Rheumatoid Arthritis: Epigenetic Drug Targets

Adam P. Crisbi1,2, Marc Feldmann1 and Udo Oppermann2,3

1Computational Genomics and Tissue Centre, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford, OX3 9DS, UK
2Biomedical Research Centre, University of Oxford, Windmill Road, Oxford, OX3 7LD, UK
3Structural Genomics Consortium, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7QD, UK

Abstract: Autoimmune diseases, such as rheumatoid arthritis (RA), arise as a result of a breakdown in immune tolerance, for reasons that are as yet unknown. RA affects up to 1% of the population worldwide and has a lifetime risk of 4% for women and 2% for men. While a number of successful immunotherapies, such as anti-TNF, CTLA-4 and anti-CD20, have revitalized the treatment of RA in recent years, many patients still fail to respond sufficiently to treatment, or the treatment is toxic, so new targets must be identified for many years to come. Although the etiology and pathogenesis of RA remains elusive, studies have revealed a genetic predisposition, with variants of several genes, including human leukocyte antigen DRB1 (HLA-DRB1), IRF5, PTPN22, CD82 and CTLA-4, having strong association with the condition. Despite this extensive genetic predisposition, the concordance of RA in monozygotic twins is low (2-20%), suggesting that environmental and epigenetic factors are important in disease development. The environmental factor most consistently associated with RA is cigarette smoke, with alcohol consumption seeming to have a mild protective effect.

The low concordance rate of RA between monozygotic twins and the large onset of RA provide evidence that epigenetic modifications may be important for development of the disease. A number of potential environmental risk factors have been implicated, one of these being periodontitis. It has been shown that Porphyromonas gingivalis, a cause of periodontitis, expresses an enzyme with peptidylarginine deiminase (PAD) activity (called P. gingivalis PAD 1), which leads to recruitment of other immune cells, such as NK cells and B cells, which in turn secrete IFNγ and immunoglobulins such as rheumatoid factor, that can heighten RA severity. One mechanism implicated in cigarette smoking is through the reduction of histone acetylation (HDAC) SIRT1 and SIRT2 expression in macrophages within the lungs.

The major goal for RA drug discovery is to identify a compound that stops the inflammatory cascade within the joint and reverses the damage associated with RA. Current medicines, while successful at preventing the joint and reverses the damage associated with RA. Current medicines, while successful at preventing

Epigenetic Modifications in RA

A number of epigenetic modifications have been identified as having pathological importance in RA. Synovial fibroblasts in RA display a DNA methylation pattern distinct from healthy fibroblasts. Similarly, T cell homoeoatlas in RA colons have been shown to exhibit dysregulated cell function. In Tregs, DNA methylation of promoter and enhancer of key genes has been shown to inhibit the ability of these cells to perform their regulatory function. RA patients display a significantly increased expression of HDAC activity in PBMCs, suggesting that this pathway is dysregulated, while studies in synovial fibroblasts have also shown an inhibition of histone methylation in the HDAC4/Cstf1B pathway. Investigations of histone methylation in the context of RA are rare, although the histone methyltransferase EZH2 has been shown to be overexpressed in RA fibroblasts, suggesting that EZH2 may be involved in RA.

Figure 2 shows some of the epigenetic modifications that may be involved in rheumatoid arthritis.

Epigenetic Pathways for Potential Intervention in RA

The major goal for RA drug discovery is to identify a compound that stops the inflammatory cascade within the joint and reverses the damage associated with RA. Current medicines, while successful at preventing the joint and reverses the damage associated with RA. Current medicines, while successful at preventing

For copies of this poster, please visit tocris.com

Tocris is a Bio-Techne brand