HIV drug adversity

In a recent study, researchers have shown that protease inhibitors used for combating HIV infection may also have adverse side effects, including coronary artery disease and premature birth in pregnant women.

John Anthony Bauer and colleagues at Columbus Children's Hospital in Ohio have investigated the side effects of the protease inhibitors (PIs) commonly used to boost the life expectancy of those infected with the AIDS virus. The PIs were fast-tracked to the market in the early 1990s by the FDA under increasing pressure to deal with the problem of HIV/AIDS.

According to Bauer, many of the potential adverse reactions to the PIs were not identified because of the rapid turnaround in premarketing trials. "As a result of the innovations with the PI drug class, HIV-positive patients are living longer, but only now are health care providers becoming aware of the complications," Bauer told the 2002 Pediatric Academic Societies annual meeting in Baltimore on May 7.

PIs were designed to block the protease enzymes essential for viral replication in HIV, but little was known about their effects on vascular endothelial cells (the cells lining blood vessels). Bauer and his colleagues have demonstrated direct toxicity of PIs to the endothelium through in vitro cellular studies. They reckon that the effects may explain the increased incidence of atherosclerosis in male HIV patients and of low-birth-weight babies born to HIV-positive women.

The health of endothelial cells is a critical factor in staving off hardening of the arteries; thus, the researchers believe that the damage from PIs is a fairly straightforward case of cause and effect. Endothelial cells in the blood vessels of the placenta are also highly vulnerable to PI toxicity, says Bauer. "When human endothelial cells were exposed to common concentrations of PIs, they were found to be more stressed than expected." It has been recently shown that PI drugs can alter blood lipid levels, which might also promote atherosclerosis.

"Now that there has been considerable success [with PIs] and patients have received long-lasting therapies, the toxicities have become relatively more obvious and important," he adds. According to Bauer, the regulatory mechanisms for fast-tracking certain drugs in a health emergency either have already been changed to address some of the safety issues or are likely to be refined in the future.

—DAVID BRADLEY

Sweet discovery for insulin resistance

The hallmark of Type 2 diabetes, a serious disease that can lead to blindness, amputation, or even death, is insulin resistance—an inability for cells to respond to a hormone that regulates the conversion of food to energy. Although scientists have known for years that high blood sugar and Type 2 diabetes go hand in hand, they have not been able to fully explain how the extra sugar might cause insulin resistance.

Scientists with the Johns Hopkins University School of Medicine's Department of Biological Chemistry (Baltimore) had previously determined that sugar is used in cells to modify proteins by changing their activities. The researchers found that if a protein had too many sugar molecules attached, it could not be properly controlled by the cell and might not function correctly. They found that insulin-resistant cells had specific proteins with more than the normal number of attached sugar groups.

Recently, Gerald Hart and his colleagues in the same department identified a mechanism that may explain how the buildup of sugar on proteins triggers insulin resistance (*Proc. Natl. Acad. Sci. U.S.A.* **2002,** *9* (8), 5313–5318). Their work centered on a glucose metabolite denoted O-GlcNAc, which modifies certain proteins at positions important for insulin signaling. By blocking the enzyme that removes O-GlcNAc from proteins using a molecule called PUGNAc, the scientists hoped to study whether increasing levels of O-GlcNAc could lead to insulin resistance.

Results showed that PUGNAc increased the amount of O-GlcNAc bound to proteins and also caused the cells to stop responding to insulin. Lance Wells, lead author of the study, and his colleagues concluded that insulin resistance is directly caused by an increase in O-GlcNAc.

"We were also able to show where in the insulin signaling cascade there was a defect, at or above a critical protein called Akt, and that two known players, the proteins β-catenin and IRS-1, in responding to insulin, were modified more heavily by O-GlcNAc in the insulin-resistant cells," adds Wells.

Wells says that the research team is now looking at the levels of O-GlcNAc in rodent models of diabetes activity. They are also using genetic and proteomic methods to document the role of O-GlcNAc in modulating insulin signaling in tissues.

—JULIE L. McDOWELL

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