

Immune Thresholds: Balancing Tolerance, Activation, and Exhaustion

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DESCRIPTION

The immune system operates not as a blunt instrument of defense but as a finely tuned network that continuously negotiates threshold points at which signals are either ignored, tolerated, or acted upon. The concept of immune thresholds is central to understanding the body maintains equilibrium in the face of constant internal and external challenges. Every day, immune cells encounter a vast array of molecular cues, from harmless environmental antigens to dangerous pathogens and altered self-components. The decision to respond or remain silent is not binary; instead, it is governed by dynamic thresholds shaped by genetic programming, environmental exposures, and cellular context. These thresholds ensure that the immune system can defend effectively without causing unnecessary damage to host tissues, highlighting a delicate balance between tolerance, activation, and exhaustion.

Tolerance represents the foundational layer of immune regulation, preventing harmful reactions against self-antigens and innocuous substances. Central tolerance mechanisms, established during lymphocyte development in primary lymphoid organs, eliminate or reprogram cells that strongly recognize self. Peripheral tolerance further refines this process by controlling mature immune cells through regulatory pathways, including the action of regulatory T cells, inhibitory receptors, and anti-inflammatory cytokines. These systems collectively set a high threshold for activation against self, thereby reducing the risk of autoimmunity. However, tolerance is not absolute; it must remain flexible enough to allow responses against emerging threats. Dysregulation of tolerance thresholds can lead to autoimmune diseases, allergies, or chronic inflammatory conditions, illustrating the consequences of a system that either reacts too readily or fails to restrain itself.

Activation as a context-dependent decision

Activation occurs when immune thresholds are surpassed, triggering a coordinated response to eliminate perceived threats. This process depends on the integration of multiple signals,

including antigen recognition, co-stimulatory interactions, and inflammatory cues. For instance, a T cell requires not only recognition of its specific antigen but also secondary signals from antigen-presenting cells to achieve full activation. This multi-signal requirement effectively raises the activation threshold, ensuring that responses are initiated only under appropriate conditions. Moreover, the strength, duration, and combination of signals influence the magnitude and quality of the response. Subthreshold stimulation may lead to partial activation or anergy, while optimal stimulation results in robust effector functions. Thus, activation is not merely about crossing a threshold but about how that threshold is modulated in real time by the immune environment.

The context in which activation occurs is equally critical. Infections typically provide strong inflammatory signals that lower activation thresholds, enabling rapid and effective responses. In contrast, non-inflammatory contexts maintain higher thresholds, promoting tolerance. This adaptability allows the immune system to prioritize threats while avoiding unnecessary activation. However, pathogens and tumors can exploit these mechanisms by manipulating thresholds to evade detection. For example, certain viruses interfere with antigen presentation or co-stimulatory signaling, effectively raising the activation threshold beyond reach. Similarly, tumor cells may create an immunosuppressive microenvironment that dampens immune activation. These strategies highlight the evolutionary arms race between the immune system and its adversaries, with thresholds serving as a key battleground.

Exhaustion and the cost of persistent stimulation

While activation is essential for defense, prolonged or excessive stimulation can push immune cells toward exhaustion, a state characterized by reduced functionality and diminished responsiveness. Immune exhaustion is most commonly observed in chronic infections and cancer, where continuous antigen exposure prevents the resolution of immune responses. Exhausted T cells exhibit distinct molecular and functional features, including

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the upregulation of inhibitory receptors, altered metabolic states, and impaired cytokine production. These changes effectively raise the threshold required for reactivation, making it difficult for the immune system to regain control over persistent threats.

Exhaustion can be viewed as a protective mechanism, preventing immune-mediated damage during prolonged stimulation. By dampening responses, the immune system avoids excessive inflammation that could harm host tissues. However, this protective aspect comes at a cost: reduced to eliminate pathogens or tumor cells. The balance between beneficial restraint and detrimental suppression is delicate, and tipping too far toward exhaustion can lead to disease progression. Recent advances in immunotherapy, particularly immune checkpoint blockade, aim to lower these heightened thresholds and reinvigorate exhausted cells. While these approaches have shown remarkable success in certain cancers, they also underscore the risks of disrupting immune balance, as excessive reactivation can lead to immune-related adverse effects.

The interplay between tolerance, activation, and exhaustion is

not static but continuously evolving. Immune thresholds are influenced by factors such as age, metabolic state, microbiome composition, and prior immune experiences. For example, aging is associated with changes in threshold dynamics, often resulting in diminished activation capacity and increased susceptibility to infections. Conversely, repeated exposures to pathogens can recalibrate thresholds, enhancing responsiveness or, in some cases, promoting exhaustion. Understanding these dynamic adjustments is crucial for developing strategies to modulate immune responses in clinical settings.

CONCLUSION

Ultimately, the concept of immune thresholds provides a unifying framework for understanding immune behavior across health and disease. Rather than viewing immune responses as simply “on” or “off,” this perspective emphasizes gradation, context, and adaptability. By appreciating how thresholds are set, maintained, and altered, researchers and clinicians can better predict and manipulate immune outcomes.