VESSELS MAY HOLD THE KEY TO HEART DISEASE AND HYBRID GRAFTS

For Immediate Release

May 7, 1990

Color & B/W Available

Pummeled by a strong current, underwater plants must adapt to changing levels of physical stress. Flow rates and soil conditions can encourage or challenge their survival. Similarly, the tiny cells rooted inside human blood vessels are manipulated by an environment that is constantly changing.

By understanding the adaptive behavior of these endothelial cells, scientists hope to learn more about certain types of heart disease such as hardening of the arteries, known as arteriosclerosis. Observations of endothelial cells seeded on different materials may also lead to artifical vascular grafts that fuse with the body.

Sponsored by the National Institutes of Health, the research was discussed during the recent American Chemical Society conference in Boston, Mass.

Dr. Robert M. Nerem at the Georgia Institute of Technology has found that endothelial cells subjected to high levels of physical stress apparently become so preoccupied with survival that they initially stop proliferating.

"When exposed to a very high flow rate and very high stress, survival is the number one priority for endothelial cells," said Nerem, co-director of Georgia Tech's Bioengineering Research Center. "They're going to do whatever is necessary to survive, which means altering their internal structure and synthesizing adhesive proteins to remain attached."

Proliferating Cells: Who's Guarding the Gate?

Certain regions within the human circulatory system -- especially areas where arteries intersect or branch -- tend to be especially vulnerable to the buildup of cholesterol containing arterial scars (arteriosclerosis), explained Dr. Eugene A. Sprague, an assistant professor at the University of Texas Health Science Center and Nerem's research partner. In the past, scientists have theorized that rapid flow rates may contribute to this blockage, by encouraging cholesterol-loaded proteins (low-density lipoproteins) to pool in low-stress areas located at arterial intersections.

But Nerem believes a slow flow rate through vascular intersections may actually encourage the cells to proliferate more rapidly. When the endothelial cells are proliferating,

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Nerem explained, larger molecules such as those containing cholesterol (LDL) may have a greater opportunity to penetrate arterial walls.

"In other words, the protective barrier is not as strong in areas with low shear stress," Sprague said. "When the flow is slower, cells are turning over faster and proliferating, and that means larger molecules can get through the endothelium." Arteriosclerosis is the leading cause of death in the U.S., Nerem noted.

Researchers examined the behavior of cells attached to either glass or a polyester film known as Thermanox. (In previous studies, Sprague said, Thermanox has been characterized as similar to the lining of human blood vessels.) Ultimately, Sprague hopes the research will result in artificial hybrid grafts. When a native artery is defective or malfunctioning, surgeons usually replace the afflicted region with a vein removed from another portion of the patient's body. Unfortunately, suitable replacement veins aren't always available, and there is some risk of infection or recurrent clotting, Sprague said. Synthetic materials which encourage the growth of native cells and tissues might eliminate these problems.

Nerem seeded glass and Thermanox substrates with a single layer of endothelial cells, then placed each sample in a flow duplicating device. Simulated blood was directed through the chamber at different stress levels, for both steady and pulsating flows. Basic counting procedures provided preliminary information about the number of cells present before and after the experiment, but Nerem's team needed to make sure that new cells weren't simply being swept away by the flow. So they also analyzed the cells to detect thymidine, one of the building blocks within DNA. Since endothelial cells must double their DNA to proliferate, thymidine measurements reveal the number of new cells in a sample.

In steady flow equivalent to 13 units of shear force, endothelium on glass stopped proliferating within 24 hours, Nerem reported. But on Thermanox, he said, the cells withstood up to 90 units of steady shear force before they would no longer reproduce. (Blood moving through the human body probably peaks at about 90 units.)

Pulsating flow produced similar but exaggerated results, Sprague noted.

Surprisingly, the cells on Thermanox resumed proliferation after 48 hours, suggesting a temporary, adaptive response to shear stress. "At some point, the effect starts reversing and the cells resume growth," Sprague said. "Frictional forces don't seem to inflict any injury on the cells; they aren't damaged. We think the initial response may be adaptational. There are still questions to be answered, of course, but as time goes on, we'll have a better and better model for things that happen inside the body."

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