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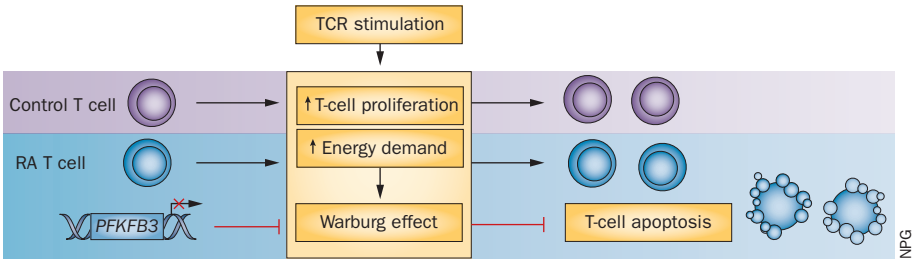
RHEUMATOID ARTHRITIS

Metabolic reprogramming of T cells in RA



Does an inability of T cells to cope with peaks in metabolic demand contribute to the development of rheumatoid arthritis (RA)? Intriguing data, obtained *in vitro* using naive CD4$^+$ T cells from patients with RA, suggest so, and implicate a failure to upregulate expression of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3). Consequences of T-cell insufficiency of this glycolytic enzyme, report Cornelia Weyand and colleagues in *The Journal of Experimental Medicine*, include prevention of the Warburg effect, deficient induction of autophagy, and T-cell apoptosis. Potentially, the findings bring metabolic pathways that have long been on the radar of investigators in cancer research into the realm of RA. The mechanistic basis of the phenomenon, however, and its place —if any—in the aetiopathogenesis of RA remain to be determined. Nevertheless, the work raises interesting possibilities for researchers hoping to restore T-cell homeostasis in patients with RA.

Weyand and co-workers purified naive CD4$^+$ T cells from a total of 128 patients with RA (positive for rheumatoid factor and anti-citrullinated protein antibodies) and 103 control individuals. These cells, which are important in synovitis and dependent for antigen recognition on MHC class II genes that occupy the locus mostly strongly associated with RA risk, are known to display altered response to activation in RA. The energetically demanding processes of T-cell activation and proliferation necessitate mechanisms to increase cellular supply of ATP, including upregulated aerobic glycolysis (the Warburg effect) and autophagy. Physiologically, most T cells are in a resting state but chronic T-cell activation in RA raises the question of how these metabolic processes are affected; Weyand and colleagues decided to find out.

In comparion with control cells, T cells from patients with RA were less able to metabolize glucose or produce ATP, and were less resistant to apoptosis. The cells were no more differentiated than those of controls, according to analysis of T-cell lineage markers, and responded robustly to T-cell receptor (TCR) ligation. Measuring the expression levels of various metabolic enzymes, however, did reveal a key difference between the control and RA cells: transcript levels of PFKFB3 were ~50% lower in the latter, with protein levels also depressed. Furthermore, whereas TCR stimulation induced PFKFB3 protein expression with a peak after 72 h, it was 35–40% lower in the RA T cells than the controls. Induced overexpression of the enzyme in RA T cells restored their activation capacity and protected them from apoptosis.

Finding that RA T cells have subnormal ability to upregulate PFKFB3, an enzyme known to cause the Warburg effect, is "novel and unexpected", says Peter Lipsky, an expert in RA cellular pathology who was not involved in the study. Lipsky notes, however, that the cells were stimulated with "rather potent and unphysiologic stimuli".

With no correlation between RA disease activity levels and PFKFB3 expression, and given that T cells from 11 patients with systemic lupus erythematosus had PFKFB3 levels not significantly different to those of 33 controls (unlike those from 16 patients with RA), the authors conclude that the effect is not secondary to inflammation and thus might precede RA. "If so," says another independent RA expert, Rikard Holmdahl of the Karolinska Institute, Sweden, "it needs to be shown that there are specific primary causes such as a specific genetic effect or unique environmental factor operating in pre-RA phase that is directly linked to regulating the PFKFB3 activity". Lipsky agrees and would like to see data from other cell populations, "to determine the specificity of this abnormality and its potential impact on the function of other cell and tissue types".

Nevertheless, the findings could, says Holmdahl, "explain the well-known low responsiveness of T cells in RA". The authors go further and suggest that lymphopenia caused by lack of T-cell resilience in RA might create a 'gap' that becomes filled by autoreactive T cells. Besides this possibility, suggests Lipsky, is that suppression of PFKFB3 might be an attempt to block autoreative clone expansion; "starving the aggressors might be a means for the body to attempt to control ongoing CD4$^+$ T cell-mediated inflammation," he muses.

Establishing the *in vivo* relevance of the data is important, and the authors suggest that comparisons of T-cell metabolism at different stages of RA and other autoimmune diseases will be a priority. "There are many ways to manipulate this pathway with available drugs," says Lipsky, but predicting whether any might be beneficial in RA "would depend upon a better understanding of the role of this defect in PFKFB3 expression in disease pathogenesis."

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