How mice and humans differ immunologically

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Edith Hessel and colleagues, at Dynavax Technologies Corporation, Berkeley, have identified the reason that humans and rodents respond differently to a molecule that is being developed to treat allergic diseases.

Molecules that trigger the protein TLR9 are being developed as a potential therapeutic for allergic diseases. While they have been shown to be safe and well-tolerated when inhaled by people, they cause severe lung inflammation and toxicity when inhaled by rodents.

In the study, the toxicity of one of the molecules under development was found to depend on TLR9 and the soluble immune molecule TNF-alpha in mice. Importantly, TLR9 is expressed on many immune cell types in the mouse (monocyte/macrophage cells, B cells, and pDCs) and only on B cells and pDCs in humans. The toxicity in mice was found to be independent of B cells and pDCs, meaning that other immune cells expressing TLR9 were responsible for TNF-alpha production.

As human TLR9-expressing cells did not produce TNF-alpha in response to stimulation by the molecules under development, the authors conclude that the differential pattern of TLR9 expression is important in determining the nontoxicity of molecules that target TLR9 in humans and that toxicity in rodents is a result of TNF-alpha production.

More information: CpG-containing immunostimulatory DNA sequences elicit TNF-alpha-dependent toxicology in rodents but not in humans, *Journal of Clinical Investigation*. www.the-jci.org/article.php?id=38294

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