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Novel roles for IL-15 in T cell survival

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Abstract

Interleukin-15 (IL-15) is generally considered to be a regulator of T cell homeostasis because it works with other common gamma-chain cytokines like IL-2 and IL-7 to control the maintenance of naive and memory T cell populations. However, recent reports highlight new roles for IL-15 during the primary immune responses that involve promoting the survival of antigen-specific $CD8^+$ T cells. These findings illuminate a previously unanticipated role for IL-15 in the generation and resolution of the effector $CD8^+$ T cell response to pathogens.

Introduction and context

IL-15 plays a pivotal role in T-cell activation and effector functions, including T cell proliferation [1], interferon-γ and tumor necrosis factor-α production [2,3], chemokine production [4], and cytotoxicity [5]. In combination with other common gamma-chain cytokines, IL-15 also influences memory T cell homeostasis through the regulation of memory T cell numbers [6-8]. In this context, IL-15 drives the generation of antigen-specific memory T cells [8], promotes the survival of memory $CD8^+$ T cells [9], and stimulates the homeostatic proliferation of memory phenotype $CD8^+$ T cells [10-12]. Recent publications have described new roles for IL-15 in primary immune responses, where it provides a survival signal to effector $CD8^+$ T cells during primary responses to pathogens [13,14].

Major recent advances

Recently, Sanjabi *et al.* [14] demonstrated that transforming growth factor-β (TGF-β) and IL-15 have opposing effects on the survival of the short-lived effector T cells (defined on the basis of KLRG1 [killer cell lectin-like receptor G1] and CD127 expression). Using a model system of *Listeria monocytogenes* infection, the authors demonstrated that TGF-β promoted apoptosis of effector $CD8^+$ T cells whereas IL-15 promoted their survival. The opposing effects of TGF-β and IL-15 were not a result of direct inhibition of signaling in the respective signaling pathways; rather, the differential survival appeared to result from the competing effects of these pathways on the anti-apoptosis molecule Bcl-2 (B-cell lymphoma 2). Importantly, these data supported a role for IL-15 in promoting the survival of effector T cells during the contraction phase of the T-cell response to infection.

This concept was extended by McGill *et al.* [15], who revealed a role for IL-15 in promoting the survival of antigen-specific $CD8^+$ T cells in the lung after influenza virus infection. Using a dendritic cell (DC) depletion/reconstitution model, their previous work had demonstrated that influenza-specific $CD8^+$ T cell responses in the lung depended on T-cell interactions with pulmonary DCs [15]. When pulmonary DCs were depleted using clodronate-liposomes, antigen-specific $CD8^+$ T cell responses were decreased, and the virus was not cleared as efficiently. The blunting of the $CD8^+$ T-cell response was not due to reduced proliferation of T cells in the absence of DC signals, as DC depletion did not significantly alter the proliferation of antigen-specific $CD8^+$ T cells responding to the infection. Instead, it appeared that the pulmonary DCs were promoting the survival of the antigen-specific T cells in the lung environment. This enhanced $CD8^+$ T-cell survival was dependent on trans-presentation of IL-15/IL-15 receptor (IL-15R) complexes by pulmonary DCs, as blocking IL-15 or IL-15R on DCs resulted in increased $CD8^+$

T-cell apoptosis in the lung. Together, these data support a two-hit model for promoting effective $CD8^+$ T cell responses: a first hit in the lymph node that primes T-cell proliferation and migration to infected tissue, and a second hit that provides a survival signal to the effector T cells.

Future directions

While IL-15 has been best-appreciated for its contributions to memory T cell homeostasis, these new findings highlight the importance of IL-15 in promoting the survival of antigen-specific $CD8^+$ T cells during primary responses to infection and suggest several areas for further investigation. First, the location of the DC-T-cell interaction that promotes the survival of the $CD8^+$ T cells needs to be determined. One possibility is that IL-15 trans-presentation by DCs takes place in inducible bronchus-associated lymphoid tissue that develops in the lungs after infection [16]. Alternatively, the DC-T-cell interactions could take place in the lung-draining lymph node, as the pulmonary DC subsets continue to migrate to the lung-draining lymph node through day 9 post-infection [17]. Second, the importance of IL-15 for the survival of memory T cell populations during a secondary pathogen challenge needs to be examined [18,19]. Finally, the contribution of IL-15 trans-presentation to the survival of $CD4^+$ T cells during the primary immune response to pathogens needs to be determined. In this regard, IL-15 promotes the activation of $CD4^+$ T cells – including their cytokine production [20], CD154 expression [21], proliferation [22], and the maintenance of memory populations [23] – yet the effect of IL-15 on $CD4^+$ T-cell survival during primary immune responses is unknown.

Manipulating T cell survival via the IL-15 pathway offers the potential for the development of novel disease therapies. One such therapeutic approach was recently reported by Wang *et al.* [24], who alleviated joint inflammation in a model of arthritis by targeting toxins to IL-15R-expressing cells. This report revealed the potential for elimination of immunopathogenic T cells and offers a possible therapeutic pathway to treat T-cell-mediated diseases like multiple sclerosis or type I diabetes. Alternatively, the anti-apoptotic effects of IL-15 could also be utilized to enhance survival of effector T cells. Toward this end, Hoyos *et al.* [25] engineered tumor-specific T cells with an IL-15 construct, which enhanced T-cell survival and resulted in improved anti-tumor effects. Together, these studies reveal the potential for therapies targeting the IL-15 pathway in the treatment of disease and reinforce a role for IL-15 in promoting the survival of effector $CD8^+$ T cells during the immune response.

Abbreviations

DC, dendritic cell; IL, interleukin; IL-15R, IL-15 receptor; TGF-β, transforming growth factor β.

Competing interests

The authors declare that they have no competing interests.

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