Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Trained immunity as a novel therapeutic strategy

Vera P Mourits[1], Jac CHM Wijkmans[2], Leo AB Joosten[1] and Mihai G Netea[1,3]

Recent studies have shown that upon certain vaccinations or infections human innate immune cells can undergo extensive metabolic and epigenetic reprogramming, which results in enhanced immune responses upon heterologous re-infection, a process termed *trained immunity*. Trained immunity has also been shown to be inappropriately activated in inflammatory diseases. This provides the potential for identifying novel therapeutic targets: potentiation of trained immunity could protect from secondary infections and reverse immunotolerant states, while inhibition of trained immunity might reduce excessive immune activation in chronic inflammatory conditions. By targeting specific mechanisms of trained immunity on either immunologic, metabolic or epigenetic level, novel therapeutic approaches could be developed.

Addresses
[1] Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands
[2] INNTREST Consultancy BV, Oss, The Netherlands
[3] Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany

Corresponding author: Netea, Mihai G (mihai.netea@radboudumc.nl)

Current Opinion in Pharmacology 2018, **41**:52–58

This review comes from a themed issue on **Immunomodulation**

Edited by **Ed Lavalle** and **James McLachlan**

https://doi.org/10.1016/j.coph.2018.04.007

Introduction

The ability to induce memory is an important feature of the adaptive immune system, yet an increasing body of evidence shows that the innate immune system is also able to mount a memory response. It is known that plants and insects, which lack adaptive immunity, show enhanced nonspecific protection to reinfection [1–3]. Moreover, in *Candida albicans* vaccinated mice it has been shown that a partial protection to reinfection can be induced through T-cell and B-cell independent mechanisms [4]. Recently, it has been shown that infections and vaccinations are able to induce an enhanced immune response in monocytes upon nonspecific restimulation, a process termed trained immunity. β-Glucan, a major cell wall component of *C. albicans*, as well as the Bacillus Calmette-Guérin (BCG) vaccine are able to induce trained immunity, whereas lipopolysaccharide (LPS) stimulation in monocytes results in tolerance [5–7]. β-Glucan and BCG induce trained immunity in monocytes via pattern recognition receptors (PRRs) dectin-1 and NOD2 respectively, leading to enhanced signaling of the Akt (protein kinase B)–mTOR (mammalian target of rapamycin)–HIF-1α (hypoxia-inducible factor-1α) pathway, modifications in metabolic pathways, and epigenetic rewiring [5,6] (Figure 1). Unfortunately, not only microbial ligands can induce trained immunity after infection or vaccination, but also endogenous ligands can inappropriately activate trained immunity, thereby contributing to chronic inflammation, as has been shown in atherosclerosis [8] or gout [9].

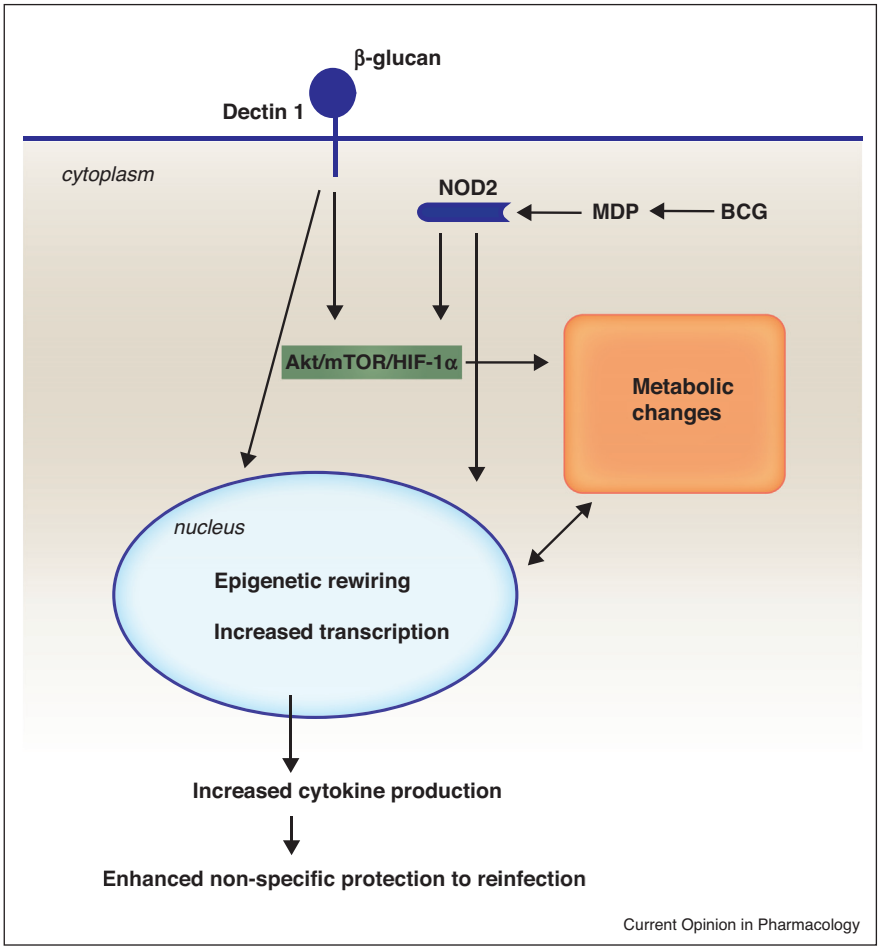
The recent insights in trained immunity could have important implications for the development of novel therapeutic targets for immune-mediated diseases. Interestingly, BCG vaccinated children in West Africa show a lower overall mortality by decreased morbidity due to infections [10••], and healthy volunteers vaccinated with BCG show an enhanced pro-inflammatory cytokine profile upon nonspecific restimulation in *ex vivo* monocytes, persisting for at least three months [5]. Currently, inducers of trained immunity are already used to treat diseases, such as muramyl tripeptide (MTP) for osteosarcoma [11] and BCG in bladder cancer [12] through mechanisms that likely involve induction of autophagy [13]. In addition to improvement of vaccines, it would be very interesting to modulate trained immunity in humans with maladaptive immune responses to restore a balanced immune function.

In this review, we will provide a short overview on the role of trained immunity in the pathophysiology of diseases, and discuss potential therapeutic targeting strategies in the context of trained immunity on the immunological, metabolic and epigenetic level.

Trained immunity in the pathophysiology of diseases

Enhanced immune responses induced by trained immunity, as reflected by an increased interleukin (IL)-6, IL-1β, and tumor necrosis factor α (TNFα) production, might lead in the long term to development and/or persistence of chronic inflammatory conditions such as arthritis or atherosclerosis. It is already known that a high glucose environment drives a pro-inflammatory profile

Figure 1



The concept of trained immunity. β-Glucan and BCG induce trained immunity in monocytes via pattern recognition receptors dectin-1 and NOD2 respectively, leading to enhanced signaling of the Akt–mTOR–HIF-1α pathway, modifications in metabolic pathways, and epigenetic rewiring. This results in increased pro-inflammatory cytokine production and enhanced non-specific protection to reinfection.

which remains even after introduction to a normal glucose environment, called hyperglycemic memory [14]. Furthermore, metformin, an mTOR inhibitor leading to inhibition of trained immunity [15••,16••], is associated with anti-inflammatory effects in atherosclerosis and is administered to type 2 diabetes patients [17,18]. Recently, it has been shown that endogenous danger ligands such as oxidized low density lipoprotein (oxLDL) or lipoprotein A, both involved in the pathogenesis of atherosclerosis, are able to induce training in monocytes *in vitro*. By training monocytes with oxLDL, genes involved in metabolic processes important for atherogenesis are induced, and histone methylation plays a crucial role in the long-term persistence of these effects. The trained monocytes have a propensity to differentiate into foam cells and show enhanced expression of scavenger receptors [8]. Moreover, a western type diet induces trained immunity in a mice model for atherosclerosis, which was dependent on the NLRP3 inflammasome. This occurs already at the level of granulocyte-monocyte precursors and persisted for several months [19•].

By contrast, enhanced immune responses induced by trained immunity might be beneficial in immunotolerant states occurring in sepsis or cancer. In sepsis, an imbalanced interaction between epigenetic and metabolic pathways in immune cells is observed [20], and *in vitro* it has been shown that tolerized and trained macrophages have a different epigenetic and metabolic state [15••,21]. Importantly, the training stimulus β-glucan is able to reverse LPS-induced tolerance in monocytes *ex vivo* from volunteers with experimental endotoxemia, by recovering the induction of ~60% of tolerized genes and reversing histone modifications [22•]. Similarly, tumor-associated macrophages have a long-term phenotype of anti-inflammatory M2 macrophages, and exert inhibitory effects on $CD8^+$ cytotoxic lymphocytes [23]. Therefore, inducers of trained immunity are of great