Protein a possible key to allergy and asthma control

January 2 2008

Activating a protein found on some immune cells seems to halt the cells' typical job of spewing out substances that launch allergic reactions, a study by Johns Hopkins researchers suggests. The findings could eventually lead to new treatments for allergic reactions ranging from annoying bouts of hay fever to deadly asthma attacks.

Previous studies by Bruce Bochner and his colleagues at the Johns Hopkins Asthma and Allergy Center had zeroed in on the protein, Siglec-8, as an important player in allergic reactions. This protein is found on the surfaces of some types of immune cells, namely eosinophils, basophils and mast cells, which have diverse but cooperative roles in normal immune function and allergic diseases. Eosinophils directly combat foreign invaders, such as parasites. Basophils and mast cells store and release substances such as histamine, prostaglandins and cytokines, which signal other immune system cells to ready for battle.

When functioning correctly, these cells 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 activated Siglec-8 on the surface of eosinophils, the cells promptly died. Expecting the same suicidal response in mast cells, the scientists tested their theory in a new study on human mast cells and mast-cell-containing tissues.

Using mast cells grown in a lab, the researchers used antibodies to activate Siglec-8. “We were surprised to see that these cells just sat there happily in their petri dishes and lived on,” says Bochner, director of the Division of Allergy and Clinical Immunology at the Johns Hopkins University School of Medicine.

With their initial theory disproven, Bochner and his colleagues suspected that Siglec-8 might be slowing down other cellular processes based on the protein’s distinctive structure. To investigate what else Siglec-8 might inhibit, the scientists activated the protein in mast cells once again with antibodies. Then, they attempted to trigger an allergic response from these cells.

Normally, mast cells respond with an outpouring of histamine, prostaglandins and other substances that spur allergic reactions in other cells. However, Bochner and his colleagues found that cells with activated Siglec-8 released less than half the typical amount of these substances.

Extending their experiment from cells to whole tissues, Bochner and his colleagues used antibodies to activate mast cells’ Siglec-8 in small pieces of human lung saved from autopsies. When the researchers triggered the cells to release their payloads-an act that typically causes airways to sharply constrict-the contractions were about 25 percent weaker than in lung tissue where the mast cells’ Siglec-8 wasn’t activated.

The researchers are still unsure exactly how Siglec-8 inhibits mast cells from releasing their immune-triggering chemicals. However, follow-up experiments suggested that activating the protein keeps calcium from moving efficiently into the cells. Mast cells need this calcium signal to release their contents.

Bochner notes that researchers might eventually use these results,

published in the February Journal of Allergy and Clinical Immunology, to develop a drug with this same effect. Such a drug would have the dual effect of blocking or reducing allergic reactions by killing eosinophils and preventing mast cells from releasing their substances.

“Both of these effects could make allergic diseases and asthma less severe,” he says. “It’s an intriguing approach because there are no drugs that specifically target both these cell types.”

Though drugs exist that affect either eosinophils or mast cells, Bochner says developing a single drug that takes aim at both types of cells could be even more effective than existing therapies and may also have a reduced risk of side effects. He and his colleagues are also searching for natural molecules in the body that activate Siglec-8, which could bring researchers a step closer to developing pharmaceuticals that target this protein.

Source: Johns Hopkins Medical Institutions