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Study details how diabetes drives atherosclerosis

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Researchers have discovered how diabetes, by driving inflammation and slowing blood flow, dramatically accelerates atherosclerosis, according to research to be published in the March 14 edition of the journal *Circulation Research*.

Experts once believed that atherosclerosis, or hardening of the arteries, developed when too much cholesterol clogged arteries with fatty deposits called plaques. When blood vessels became completely blocked, heart attacks and strokes occurred. Today most agree that the reaction of the body's immune system to fatty build-up, more than the build-up itself, creates heart attack risk. Immune cells traveling with the blood mistake fatty deposits for intruders, akin to bacteria, home in on them, and attack. This causes inflammation that makes plaques more likely to swell, rupture and cut off blood flow.

Making matters worse, nearly 21 million Americans have diabetes, a disease where patients' cells cannot efficiently take in dietary sugar, causing it to build up in the blood. In part because diabetes increases atherosclerosis-related inflammation, diabetic patients are twice as likely to have a heart attack or stroke.

Past work has shown that high blood sugar has two effects on cells lining blood vessels as part of atheroslerosis. First, it increases the production of free radicals, highly reactive molecules that tear about sensitive cell components like DNA, causing premature cell death (apoptosis). This process also reduces the availability of nitric oxide (NO), which would

otherwise enable blood vessels to relax and blood flow to increase.

In contrast to diabetes, exercise and good diet bring about faster blood flow through blood vessels. The force created by fast, steady blood flow as it drags along blood vessel walls has been shown by recent studies to protect arteries from atherosclerosis. Physical force has emerged recently as a key player in bodily function, capable of kicking off biochemical processes (e.g. weightlifting thickens bone).

“Inflammation is blood vessels is one of the main drivers of atherosclerosis, and diabetes makes it much worse,” said Jun-ichi Abe, M.D., Ph.D., associate professor with the Aab Cardiovascular Research Center at the University of Rochester Medical Center, and a study author. “Our study argues that a pathway surrounding a key signaling enzyme both protects the heart in normal cases, and is sabotaged by the chemicals produced in diabetes. We believe we have found a new therapeutic target for the treatment of diabetes-related damage to blood vessels.”

How Diabetes Does It

In people without diabetes, fast blood flow triggers an enzyme called extracellular signal-regulated kinase 5 (ERK-5). ERK5 in turn signals endothelial nitric oxide synthase (eNOS) to produce more nitric oxide and dilate blood vessels. It also activates Kruppel-like factor 2 (KLF2) and peroxisome proliferator-activated receptor-g (PPARg), both of which block the ability of pro-inflammatory immune cells to home in on and adhere to diseased portions of blood vessels.

Past studies had shown diabetes to worsen atherosclerosis, but its exact link to related inflammation had remained unclear. The current results provides the first mechanistic description of how diabetes takes away the ability of fast blood flow force to protect blood vessels, arguing that it

does so by interfering with ERK5 and its signaling partners.

Abe's team showed that molecules called advanced glycation end products (AGEs), produced in greater levels by patients with diabetes, interfere with ERK5 cardioprotection. Glycation reactions cause the release of oxidizing side products like hydrogen peroxide (H202) that drive free radical production, inflammation and cell damage in many diseases.

Researchers found that AGEs and H202 sabotage ERK5 by encouraging the attachment to it of a small ubiquitin-related modifier (SUMO), a protein tag used by cells to fine-tune their control over proteins. In normal function, a cell may extend a protein's lifespan, or send it from one part of the cell to another, by attaching a SUMO tag. In the current study, researchers found that AGEs and H202 induced ERK5-SUMOylation as part of disease. In addition, the team found that ERK5-SUMOylation was increased in the aortas of diabetic mice.

Along with Abe, Chang-Hoon Woo, Tetsuro Shishido and Carolyn McClain contributed to the work within the Aab Cardiovascular Research Center. Jae Hyang Lim and Jian-Dong Li within the Department of Microbiology & Immunology at the Medical Center contributed expertise, along with Jay Yang, professor of Anesthesiology at Columbia University. This work is supported by grants from the America Heart Association and the National Institutes of Health.

"Our experiments found that taking away the "SUMO tag" from ERK protects blood vessels against diabetes," Abe said. "We believe that the SUMOylation of ERK turns off 'good' genes that are important in countering atherosclerosis. In the next phase, we will be looking for drug candidates that can turn on ERK5 as diabetes attempts to shut it down."

Source: University of Rochester