The molecular basis of trained immunity: transcriptional and epigenetic reprogramming.

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Introduction

The immune system's ability to remember previous encounters with pathogens is a fundamental defense mechanism that protects organisms against recurrent infections. Traditionally, immunological memory has been associated with adaptive immunity, where B and T lymphocytes acquire specificity against specific antigens. However, emerging research has revealed a fascinating phenomenon known as "trained immunity." This concept suggests that the innate immune system, particularly innate immune cells like monocytes and macrophages, can undergo transcriptional and epigenetic reprogramming following exposure to certain stimuli, leading to enhanced responsiveness upon reencounter with the same or unrelated pathogens. In this article, we explore the molecular basis of trained immunity and its implications for human health [1].

Trained immunity was first described as the long-term and nonspecific enhanced functional responses of innate immune cells following their initial activation by a stimulus. The primary stimuli responsible for inducing trained immunity include certain pathogens, vaccines, and pathogen-derived molecules. Specifically, the most extensively studied phenomenon of trained immunity occurs after exposure to β-glucan, a component found in the cell walls of fungi. Other stimuli, such as certain viral and bacterial infections, also induce trained immunity. The molecular basis of trained immunity involves significant changes in gene expression profiles within innate immune cells. Key transcription factors, such as NF-κB and AP-1, play pivotal roles in orchestrating this process. The initial exposure to a trained immunity-inducing stimulus activates these transcription factors, leading to the up regulation of pro-inflammatory cytokines and antimicrobial effectors. Additionally, the induction of long-lasting changes in chromatin accessibility also contributes to the establishment of trained immunity. This process involves the remodelling of chromatin structure through the addition or removal of chemical tags, such as DNA methylation and histone modifications. These epigenetic modifications can lock immune genes in an "on" state, enabling a more rapid and robust response upon secondary exposure to a pathogen. Epigenetic modifications, particularly DNA methylation and histone modifications play a crucial role in trained immunity. Following stimulation, innate immune cells undergo alterations in DNA methylation patterns, particularly at enhancer regions of immune-related genes [2,3].

This DE methylation of enhancer regions allows for increased accessibility of transcription factors, enabling enhanced gene expression upon reactivation. Histone modifications, including acetylation, methylation, and phosphorylation, also participate in the epigenetic reprogramming process. These modifications can either promote or inhibit transcription, thereby regulating the expression of immune genes. For instance, the acetylation of histones is associated with increased gene expression, while histone methylation can have both activating and repressive effects depending on the specific residue modified. Trained immunity not only enhances the response to the original stimulus but also provides cross-protection against unrelated pathogens. This phenomenon, known as heterologous immunity, involves the crosstalk between different signalling pathways in innate immune cells. For example, β-glucan-induced trained immunity can enhance the response to subsequent bacterial infections, showcasing the versatility and broader implications of this mechanism. Innate immunity is a remarkable and indispensable defence mechanism that acts as the body's first line of defence against a wide array of pathogens. From physical and chemical barriers to cellular defences and inflammation, these innate responses work together to protect us from infections and maintain our well-being. Understanding innate immunity not only sheds light on the fascinating intricacies of our immune system but also provides valuable insights for the development of therapies and vaccines to combat infectious diseases and other immune-related disorders [4,5].

Conclusion

Trained immunity represents a ground-breaking concept in immunology, challenging the traditional view of memory confined only to adaptive immunity. The molecular basis of trained immunity involves intricate transcriptional and epigenetic reprogramming within innate immune cells. This reprogramming results in an enhanced and sustained immune response upon exposure to a pathogen, providing improved protection against infections. Understanding the mechanisms underlying trained immunity opens up new avenues for the development of novel vaccines and immunotherapies that harness the innate immune system's potential to combat

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diseases more effectively. As research in this field continues to advance, it holds great promise for revolutionizing the way we approach immune-mediated diseases and infectious threats.

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