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Review

Trained immunity: A smart way to enhance innate immune defence

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ABSTRACT

The innate arm of the immune system is generally viewed as primitive and non-specific and – in contrast to the adaptive immune arm – not to possess memory.

However in plants and invertebrate animals that lack adaptive immunity, innate immunity will exhibit a prolonged enhanced functional state after adequate priming. A similar enhancement of function of the innate immunity has occasionally been described in vertebrates, including humans.

Over the past few years we have studied this phenomenon in greater detail and we have coined the term 'Trained (innate) immunity' (TI).

TI can be induced by a variety of stimuli, of which we have studied BCG and β-glucan in greater detail. The non-specific protective effects of BCG that have been observed in vaccination studies in the literature are probably due to TI.

Monocytes and macrophages are among the main cells of the innate immune arm that can be trained. We have discovered that both BCG (via NOD2 signalling) and β-glucan (via dectin-1) induce epigenetic reprogramming, in particular stable changes in histone trimethylation at H3K4. These epigenetic changes lead to cellular activation, enhanced cytokine production and a change in the metabolic state of the cell with a shift from oxidative phosphorylation to aerobic glycolysis.

TI is not only important for host defence and vaccine responses, but most probably also for diseases like atherosclerosis. Modulation of TI is a promising area for new treatments.

1. Introduction

Immunological textbooks teach that the immune system comprises of two arms: the innate and the adaptive immunity arms. The innate arm also indicated as natural or non-specific is generally viewed as primitive and perhaps even inferior to the adaptive, specific component, which is considered sophisticated due to its specificity and the capacity to mount memory. In this review we will challenge this view showing that there is considerable more sophistication in the innate component of the immune system than thought.

It should be realised that the dichotomy between the innate and the adaptive components of the immune system is a man-made simplification and it is not so sharp as generally thought. Many cell types of the immune system play a role in both arms. For instance, the various T lymphocyte subsets are not only operating in the adaptive arm but also as nonspecific cell populations such as innate lymphoid cells (ILCs) or γδ T-lymphocytes that produce cytokines. Likewise macrophages, activated by secretory products of specific T cells, are an important set of effector cells within the adaptive arm. This means that the paradigm that we will discuss in this paper, that of trained innate immunity (TI), does not pertain only to the innate immune component but is likely also to play a major role in the adaptive arm.

2. Some basic observations

A couple of years ago, we performed a series of experiments in human volunteers who were vaccinated with the mycobacterial vaccine BCG. Before and 2 weeks after vaccination the peripheral mononuclear blood cells were isolated and exposed to stimuli such as BCG, *Staphylococcus aureus*, *Candida albicans*, or bacterial lipopolysaccharide (LPS). As expected after the vaccination, there was a clearly enhanced production of cytokines like interferon-γ compared to the production before vaccination. The likely explanation would be that a population of T lymphocytes specific for BCG would be responsible for the enhanced production. Serendipitously, however, we observed that also the responses to the other, unrelated stimuli were significantly enhanced.

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A search of the literature taught us that such non-specific effects of BCG had been seen before. Most impressive in this respect were the observations of Garly et al. (2003) with BCG vaccination in West-African young children. They observed that BCG has an impressive effect on childhood survival, which cannot be explained by the specific effect of BCG, i.e., prevention of death due to mycobacterial infection.

Also in experimental animals, BCG had been shown to have such non-specific effects. The survival of mice infected with systemic candidiasis was significantly improved by preceding BCG vaccination (Van't Wout et al., 1992).

A similar observation, albeit not with BCG, but with a *C. albicans* strain with attenuated virulence due to incapacity to form hyphae, was made by Bistoni and coworkers. Inoculation with this strain not only protected the mice against a virulent *C. albicans*, but also against bacteria (Bistoni et al., 1986). Unexpectedly, the protection was independent of T lymphocytes (Bistoni et al., 1988), but dependent on macrophages (Bistoni et al., 1986) and proinflammatory cytokines (Vecchiarelli et al., 1989).

In recent years, Mantovani and coworkers have also described adaptive properties of the innate immune system related to plasticity of macrophages (Biswas and Mantovani, 2010; Bowdish et al., 2007).

3. Phylogenetic observations

A more thorough search of the literature led us to reports in the literature on similar enhancement of antimicrobial function in invertebrates. Priming of the invertebrate organisms with non-specific stimuli had been found to be protective against secondary challenge with a range of pathogens unrelated to the priming stimulus. For example, LPS injection in mealworm beetles was shown to protect them against fungi. There are many other examples, which we have reviewed elsewhere (Netea et al., 2011). The protection provided in this manner, however, was found not to be totally non-specific (Pham et al., 2007). Regarding the mechanism behind the protective effect, activation of haematocytes of the invertebrates through activation of Toll was found (Pham et al., 2007). The phenomenon of enhanced innate resistance to infection appeared also to be present in plants and has been described in the literature as "systemic acquired resistance" (SAR) since 1933 (Chester, 1933). This phenomenon is found in a large variety of plants against a wide spectrum of microorganisms; significant resources and research have been devoted to elucidate the mechanisms behind SAR (for reviews see e.g., Durrant and Dong, 2004).

Based on our own observations described above and these data in the literature, we proposed the term 'Trained immunity' (TI) for these memory characteristics of the innate immunity (Netea et al., 2011), and decided to investigate it in more detail.

4. Trained immunity induced by *Candida* and β-glucan

In this research we focused on TI induced by *C. albicans* and TI induced by mycobacteria (i.e., BCG). Using the *Candida* model in vivo, we could confirm the earlier studies of Bistoni's group (Bistoni et al., 1988) that exposure to a low dose of *C. albicans* was able to induce protection against reinfection with *C. albicans* in mice deficient in functional T and B cells (Quintin et al., 2012). The protective effect appeared to be dependent on monocytes. The *Candida* cell wall component that appeared most potent in inducing this effect was β-1,3-(D)-glucan (β-glucan). In vivo as well as in vitro, enhanced cytokine production after the second challenge, characteristic of TI, was induced.

To demonstrate the training effect in vitro, the following set up was chosen using human cells (Quintin et al., 2012). Purified

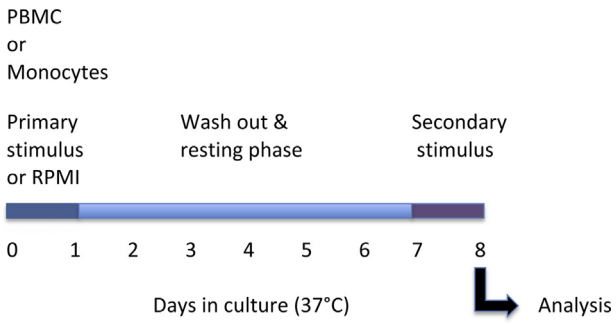

Fig. 1. The in vitro method to induce trained immunity.

monocytes (or peripheral blood mononuclear cells) are pre-incubated with 10^4/ml heat killed Candida for 24 h under serum free conditions. Of note, this concentration of Candida does not lead to a detectable cytokine response. After 24 h, the Candida is washed away and the cells are re-incubated with culture medium alone for an additional 6 days. Thereafter the cells are exposed to a secondary stimulus (e.g., LPS, Pam3Cys, *S. aureus*, BCG, *C. albicans* or β-glucan) in a cytokine-inducing concentration. Again 24 h later, supernatants are harvested to measure cytokine concentrations, and in this way the enhanced cytokine production after the priming with a low concentration of *Candida* can be demonstrated (Fig. 1).

This in vitro model allowed us to show that training induced by *C. albicans* or β-glucan was mediated by the β-glucan receptor dectin-1 and through the non-canonical Raf-1-dependent pathway. In this way, a functional reprogramming of monocytes is induced, which is associated with epigenetic changes, in particular stable changes in histone trimethylation at H3K4 (Fig. 2). These findings were confirmed and extended in a subsequent study in which we observed genome-wide changes in epigenetic marks such as H3K4me1, H3K4me and H3K27Ac. Pathway analyses led to the identification of cAMP–PKA-dependent signalling as an important mechanism of trained immunity activation (Saeed et al., 2014).

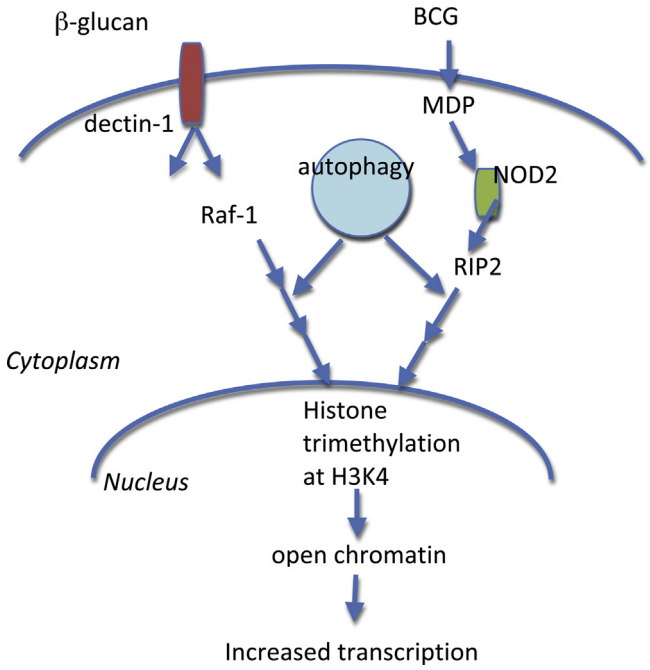

Fig. 2. Schematic representation of the pathways for training of monocytes by β-glucan and BCG, respectively. The exact way in which autophagy helps inducing training is currently unknown.