Herpes and Heart Disease

Could viruses encourage coronary clogging?

By KATHY A. FACKELMANN

Members of the herpesvirus family are known troublemakers for humans. They cause fever blisters, genital sores, and a flu-like illness. Now, scientists may be about to add another health problem to that list.

Surprising new research findings suggest that some herpesviruses play a key role in the development of coronary artery disease, the leading cause of death in the United States.

Coronary artery disease begins when cholesterol and other fats accumulate on the normally smooth inner lining of the artery wall, a process called atherosclerosis. Eventually, the vessel becomes narrowed by a hardened material known as plaque, which consists of fat and other debris. If a blood clot blocks an already narrowed coronary artery, a heart attack can result.

What might trigger such dangerous clots in people with atherosclerosis? Biochemist David P. Hajjar suggests that one type of herpesvirus, herpes simplex type 1, encourages the buildup of plaque while also revving up the blood's tendency to gel and form clots.

"Herpesvirus is the missing link between thrombosis and atherosclerosis," says Hajjar, who performs laboratory research at the Cornell University Medical College in New York City. He presented his provocative data on herpes and heart disease at the American Heart Association's Science Writers Forum, held in January in Monterey, Calif.

Hajjar isn't the only scientist who suspects that some herpesviruses may accelerate atherosclerosis. Others have data that seem to implicate another type of herpesvirus in the evolution of coronary artery disease. If researchers can confirm such connections, physicians may eventually prevent many cases of atherosclerosis — the major cause of heart attacks — by blocking the damage wrought by herpesviruses.

The link between herpesvirus and atherosclerosis emerged in research conducted not on humans but on fowl.

During the late 1970s, Catherine Fabricant and her colleagues at Cornell University's College of Veterinary Medicine in Ithaca, N.Y., infected some chickens with an avian herpesvirus. They fed these birds a cholesterol-free diet, yet the birds developed a condition that looked strikingly similar to the atherosclerosis that afflicts humans. Another group of herpes-infected chickens — whose feed contained added cholesterol — suffered even more clogging of the heart arteries.

In contrast, chickens vaccinated against infection by the avian herpesvirus *resisted* development of fat-laden arteries, regardless of the concentrations of cholesterol in their blood.

"We were very intrigued by those findings," Hajjar says. Fabricant's work spurred him to embark on a series of biochemical studies aimed at unraveling the complex relationship between herpesviruses and atherosclerosis.

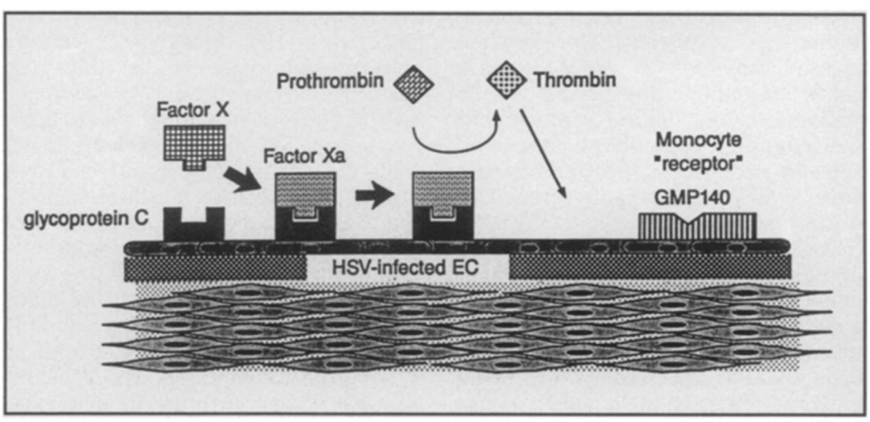
Hajjar and his co-workers began to look at the molecular activities that take place after herpes simplex type 1 infects endothelial cells, which form the skin-like interior lining of blood vessels. Traditional thinking holds that the endothelial lining helps prevent blood clotting by acting as a nonstick surface. But Hajjar's team has data suggesting that herpes-infected endothelial cells turn against the body by participating in a process that leads to an explosive clotting reaction. At the same time, these infected cells may accelerate an insidious layering of plaque within the artery.

That fat-clogged artery, coupled with the overactive clotting mechanism, provides a recipe for a heart attack. Here's how Hajjar believes herpes infection boosts coronary risk.

Imagine you're a traveler aboard a microscopic submarine injected into the bloodstream of a person infected with herpes simplex type 1. This type of herpesvirus causes the common "cold sores" found in and near the mouth. It also infects many cells throughout the body, including endothelial cells in blood vessels. Your ship cruises along miles and miles of blood vessels, stopping in front of a herpes-infected endothelial cell within a coronary artery.

When a herpes simplex type 1 virus invades an artery's endothelial cell, it commandeers the cell's protein-making machinery. Hajjar's research indicates that the virus forces the endothelial cell to spit to its surface a receptor molecule called glycoprotein C.

Your shipmates crowd to the window to



Courtesy Hajjar

When herpes simplex virus (HSV) infects an endothelial cell (EC) lining an artery, it may activate the clotting process by stimulating the formation of the enzyme thrombin from a precursor protein known as prothrombin.

get a close look at that surface receptor. Suddenly, a protein floating by in the bloodstream heads toward the cell surface and docks with the glycoprotein receptor.

That protein, known as Factor X, is one component of the blood's clotting mechanism. The docking process sparks the production of an enzyme called thrombin, which causes the disk-shaped blood cells called platelets to clump and stick together.

Your ship backs off to watch at a safe distance as thrombin leads to the formation of a web-like meshing that traps platelets and red blood cells into a gelatinous clot. At the same time, you notice a swarm of white blood cells traveling to the area. These cells are known as monocytes, and they've answered a chemical call sent out by thrombin. But instead of playing their normal, beneficial role in injury healing, the monocytes bind with another receptor molecule, called GMP140, on the surface of the endothelial cell. Then they worm their way into the artery wall.

Hajjar's studies suggest that once inside the artery wall, the monocytes turn into scavenger cells that gobble up cholesterol and other fats. When scavenger cells become engorged with fat, they are called foam cells. Foam cells represent the very beginnings of the fatty streaks that can arise in blood vessels as early as adolescence and can lead to full-fledged atherosclerotic plaque later in life (SN: 1/20/90, p.37).

Being unable to hop aboard a microscopic submarine, Hajjar teamed up with vascular biologist Dario C. Altieri and turned to a computer for help in visualizing the scene at the surface of the endothelial cell.

Hajjar and Altieri, who is based at the Scripps Research Institute in La Jolla, Calif., wanted to take a close look at the interaction between Factor X and glycoprotein C. First, they used a computer modeling system to depict the three-dimensional configuration of the parts of the Factor X molecule that dock with that receptor. Then they created synthetic peptides that resembled the active sections of Factor X. In test-tube experiments, those lab-made molecules prevented Factor X from binding to glycoprotein C.

According to Hajjar, this suggests that such peptides might stop the overzealous clotting reaction as well as the start of atherosclerosis. "We don't want Factor X binding, so we trick it," he explains.

Could such a method work to prevent dangerous clotting and atherosclerosis in humans? Scientists don't know the answer to that question. The next step, says Hajjar, is to see whether such synthetic peptides will prevent Factor X from initiating blood clotting in an animal model.

Seven types of herpesviruses plague people. Scientists don't have proof that any of these – not even herpes simplex type 1 – can trigger coronary artery disease, Hajjar says. Yet the herpes theory remains compelling because it would help explain certain puzzling cases in which people suffer heart attacks despite low or normal concentrations of cholesterol in the bloodstream, notes Joseph L. Melnick, a virologist at Baylor College of Medicine in Houston.

"Herpesvirus is the missing link between thrombosis and atherosclerosis."

—David P. Hajjar

The idea, says Melnick, is that many people get infected with some sort of herpesvirus early in life. The virus then hides out in various body cells, including endothelial cells, where it may kick off the molecular steps outlined by Hajjar. The herpes-induced vascular damage would take place invisibly at first, setting the stage for heart disease later in life.

Melnick and others have found evidence suggesting that cytomegalovirus (CMV), another type of herpesvirus, may help initiate atherosclerosis. CMV can cause a flu-like illness in adults and in children, as well as infertility in women and birth defects in developing fetuses. Melnick and his co-workers detected unusually high concentrations of antibodies to CMV in the blood of people suffering from atherosclerosis (SN: 5/5/90, p.277).

Other studies have hinted at a link between CMV and atherosclerosis. For example, a University of Minnesota team studied 102 people who received heart transplants – complete with new coronary arteries – between 1983 and 1987. The researchers noted that 32 of these patients carried CMV infection. The CMV-infected people had a 68 percent probability of remaining free of severe atherosclerosis two years after receiving the transplant. Patients without the virus had a much better outlook: 90 percent were clear of severe atherosclerosis two years after the transplant.

One of the biggest problems facing heart transplant patients is the threat of severe and rapidly forming plaque, which can clog the new coronary arteries and cause a heart attack, Melnick notes. Infection with some type of herpesvirus may help explain that risk, he says.

Paul D. Sorlie, an epidemiologist who studies CMV at the National Heart, Lung, and Blood Institute in Bethesda, Md., agrees that herpesviruses may play an intriguing role in the development of coronary artery disease. But confirmation of that role wouldn't negate the importance of cholesterol, he says. People infected with herpesvirus who eat a high-fat, high-cholesterol diet might face an even greater risk of artery disease than similarly infected people who shun fatty foods, Sorlie says.

"Coronary disease is known to be multifactorial in origin," he explains. If further research nabs herpes as a player, it would suggest that these viral invaders can kick off or accelerate the process of plaque formation. Herpesviruses and cholesterol would thus act as separate players in the disease process.

Hajjar concurs that herpes infection may serve as a very early factor – but not necessarily the only one – leading to atherosclerosis. The infection might represent one environmental factor that aggravates a process already under way, he says.

In the future, Melnick would like to see a large-scale trial in which children and young adults receive experimental vaccines to ward off herpesvirus infections. Researchers would then follow those individuals for decades to determine whether their rates of coronary artery disease dropped to lower-than-average levels. Despite the simplicity of the study design, such a trial would be expensive and would have to continue for nearly half a century before results came in, Sorlie points out. It comes as no surprise, then, that no scientist or drug company has stepped forward to propose such a trial, notes Melnick.

As long as the herpes-heart connection remains speculative, the practical advice for people worried about coronary artery disease will continue to focus on the known risk factors, such as cigarette smoking, fatty foods, and a couch potato lifestyle. Even if herpesvirus infection is one factor accelerating atherosclerosis, there's little modern science can do to dampen that risk, at least for now. In the meantime, notes Hajjar, a steady diet of burgers and fries will surely speed the pileup of arterial plaque. □