Sweet -- sugared polymer a new weapon against allergies and asthma

November 19 2009

Scientists at Johns Hopkins and their colleagues have developed sugar-coated polymer strands that selectively kill off cells involved in triggering aggressive allergy and asthma attacks. Their advance is a significant step toward crafting pharmaceuticals to fight these often life-endangering conditions in a new way.

For more than a decade, a team led by Bruce S. Bochner, M.D., director of the Division of Allergy and Clinical Immunology at the Johns Hopkins University School of Medicine, has studied a unique protein known as Siglec-8. This protein, whose name is an acronym for Sialic Acid-binding, Immunoglobulin-like LECtin number 8, is present on the surfaces of a few types of immune cells, including eosinophils, basophils and mast cells. These different cell types have diverse but cooperative roles in normal immune function and allergic diseases. When functioning correctly, they are a valuable aid to keeping the body healthy and infection-free. However, in allergic reactions and asthma attacks, the cells unleash an overwhelming response that typically harms the body more than it helps.

The researchers found in previous studies that when they bound antibodies that specifically target Siglec-8 to the protein on eosinophils, the cells promptly died, an effect that might be useful in stemming an allergy or asthma attack. Since producing antibodies can be expensive—a potential roadblock to using them as pharmaceuticals in the future—the researchers sought another way to activate this protein.

Several years ago, Bochner and his colleagues discovered an unusual sugar that could uniquely and selectively attach to and activate Siglec-8. "The trick is that you need to engage several clusters of Siglec-8 on each cell at once to trigger cell death. You're not going to be able to do that with individual sugar molecules in solution," Bochner says.

To accomplish this goal, the team developed soft, flexible polymer strands coated with the sugar, "like microscopic spaghetti candy," says Bochner.

Using cells genetically modified to produce Siglec-8 on their surfaces and cells without the protein, the researchers tested whether the polymer bound when applied to the cells. As expected, the polymer bound only to the cells that produced Siglec-8. Polymer strands without the sugar, or with different attached sugars, could not bind to the cells. Additionally, when the researchers pretreated Siglec-8-producing cells with antibodies that target the protein, the polymer couldn't attach, suggesting that it specifically targets Siglec-8 and not another protein on the cells.

The researchers validated these results further by testing whether cells adhered to polymer strands immobilized in a petri dish. Cells expressing Siglec-8 bound firmly to the polymer, but didn't bind to polymers without the Siglec-8 specific sugar.

Finally, to test the polymer in a more physiologically relevant setting, the researchers added the polymer to vials of whole human blood to see which blood cells it attached to. They found that the polymer only attached to eosinophils. Using only purified eosinophils, the researchers examined whether the polymer could kill the cells, as the targeted antibodies had in previous experiments. While their results showed that the polymer killed about 65 percent of the eosinophils over 72 hours, it was not as effective as the antibody, which killed up to 90 percent of the cells in 24 hours.

"This is initial proof that delivering the sugar through a polymer can give you the desired result of selectively engaging Siglec-8 and killing eosinophils, but we still have a long way to go," says Bochner. He and his team plan to try to optimize these results, reported in the August *Journal of Pharmacology and Experimental Therapeutics*, by experimenting with other formulations to deliver the sugar to cells, including more rigid polymers, those with denser sugars, or nanoparticles coated with the sugar instead of polymers.

Source: Johns Hopkins Medical Institutions