CORONARY ARTERY DISEASE

CMV-p53 Interaction May Help Explain Clogged Arteries

Every year in the United States about 330,000 patients undergo a procedure called coronary angioplasty. Its goal: to open up coronary arteries clogged by dangerous atherosclerotic plaques and thereby restore normal blood flow to the heart. For the majority of these patients, the operation works just as intended. But in a substantial minority—roughly a third—the treated coronary arteries quickly become clogged again, leaving the patients no better off—and sometimes even worse off—than they were before treatment. Although researchers have known for some time that excessive proliferation of smooth muscle cells in the blood-vessel walls contributes to this "coronary restenosis," they have not been able to pin down exactly what causes the abnormal cell proliferation.

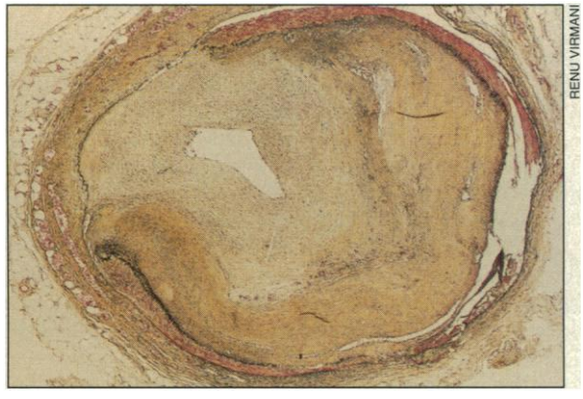
Now, on page 391, a research team led by Edith Speir and Stephen Epstein of the National Heart, Lung, and Blood Institute (NHLBI) provides evidence that may explain at least some cases. Their work is especially intriguing because it links the arterial disease to one of the hottest targets of cancer research—the *p53* gene, a tumor suppressor whose loss or inactivation may contribute to as many as 50% of all human cancers (also see Perspective, p. 334; Research Article, p. 346; and Report, p. 386).

The Speir-Epstein group's results suggest that in some angioplasty patients, restenosis may be triggered by activation of latent cytomegalovirus (CMV), a common virus that usually produces symptomless infections in healthy people. As a result, they postulate, a cascade of effects occurs, including one in which a CMV protein combines with and inactivates the p53 protein in smooth muscle cells. This, in turn, could predispose the cells to increased growth, in much the same way as p53 inactivation is believed to contribute to the formation of malignant tumors. If confirmed, this scenario could suggest new strategies for combating restenosis. Patients undergoing coronary angioplasty might be given anti-viral drugs to inhibit CMV activity or perhaps drugs to replace p53's growth-suppressive activity.

What's more, the result may also apply to atherosclerosis in general, since the formation of the plaques that clog arteries in the first place has several features in common with restenosis, including abnormal growth of arterial smooth muscle cells. "I find it [the paper] fascinating," says virologist Joseph Melnick of Baylor College of Medicine in Houston. "Not only did they find CMV, they found p53. Here we have two of the chief diseases of our society—arterial disease and cancer—coming together."

Epstein says he became interested in looking for the cause of the excessive smooth-muscle growth of restenosis about 3 years ago. At the time, there was already evidence that atherosclerotic lesions resemble benign tumors in some respects. In particular, Epstein cites work done in the early 1970s in Earl Benditt's lab at the University of Washington in Seattle indicating that the smooth muscle cell populations in the lesions are monoclonal—all derived from a single cell—as may happen in tumors.

That finding has remained somewhat controversial, and even if correct, it left unanswered the question of what might give a muscle cell a selective growth advantage, as growth-control mechanisms were then poorly understood. Now, of course, many growth-control genes have been identified, and



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Replugged. Coronary artery almost completely occluded 8 months after it was opened up by angioplasty.

when Speir and Epstein began their work in the early 1990s, they looked first for an abnormality in the *p53* gene, which was just being recognized as a major tumor suppressor.

Their early results were encouraging. They found that 38% of the 60 restenosis lesions they examined contained p53 protein that could be detected by antibody staining. This finding suggested that the *p53* gene might have undergone a mutation that destroyed its growth-suppressive activity. Cancer researchers have shown that the mutant proteins produced by such genes are often more stable than their normal counterparts, which are so short-lived they can't be detected by the antibody assay.

But when the NHLBI workers went on to sequence the *p53* gene to try to confirm that it was mutated in the cells that stained positive for the protein, they had a temporary setback. "We were amazed and disappointed to find wild-type [normal] *p53*," Epstein says. "We were really crestfallen." Again, work on p53 and cancer pointed to a possible explanation. Several researchers had shown that certain viruses linked to human or animal tumors, including adenovirus, simian virus 40, human papilloma virus, and Epstein-Barr virus, make proteins that bind to p53, also inactivating and stabilizing it. This is part of how viruses keep cells dividing so that the viruses themselves can replicate. "There's no doubt about it. Viruses have to deal with this protein," notes *p53* expert Arnold Levine of Princeton University.

The Speir-Epstein group decided to see if a virus might be "dealing" with p53 in the restenosis lesions. Their primary suspect was CMV because work by other investigators, including Melnick, had already linked it to atherosclerosis. And their suspicion that CMV is taking p53 out of action strengthened when the NHLBI workers consistently found signs of infection in restenosis lesions containing cells that stain for p53, but only occasionally in lesions without p53 staining.

Further work suggested a modus operandi for CMV. Epstein and his colleagues propose that the injury done to the coronary artery wall by the original angioplasty procedure activates latent CMV. The virus then produces proteins, including one called IE84, which Epstein and Speir have found can bind to and inactivate p53. By conferring a selective growth advantage on the infected smooth-muscle cells, this may contribute to restenosis in some patients, although Epstein cautions that this is just one of many potential mechanisms by which the virus may produce restenotic lesions.

And CMV activation apparently can't explain all cases of restenosis, as signs of a CMV-p53 interaction haven't been found in about two thirds of the restenosis samples, the causes of which remain a mystery. Still, cardiologists are grateful for all the help they can get in understanding restenosis, which currently forces many patients to undergo another coronary angioplasty or have their diseased arteries replaced in coronary bypass operations. And so far, efforts to prevent restenosis have not shown much promise, says cardiologist Robert Meidell of the University of Texas Southwestern Medical Center in Dallas, "because we haven't dissected out the basic biology yet." The Speir-Epstein group may finally have begun to do just that for some restenosis cases, and possibly for atherosclerosis as well.

–Jean Marx