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Opinion Article

Bystander Activation of T Cells in Viral and Autoimmune Diseases

Xia Yuze*

Department of Immunology, Tsinghua University, Beijing, China

DESCRIPTION

The immune system is a finely tuned network designed to detect and eliminate pathogens while preserving self-tolerance. Central to this defense are T cells, that recognize specific antigens presented by Major Histocompatibility Complex (MHC) molecules. While conventional T cell activation depends on antigen recognition through the T Cell Receptor (TCR), an alternative mode of activation bystander activation occurs independently of specific antigen engagement. In this process, T cells become activated by inflammatory cytokines or other environmental cues rather than direct TCR signaling. Bystander activation has emerged as an important phenomenon in both viral infections and autoimmune diseases, influencing disease progression, tissue damage, and the balance between protective immunity and pathological inflammation. Understanding this mechanism provides crucial insights into immune regulation and potential therapeutic strategies.

Bystander activation in viral infections

During viral infections, the immune system is exposed to a surge of inflammatory cytokines, such as interleukin-12 (IL-12), interleukin-18 (IL-18), and interleukin-15 (IL-15). These cytokines can stimulate memory or naive T cells independently of TCR engagement, leading to bystander activation. This process allows for a rapid, broad-spectrum immune response, potentially enhancing antiviral defense before pathogen-specific T cells expand.

For instance, in viral infections like influenza, Cytomegalovirus (CMV), or hepatitis B, bystander activation contributes to early cytokine production, including interferon-gamma, that helps control viral replication. Natural Killer (NK) cells, along with T cells undergoing bystander activation, synergize to produce inflammatory mediators that amplify the antiviral response. However, this rapid activation comes with risks. Excessive bystander activation can lead to immunopathology, as activated T cells may target healthy tissues or amplify local inflammation. In severe viral infections, such as COVID-19, bystander T cell activation has been implicated in hyperinflammatory responses, contributing to tissue damage and disease severity.

Notably, bystander activation is more prominent in memory T cells, that possess heightened sensitivity to cytokines compared to naive T cells. This property ensures a faster response but also predisposes tissues to collateral damage. The balance between protective bystander responses and pathological inflammation is therefore a critical determinant of disease outcome in viral infections.

Bystander activation in autoimmune diseases

In autoimmune diseases, bystander activation contributes to the breakdown of self-tolerance and the amplification of pathogenic immune responses. Inflammatory environments, often triggered by infections, tissue injury, or dysregulated innate immunity, generate cytokines that can activate T cells independently of antigen specificity. Once activated, these T cells produce effector cytokines and chemokines, that recruit additional immune cells to the affected tissue, exacerbating inflammation.

For example, in Multiple Sclerosis (MS), pro-inflammatory cytokines such as IL-6, and IL-23 can induce bystander activation of T cells in the central nervous system. These T cells, although not specific for myelin antigens, release inflammatory mediators that amplify local tissue damage. Similarly, in type 1 diabetes, viral infections have been proposed to trigger bystander activation of autoreactive T cells, accelerating the destruction of pancreatic cells. This phenomenon underscores the connection between infections, immune activation, and the initiation or exacerbation of autoimmune disease.

Bystander activation is also implicated in systemic autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). In these conditions, dysregulated cytokine networks, including type I interferons and tumor necrosis factor-alpha, can activate T cells broadly, promoting autoantibody production and tissue inflammation. The process highlights a key challenge in autoimmunity: immune activation is not strictly antigen-specific, meaning that inflammatory triggers can broadly activate T cells, amplifying disease even in the absence of new autoantigens.

Importantly, bystander activation may explain infections often precipitate flares in autoimmune diseases. Viral or bacterial

Correspondence to: Xia Yuze, Department of Immunology, Tsinghua University, Beijing, China, Email: xia@gmail.com

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pathogens trigger cytokine storms, activating T cells indiscriminately and amplifying pre-existing autoimmunity. Conversely, controlled modulation of bystander activation could be harnessed therapeutically to enhance immune responses against infections or tumors without inducing autoimmunity.

CONCLUSION

Bystander activation of T cells represents a critical mechanism by that the immune system can respond rapidly to inflammatory cues without direct antigen recognition. In viral infections, this process provides early protection by amplifying cytokine responses and supporting innate immunity, yet it carries the risk of immunopathology when excessively activated. In autoimmune diseases, bystander activation contributes to the amplification of tissue-damaging immune responses, linking infections or inflammatory triggers to disease flares. The phenomenon illustrates the dual-edged nature of immune activation it can be protective in the context of infection but pathological in the setting of autoimmunity. Understanding the molecular pathways, cellular targets, and regulatory checkpoints of bystander T cell activation offers significant opportunities for therapeutic interventions. Modulating this response may help enhance antiviral immunity while minimizing tissue damage, or conversely, suppress pathogenic bystander activation to control autoimmune disease progression. Ultimately, the study of bystander T cell activation deepens our understanding of immune system plasticity and the fine balance between defense and self-damage.