Autoinflammatory disease model reveals role for innate, not adaptive, immunity

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Researchers at the University of California, San Diego School of Medicine have developed the first mouse model for auto-inflammatory diseases, disorders that involve the over-activation of the body's innate, primitive immune system. Their study, published early on-line in *Cell Immunity* on June 4, suggests that the innate - not adaptive - immune system drives auto-inflammatory diseases. The findings could open new therapeutic directions for research into disorders such as gout or inflammatory bowel disease.

"Auto-inflammatory diseases are a relatively new classification of diseases that are different from autoimmune diseases or allergies," said Hal Hoffman, MD, associate professor of medicine at UC San Diego School of Medicine. Hoffman studies a group of rare, inherited auto-inflammatory conditions called Cryopyrin-Associated Periodic Syndromes (CAPS), which includes Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Autoimmune diseases arise from an overactive response of the body's adaptive, or acquired, immune system against substances and tissues normally present in the body. Allergies are also a product of the adaptive immune system, but in response to environmental substances. Both involve the action of lymphocytes such as B cells and T cells. The older innate immune system, on the other hand, recruits immune cells to sites of infection and inflammation, but doesn't confer long-time protection. Pathogens evoke an inappropriate response that doesn't involve antibodies or lymphocytes.

With CAPS, Hoffman had earlier discovered that mutations of the NLRP3 gene caused the auto-inflammatory disease symptoms because the gene causes alterations in the protein called cryopyrin. Cryopyrin regulates the release of interleukin-1, an important mediator of fever and systemic inflammation during the body's innate immune response, and alterations in cryopyrin lead to over-production of Il-1.

Mutations in the NLRP3 gene are thought to result in inappropriate activation of a multi-protein complex called an inflammasome, leading to excessive Il-1β release and manifestation of CAPS disease symptoms. Treatment with Il-1β inhibitors reduces the inflammation and symptoms in auto-inflammatory diseases; however, NLRP3 may have other effects in addition to increased Il-1β.

"Patients treated with the Il-1β inhibitors got much better, but still exhibited some symptoms," said Hoffman.

In order to examine the role of inflammatory mediators and adaptive immune responses in CAPS, the researchers developed two NLRP3 mutant knock-in mouse models. (In "knock-in" models, genetic information is inserted into a particular part of the genome; in contrast to "knock-out" mouse models, in which genetic information is removed.) These mice had systemic inflammation and poor growth, similar to some human patients.

By mating these mice to mice with various gene mutant backgrounds, the scientists showed that CAPS requires an intact inflammasome, is only partially dependent on Il-1β and is independent of T cells. Their findings may help lead to more effective treatments for CAPS syndromes.

"The data shows that CAPS are true inflammasome-mediated diseases and that the adaptive immune system is not necessary for this disease," said Hoffman.

"In the larger picture, our findings also suggest that innate and adaptive immune systems don't necessarily always 'cross talk' or communicate with one another."

According to the researchers, given the importance of IL-B and the inflammasome to innate immunity, NLRP3 knock-in mice may be applied to the study of many diseases along the autoinflammatory-autoimmune spectrum.

Source: University of California - San Diego (news : web)