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"Meccanismi di controllo della risposta immune: il modello dei linfociti Th17 nell'uomo"

"Mechanisms controlling the adaptive immune responses: the human Th17 cell model"

In humans, Th17 cells have been implicated in the pathogenesis of chronic inflammatory disorders such as autoimmune diseases (Crohn's disease [CD], multiple sclerosis, psoriasis, rheumatoid arthritis) and allergic disorders (bronchial asthma, atopic dermatitis, and contact dermatitis). However, the assessment of IL-17A-producing CD4+ T cells in both inflamed tissues and biological fluids consistently revealed a low frequency of these cells in comparison with the high numbers of Th1 cells. The reason of the unexpected rarity of Th17 cells in the tissues and biological fluids of patients with autoimmune and chronic inflammatory disorders, despite their suggested pathogenic role, has remained unclear. One possible explanation may be that Th17 cells show a transient phenotype, resulting from their tendency to shift into Th1 cells in the context of inflammatory microenvironments. However, such a hypothesis could only partially account for this phenomenon, because very rare Th17 cells can be detected even in the initial phases of inflammation. Recently it has been demonstrated that Th17, unlike Th1, cells do not proliferate in response to stimulation with anti-CD3 plus anti-CD28 (anti-CD3-CD28), mainly because of both their inability to produce IL-2 and of a reduced IL-2 responsiveness. The defective IL-2 production by Th17 cells appeared to be related to their reduced c-Fos, c-Jun and nuclear factor of activated T-cells (NFAT) activity which associated with high expression of the IL-4-induced gene 1 (IL4I1) mRNA, encoding for a L-phenylalanine oxidase that has been shown to down-regulate CD3 expression in T cells. In the same study, a reduced S6ribo phosphorylation was found in human TH17 cells, suggesting a defect in PI3K-AKT-mTORC1 axis activation that could account for their lower responsiveness to IL-2. However, the mechanisms responsible for reduced IL-2 responsiveness of human IL-17 cells was not extensively investigated. Recent data demonstrate that this event is mainly related to high expression of musculin (MSC)/myogenic repressor (MyoR)/activated B-cell factor-1

(ABF-1) by Th17 cells.