Novel technique uses RNA interference to block inflammation

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Massachusetts General Hospital (MGH) researchers – along with collaborators from Massachusetts Institute of Technology (MIT) and Alnylam Pharmaceuticals – have found a way to block, in an animal model, the damaging inflammation that contributes to many disease conditions. In their report receiving early online publication in *Nature Biotechnology*, the investigators describe using small interfering RNA technology to silence the biochemical signals that attract a particular group of inflammatory cells to areas of tissue damage.

"The white blood cells known as monocytes play a critical role in the early stages of the immune response," says Matthias Nahrendorf, MD, PhD, of the MGH Center for Systems Biology, the paper's senior author. "We now know there are two subsets of monocytes – an inflammatory subset that defends against pathogens and a reparative subset that supports healing. But if the inflammatory response is excessive, it can block the healing process and exacerbate conditions such heart disease and cancer."

Cells damaged by injury or disease release a cocktail of chemicals called cytokines that attract immune cells to the site of the damage. Inflammatory monocytes are guided to sites of tissue injury by a receptor protein called CCR2, and the MGH-led team devised a strategy targeting that molecule to block the inflammatory process but not the action of the reparative monocytes.

Small interfering RNA (siRNA) technology prevents production of

specific proteins by binding to associated messenger RNA molecules and preventing their translation. Because the technique requires extreme precision in developing the right siRNA molecule and delivering it to the correct cellular location, the MGH team collaborated with Alnylam scientists who are experts in RNA-interference-based therapeutics and with MIT investigators Robert Langer, ScD, and Daniel Anderson, PhD, who have developed a nanoparticle-based system for delivering molecules to specific cellular compartments.

To make sure that their siRNA preparation targeted the right monocytes, the investigators first confirmed that its use reduced levels of CCR2 in monocytes and increased levels of the fragments produced when siRNA binds to its target. They then showed that monocytes from mice treated with the siRNA preparation were unable to migrate towards CCR2's usual molecular target. Experiments in animal models of several important diseases showed that the siRNA preparation reduced the amount of cardiac muscle damaged by a heart attack, reduced the size and the number of inflammatory cells in atherosclerotic plaques and in lymphomas, and improved the survival of transplanted pancreatic islets.

"These inflammatory monocytes are involved in almost every major disease," Nahrendorf explains. "Anti-inflammatory drugs currently on the market hit every inflammatory cell in the body, which can produce unwanted side effects. This new siRNA treatment doesn't affect inflammatory cells that don't rely on the CCCR2 receptor. That makes a big difference." Nahrendorf is an assistant professor of Radiology at Harvard Medical School.

Provided by Massachusetts General Hospital

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