Nature Reviews Immunology | AOP, published online 13 December 2013; doi:10.1038/nri3587

INNATE IMMUNITY

Making mice more human the TLR8 way

> mice expressing high levels of *TLR8* spontaneously developed arthritis

In addition to responding to pathogen-derived ligands, Toll-like receptors (TLRs) can respond to endogenous ligands and thus have been linked with the pathogenesis of autoimmunity. Guiducci *et al.* have now generated transgenic mice that express human *TLR8*, and they reveal a role for this receptor in autoimmune disease.

In humans, both TLR7 and TLR8 recognize viral RNA, single-stranded self-RNA and synthetic small molecule agonists. TLR7 has a role in autoimmune diseases, but although TLR8 belongs to the same TLR family as TLR7, its role in inflammation and disease has been unclear owing to the lack of a suitable animal model.

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In mice, TLR8 is non-functional because it lacks five amino acids, so the authors generated transgenic C57BL/6 mice that express different levels of human *TLR8*. Peripheral blood mononuclear cells isolated from *TLR8* transgenic mice, but not from wild-type mice, were responsive to an RNA-based ligand of human TLR8 and produced pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1, interferon-γ and tumour necrosis factor; hence, human TLR8 is functional when expressed in mice. Mice expressing high levels of *TLR8* mRNA developed a wasting disease, showed severe inflammation in the pancreas, salivary glands and joints and failed to breed, whereas mice expressing lower levels of *TLR8* bred normally. The severity of the inflammatory phenotypes closely correlated with the expression levels of *TLR8*.

Previous work has shown that increased expression of mouse TLR7 is sufficient to break immune tolerance in mice. Interestingly, the authors found that high levels of human *TLR8* result in a range of diseases that are strikingly distinct from those related to TLR7 signalling. The different responses are probably due to the fact that *TLR7* is primarily expressed by B cells and plasmacytoid dendritic cells, whereas *TLR8* is expressed by monocytes, myeloid dendritic cells and neutrophils.

Next, the authors examined the development of arthritis in *TLR8* transgenic mice; mice expressing high levels of *TLR8* spontaneously developed arthritis, whereas mice expressing low levels of *TLR8* did not. However, in contrast to wild-type mice, the disease progression of collagen-induced arthritis continued beyond 4 weeks in mice expressing low levels of *TLR8*. Hence, TLR8 signalling seems to have a role in the progression and exacerbation of collagen-induced arthritis rather than in the initial phase of the disease.

Finally, the authors determined the level of *TLR8* mRNA in blood cells from patients with arthritis and found that patients with systemic-onset juvenile arthritis or Still's disease had increased levels of *TLR8* expression. *TLR8* levels in these patients correlate with increased expression of IL-1β, which is an important driver of arthritis. Together, these data suggest that human TLR8 has an important role in the pathogenesis of arthritis.

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ORIGINAL RESEARCH PAPER Guiducci, C. *et al.* RNA recognition by human TLR8 can lead to autoimmune inflammation. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20131044 (2013)