

Trained Innate Immunity: New Immunological Memory Mechanisms



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Abstract

Trained innate immunity attracts more and more attention in recent years. Innate immune memory is observed in natural killer cells, monocytes and macrophages after being trained by certain antigens and non-specific strong immune responses may occur after the secondary stimulation. Mechanism studies reveal that induction of trained innate immunity depends on epigenetic reprogramming. In this article, the phenomenon, mechanisms and possible applications of the trained innate immunity are reviewed.

Keywords: Trained Innate Immunity; Bacillus Calmette-Guerin; β -Glucan; Epigenetic Reprogramming

Abbreviations: NK cells: Natural Killer cells; BCG: Bacillus Calmette-Guerin; HSV: Herpes Simplex Virus; LPS: Lipopolysaccharide; MDP: Muramyl Dipeptide; NOD2: Nucleotide Binding Oligomerization Domain Containing 2; Raf-1: Raf-1 Proto-Oncogene Serine/Threonine Kinase; RIP2: Receptor-Interacting Protein Kinase; cAMP: Cyclic Adenosine Monophosphate; PKA: Protein Kinase A; mTOR: Mammalian Target of Rapamycin complex

Introduction

Innate immune cells can be trained by certain vaccines, pathogens or antigens and exhibit strong non-specific immune responses upon secondary infections, which is similar to the memory of acquired immunity [1]. This phenomenon is called trained innate immunity. A character of trained innate immunity is significantly more cytokines production after the secondary stimulation, single or multiple pathogens, on trained innate cells [2].

The Trained Innate Immune Cells and Antigens

presently, studies on the trained innate immunity mainly focus on NK cells, monocytes and macrophages [3]. The trained NK cells induced by BCG showed protective effects on the following systemic *Candida albicans* infection after 1 week [1]. In addition to the stimulation of pathogens or vaccines, the memory of NK cells could also be trained by cytokine combinations including IL-12, IL-15 and IL-18 [4,5]. Besides NK cells, macrophages or monocytes could be trained by various fungi, bacteria, virus or purified legends [6]. BCG trained monocytes and macrophages play important roles in non-specific protections against infections caused by *C. albicans* [7,8], *Staphylococcus aureus*, *Salmonella enteritidis*, *Mycobacterium fortuitum*, *Yersinia pestis*, *Klebsiella pneumoniae*, *Schistosoma mansoni*, HSV, vaccinia virus, and *Leishmania major* in mice [9]. Moreover, mac

rophages trained by *C. albicans* could protect mice against reinfections by not only virulent *C. albicans* but also Gram-positive bacteria *S. aureus* [10]. Monocytes trained by *Saccharomyces cerevisiae* or *S. cerevisiae*-derived chitin exhibited enhanced ability to kill live *C. albicans*, *S. aureus*, and *Escherichia coli* in contrast to non-trained control cells [11].

In recent years, more and more researchers have focused their interest on antigens that could induce trained innate immunity. Besides BCG and β -glucan, two widely studied antigens, many other antigens have also been reported to induce trained innate immunity [12], such as *S. cerevisiae*, *S. cerevisiae*-derived chitin, LPS of low dose, *Plasmodium falciparum* [13], vaccinia virus vaccine [14], measles vaccine [15] and TLR9 legend CpG ODN [16]. Collectively, antigens that could induce trained innate immunity include bacteria, fungi and viruses. We believe that more antigens can be found in the future.

The Mechanisms of Training on Innate Immune Cells

The trained innate immunity was originally studied in plants, which are lack of adaptive immune responses. The immune responses of plants were divided into systemic acquired resistance

(SAR) and induced systemic resistance (ISR) according to different inducing factors and pathways. When secondary infections occurred in plants, both SAR and ISR could produce strong non-specific immune responses to the pathogens, which were persistent or even permanent [17]. Recent evidence showed that the SAR of plants was mainly regulated by chromatin remodeling and epigenetic modifications. Those immune mechanisms of plants provided important insights into the molecular mechanisms of trained immunity in mammals.

Some research progress has been made on trained immunity in mammals. Mice vaccinated with BCG showed enhanced pro-inflammatory cytokine production in response to secondary pathogenic infections, and that was attributed to the trained immunity of NK cells and monocytes. The BCG-induced trained immunity depended on phagocytosis and the recognition of MDP through intracellular NOD2 receptors. Through NOD2 receptors, Rip2 kinase was activated and further the activated kinase promoted an epigenetic reprogramming through histone tri-methylation at H3K4 (H3K4me3) (Figure 1) [18]. The epigenetic programming induced by BCG in vivo could persist for more than one year [19]. In addition to the BCG-induced H3K4me3, training induced by *C. albicans* or β -glucan was also associated with epigenetic modifications, particular stable changes in histone tri-methylation at H3K4 and histone acetylation at H3K27. Further mechanism studies identified two crucial signal pathway in the trained immunity induced by *C. albicans* or β -glucan. One was the non-canonical Raf-1-dependent pathway, which can be activated by C-type lectin receptor Dectin-1. The other was the cAMP-PKA-dependent signal pathway. Besides, trained innate cells exhibited great changes in the cellular metabolisms, as the genes involved in glucose and amino acids metabolisms were unregulated [10]. More specifically, training with β -glucan resulted in a Dectin-1/Akt/mTOR/HIF-1 α pathway activation that switched cellular metabolism from oxidative phosphorylation to glycolysis (Figure 1) [20]. Trained by *C. albicans* or β -glucan, murine monocytes or macrophages became more capable of producing inflammatory cytokines, as well as improved ability of phagocytosis and killing pathogens [21].

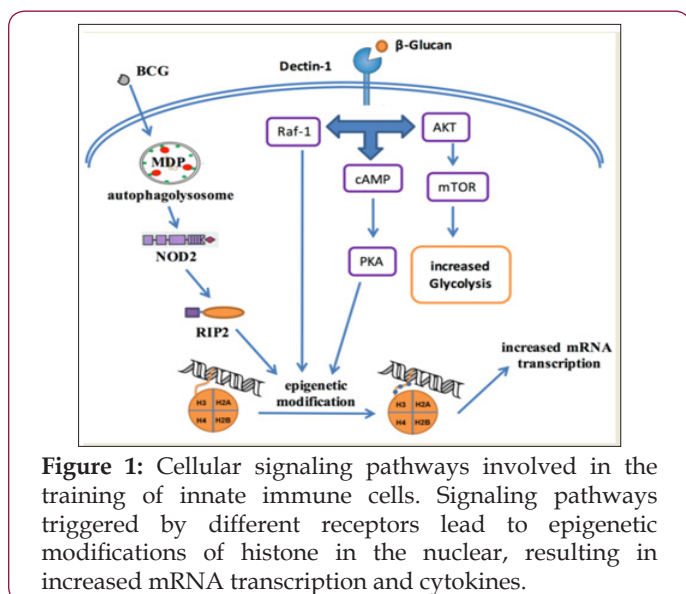


Figure 1: Cellular signaling pathways involved in the training of innate immune cells. Signaling pathways triggered by different receptors lead to epigenetic modifications of histone in the nuclear, resulting in increased mRNA transcription and cytokines.

Conclusion

The reveal of trained innate immunity has updated our understanding of immune memory. In the NK cells, monocytes and macrophages, after training by various antigens, epigenetic changes/modifications and rewiring of gene transcription occurred, which may lead to immune memory. This feature of innate cells could bring benefits to the host, such as protection against infectious pathogens or reversion of some tumor processes. Discovering new immune adjuvants based on the theory of trained immunity is a promising strategy to conquer infectious diseases [22]. Nevertheless, further studies concerning trained immunity in different diseases are still needed [23], which will benefit the discovery of new therapeutic agents?

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