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The role and impact of tissue-resident memory T cells in allergic contact dermatitis

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Dear Editor,

Allergic contact dermatitis (ACD) is a type IV (delayed-type) hypersensitivity reaction, mediated by the host immune response to small molecules (< 500 Daltons), known as haptens, that contact the skin of sensitized individuals. The process is divided into 2 main phases: the induction phase and the elicitation phase. During induction, the hapten binds to a skin protein to form a complex recognized by the immune system. This complex activates and expands allergen-specific T cells, a process known as sensitization. After sensitization, during elicitation, re-exposure to the allergen leads to an intense immune response, resulting in the onset of dermatitis. ACD accounts for approximately 20% of contact dermatoses, and allergens differ greatly based on geographical region, personal habits, and hobbies.[1]

The discovery of tissue-resident memory T cells (TRM) in mice has transformed our understanding of skin immunity. These cells are not merely part of immune surveillance, they also form long-lived sentinels in the epidermal and dermal compartments, acting as central mediators of human skin health and disease. TRM cells play a key role in the defense against pathogens, cancer, and inflammatory skin diseases. They can arise from circulating memory T cells or from pre-existing cell populations in the skin, acting as the first line of defense against invading antigens in non-lymphoid peripheral tissues, including the skin, respiratory tract, and intestines. TRM plasticity enables them to differentiate into central memory T cells, depending on tissue microenvironment, which is regulated by local cytokines. The transcription factors HOBIT and BLIMP-1 are essential for their resident phenotype. In addition, TRM cells develop in response to skin infection and play a critical role in inflammatory response, contributing to the diverse pool of local memory T cells. TRM differentiation and maintenance are guided by signals such as IL-7, IL-15, and TGF-β, ensuring long-lasting defense without displacement of pre-existing populations.[2]

Recent studies have highlighted the pivotal contribution of TRM cells to the modulation of adaptive immune responses in allergic disorders such as rhinitis, asthma, atopic dermatitis, and contact dermatitis, with profound implications for prevention and treatment.[3]

TRM cells have a dual role in allergic diseases, acting as mediators and regulators. They coordinate allergic responses through the release of pro-inflammatory and chemotactic factors, activating tissues at the affected sites and recruiting immune cells to amplify the response. These cells also express ligands that attract resting memory T cells from the circulation, maintaining a feedback loop in the allergic response. In addition, they can reactivate $CD4^+$ and $CD8^+$ T cells in the presence of allergens and enhance antigen presentation by dendritic cells (DCs). Recent studies have shown that, upon allergen re-exposure, $CD4^+$ TRM cells produce cytokines such as IL-4, IL-5, and IL-13 (Th2 profile), IL-17 (Th17), and IFN-γ and TNF-α (Th1). IFN-γ, in particular, activates epithelial tissues and recruits immune cells, inducing the expression of CXCR3, CXCL9, and CXCL10. In the lungs, TRM cells reactivate $CD4^+$ and $CD8^+$ T cells, attracting eosinophils and $CD11c^+$ DCs to the inflamed site. However, TRM cells also express inhibitory checkpoints such as PD-1 and TIM-3, which attenuate allergic reactions, and their blockade may exacerbate these reactions. Whereas earlier studies associated $CD8^+$ TRM cells with the intensification of allergic conditions, recent evidence reveals their dual function in both the induction and regulation of allergic reactions.[3]

In ACD, TRM cells accumulate at the site of allergen contact during sensitization and trigger rapid and intense responses to re-exposure. They also play a key role in disease flare-ups, chronicity, and severity, positioning them as promising therapeutic targets.[4]

Active ACD lesions contain a mixed $CD4^+$/$CD8^+$ lymphocytic infiltrate, predominantly composed of $CD4^+$ cells expressing CCR10. Murine hapten-induced ACD studies have shown that long-term immunological

memory is mediated by CD4+ TRM cells, initially confined to sensitized areas until re-exposure to the allergen. Recent studies suggest that the severity of flare-ups is related to the density of epidermal CD8+ TRM cells. In mice, depletion of CD4+ TRM cells resulted in increased inflammatory response, suggesting a potential regulatory role, whereas CD8+ TRM cells appear to contribute to persistent inflammatory responses through rapid reactivation after allergen re-exposure. Although murine models have provided valuable insights into TRM functions, there are still significant differences compared to human immune responses. Additional translational studies will be required to determine how TRM cells interact with other cell populations in the skin and how their metabolism and functional profile may be modulated in order to develop new therapeutic approaches to ACD.[2]

Using various mouse models and cell depletion protocols, Gadsbøll et al. investigated the role of TRM cells in ACD flare-ups induced by the experimental allergen 1-fluoro-2,4-dinitrobenzene. The study demonstrated that CD8+ TRM cells promote massive neutrophil infiltration into the epidermis within 12 hours of re-exposure to the allergen. Neutrophil depletion before allergen re-exposure resulted in rapid resolution of flare-ups. In addition, CD8+ TRM cells were responsible for mediating neutrophil recruitment, inducing CXCL1 and CXCL2 production in the skin. Blocking the receptors of these chemokines inhibited both neutrophil infiltration and inflammatory reactions, suggesting that CD8+ TRM cells play a crucial role in flare-ups, facilitating neutrophil recruitment to the epidermis. Regarding the dynamics of skin-resident T cells, allergen exposure led to an accumulation of CD8+ TRM cells and displacement of dendritic epidermal T cells (DETCs), which are Tγδ cells specialized in epidermal immune surveillance. DETCs play a vital role in detecting pathogens or allergens and modulating local inflammatory response. DETC displacement after allergen exposure was mediated by the requirement for CD8+ T cells, as their absence prevented DETC migration. Compared with DETCs, CD8+ TRM cells exhibited a more robust inflammatory response and greater proliferative capacity, suggesting a metabolic advantage. These findings indicate that the metabolism of CD8+ TRM cells may be a promising therapeutic target for the treatment of ACD, since the magnitude of allergic reactions is directly related to the number of these cells in the skin.[5]

Future research should focus on unraveling the complex mechanisms underlying the longevity of TRM cells, their tissue-specific functions, and their dual role in flare-ups and regulation of allergic reactions. This will pave the way for innovative, targeted therapies, making allergy management more efficient and personalized. Ongoing efforts into integrating molecular, immunological, and clinical studies are essential for translating these insights into practical applications in allergy treatment.[3] We must remain attentive to these developments.

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