SESSION II

IMMUNITY AND INFLAMMATION

Inflammatory Pathways in Immune-Mediated Diseases: What is downstream?

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Various T cell subsets, their differentiation pathways, and their signature cytokines have been identified as pivotal drivers of gut inflammation in patients with inflammatory bowel diseases (IBD). Cytokines have a crucial role in disease pathogenesis, as they control multiple aspects of the inflammatory response. In particular, the imbalance between pro- and anti-inflammatory cytokines that occurs in IBD perpetuates inflammation and tissue destruction. Crohn's disease is characterised by interleukin (IL)-12-induced mucosal TH1 cells producing Interferon (IFN)γ, tumor necrosis factor (TNF) and IL-6, while ulcerative colitis is marked by TH2-type cytokines such as IL-5 and IL-13. Furthermore, TH17 cells that are activated by IL-23 are present in increased numbers in in both Crohn's disease and ulcerative colitis. Cytokine signalling is mediated upon binding of cytokines to their specific receptors via intracellular activation of Janus kinases (JAKs: JAK1, JAK2, JAK3, TYK2). Some of the cytokines and JAK kinases are established targets for therapeutic approaches in IBD to suppress cytokine signalling in mucosal immune cells.[1] Here, improved understanding of molecular resistance mechanisms derived from modifications in the composition of mucosal immune cells in response to therapeutic pressure are essential to optimize personalized therapy in IBD. Developing therapeutic approaches that target anti-inflammatory pathways, the reduced ratio between regulatory and effector T cells in the inflamed mucosa, as well as the disturbed barrier function, might offer additional treatment options.[2]

Immune-mediated inflammatory diseases (IMIDs) are traditionally classified based on the predominant organ involvement (e.g., gut, joints, skin), but growing insights into key immune pathways and the development of specific antibodies that target signature cytokine hubs, have indicated that molecular classification would better reflect pathophysiological commonalities and mechanistic differences across IMIDs. Insights into signature cytokine hubs (e.g., TNF, IL-23, IL-17) and specific signalling pathways will have important clinical implications, as they might also enable us to identify molecular subtypes, improving individual clinical responses, and offering novel avenues for targeted intervention.[3]

References

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3. Schett G, McInnes IB, Neurath MF. Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs. *N Engl J Med*. 2021;385(7):628–39.