Methylation Markers and a Downstream Drug Target in RA

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New information points to epigenetic differences as well as sequence variations in the etiology of RA. In other research, a downstream immune modulator far more specific than TNF-α looks promising in a mouse model of RA.

Rheumatoid Arthritis

Epigenome-wide association data implicate DNA methylation as an intermediary of genetic risk in rheumatoid arthritis
Nature Biotechnology published online Jan. 20, 2013 Full text $32

DNA methylation at ten locations increases the risk of anti-citrullinated peptide antibody (ACPA)-associated rheumatoid arthritis (RA). Nine of these locations are on the major histocompatibility (MHC) cluster, and one is outside it on the same chromosome. Although nearly 40 genetic variations in DNA sequences are associated with increased risk for ACPA-associated RA, most of them also on the MHC cluster. By identifying associations with methylation, this study implicates epigenetic (DNA control) in addition to sequence variation as important in the etiology of RA.

iRHOM2 is a critical pathogenic mediator of inflammatory arthritis
J Clin Invest Feb 1, 2013 (online first) Free full text.

Blocking iRHOM2, a protein on the tumor necrosis factor α (TNF-α) pathway, might treat rheumatoid arthritis (RA) with fewer side effects than blocking TNF-α itself, mouse models suggest. Several drugs treat rheumatoid arthritis (RA) by blocking TNF-α, but TNF-α acts throughout the body and TNF-α inhibitors have systemic side effects. In the search for drugs that block other parts of the TNF pathway in ways more specific to RA, one target is TNF-α converting enzyme (TACE), which releases TNF-α from the plasma membrane. Blocking TACE would prevent TNF-α from being released, but a more specific target is needed because r TACE is also important in many physiological processes.

Researchers have moved upstream of TACE to iRHOM2, which regulates TACE on monocytes. (Its counterpart iRHOM1 regulates TACE elsewhere in the body, such as on cells in the brain, heart, kidney, liver, lung and spleen.) Therefore, iRHOM2 inhibitors should be selective to immune cells. A mouse model of RA, iRHOM2-knockout mice, were healthy, and didn’t develop RA. Drugs that block iRHOM2, logically, should also safely prevent RA.

In a commentary, Stefan Lichtenthaler explains the TNF-α/TACE/iRHOM pathway, and evaluates the prospects for using iRHOM2 as a drug target.

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