Reduced glucose metabolism in CD4 T cells linked to rheumatoid arthritis

Ann L. Jagger
Department of Cardiovascular Medicine, Stanford University, Stanford, CA
Email: ajagger@stanford.edu

Rheumatoid arthritis (RA) is an inflammatory disease of the joints that, if untreated, leads to cartilage destruction, bone erosion and ultimately loss of joint mobility (Scott, 2010). Inflammation is both the principal clinical manifestation of the disease, as well as the driver of synovial tissue damage. As the incidence of RA strongly correlates with advancing age, it is believed that age-related dysregulation of the immune system may play an important role in its pathogenesis and chronicity (Lindstrom, 2010). This age-related decline of the immune system, known as immune senescence, appears to follow an accelerated trajectory in patients with RA.

In a recent publication in the Journal of Experimental Medicine, Yang et al set out to elucidate the molecular mechanisms underlying immune senescence in RA. They looked into the – often overlooked by immunologists – topic of cell metabolism in CD4 T cells, specialized immune cells that are central in immune responses. They found that CD4 T cells of RA patients have a defect in glucose metabolism. This defect could be mapped to 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKB3), a rate-limiting enzyme of the glycolytic pathway. PFKB3 induction following activation was reduced in CD4 T cells from RA patients compared to controls. Knock-in and knock-out experiments on patient and healthy control CD4 T cells confirmed that reduced induction of PFKB3 resulted in a reduction in autophagy, an alternative source of energy for cells, and was responsible for increased apoptosis and senescence of RA CD4 T cells (Yang, 2013).

This work demonstrates that RA CD4 T cells show hypo-metabolism of glucose coupled to reduced autophagy, due to deficient induction of the PFKB3 enzyme in the glycolytic pathway. This defect is linked to functional outcomes, namely increased apoptosis and senescence of CD4 T cells in patients with RA. The cause of the PFKB3 defect, the applicability to other immune cells involved in RA development and its physiological or pharmacological reversibility remain unknown. While the effects of PFKB3 deficiency are striking in terms of cell fate, determining whether this is an independent dysregulation event acting in addition to the presence of aberrant immune activation or whether it is causative will be critical in evaluating the potential therapeutic applicability of this novel mechanism. The authors claim that the PFKB3 defect was specific to RA and was not observed in patients with another inflammatory disease, systemic lupus erythematosus (SLE), concluding that the defect is not due to inflammation (Yang, 2013). However, there have been previous studies linking defects in autophagy with Crohn's Disease, an inflammatory disease of the bowel (Scharl, 2012). Delineating the role of inflammation is therefore critical. Treatments that suppress inflammation have been relatively successful in RA, although a significant number of patients remain unresponsive to treatment. This discrepancy in treatment responsiveness has often been attributed to differences in underlying pathogenic mechanisms leading to the same presenting clinical cluster: inflammation of the joint (van der Helm-van Mil, 2008). If the defect of PFKB3 is confirmed to be an inflammation-independent mechanism, targeting this pathway therapeutically may address the needs of the non-responding patients. With inflammation and particularly production of inflammatory cytokines IL-1β, IL-6 and TNF-α still being

considered the core mediators of tissue destruction in RA (Scott, 2010), it will be interesting to see how these new findings help complete or even revise the puzzle of RA pathogenesis.

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