Ivanyi, Diagn Pathol Open 2023, 8:2

Diagnostic Pathology: Open Access

Mini Review Open Access

Detrimental Role of 'Decoy' Constituents in Tuberculosis Vaccination

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Abstract

Infection with *Mycobacterium tuberculosis* (Mtb) is being continually transmitted by cases with active pulmonary Tuberculosis (TB), prior to their late detection. Consequently, TB remains a major global health problem, despite its effective, though protracted, sterilizing chemotherapy. The widely used vaccination with attenuated viable *Mycobacterium bovis Bacillus* Calmette Guerin (BCG) is known to be protective against meningitis and disseminated TB in children, but not against the most common, reactivated pulmonary disease in adults. Therefore, research and development toward a more effective vaccine has been targeted by many scientists for a number of decades. However, testing of the molecularly defined vaccine candidates in experimental models has been done mostly following BCG priming of the test animals on the grounds, that it might be problematic to withdraw the well-established BCG vaccination of human populations in several countries, though not in the USA. The possible downside of this 'prime boost' approach to vaccine testing, as well as the expression of protective subunits in modified mycobacterial constructs has recently been debated on the grounds, that BCG might have retained some of the antigenic and immunomodulatory 'decoy' constituents, which evolved in support of mycobacterial pathogenicity. This may involve evasion from natural host resistance and evolutionary selection of genetically permissive immunodominant epitopes, leading to immune responses which sustain a long persisting form of latent infection.

Keywords: Mycobacterial pathogenicity; Decoy; *Mycobacterium bovis;* Prime boost; *Mycobacterium tuberculosis* (Mtb)

Introduction

Nevertheless, reactivation of latency in a minority (5%-10%) of individuals leads most often to pulmonary pathology which is also mandatory for the transmission of the infection. This mini review is summarizing a previous article, which reviewed the published literature and discussed the role of mycobacterial 'decoy' constituents, some shared by BCG and presumed to be favourable to the tuberculosis pathogen, by involving mechanisms which are outlined in the following text [1].

Early after infection, tubercle Bacilli avoid their killing by repressing the apoptosis of infected macrophages by metabolic reprogramming of their 'pattern recognition receptors'. Subsequently, the antigen presenting function of dendritic cells is subverted by the action of mycobacterial glycolipid constituents. Paradoxically, the dampening of myeloid cell and T cell responses by Mtb glycolipids was recently interpreted to be in favour of host protection on the grounds that it was higher in latent, than in active TB, but omitting, that Mtb latency is an integral pathogenic mechanism, with potential for reactivation to the active disease, which transmits the infection [2]. BCG also produces the immunomodulatory glycolipids and survives within phagosomes, resisting their bactericidal actions. Of the immunodominant antigens, the 'decoy' nature of the PstS1 glycolipoprotein is based on grounds of inducing high antibody levels in multibacillary TB by diverting the bacilli from dendritic cells to B cells with help from T cells with the pathogenic Th2 phenotype. Consequently, removal of Th2 inducing epitopes from candidate vaccine antigens could be beneficial. Mtb infection can suppress host innate protection by upregulating autophagosome genes, which attenuate autophagy. The mycobacterial ESX-1 secretion system and inflammasome signalling mediate the translocation of infected alveolar macrophages from airways to the interstitium of lungs. Neutrophils, deficient in phagocytosis and oxidative burst prevent the mycobactericidal action of Th1 cell mediators, and when necrotic, they increase IL-10 production. These pathogenic mechanisms, including excessive IL-1 production lead to cavitary granulomas which transmit the infection.

Literature Review

T cell responses, abundant in TB, have long been considered to be protective, but no reliable bioassay has been found, while cytokine levels can be either elevated without protection or not elevated following protection by mucosal vaccination; moreover IFN-γ *in vitro* can even enhance the infection of human macrophages. The 'decoy' aspect of BCG stimulated T cells is reflected by their terminally exhausted non-protective 'effector' phenotype and mis-localization into uninfected areas of the lungs. BCG induced protection against reactivation of latent lymphatic TB was reported to be T cell independent, while dysregulated CD4-T cell responses may be deleterious by amplifying lung pathology. The 'decoy' function of Th2 cells is supported by the association of the IL-4 cytokine with destructive lung granuloma development and by the finding that anti-IL4 treatment enhanced IgA monoclonal antibody mediated passive protection. A combined role of T cell phenotype and epitope specificity

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Received: 13-February-2023, Manuscript No. DPO-23-89319; **Editor assigned:** 15-February-2023, PreQC No. DPO-23-89319 (PQ); **Reviewed:** 01-March-2023, QC No. DPO-23-89319; **Revised:** 01-May-2023, Manuscript No. DPO-23-89319 (R); **Published:** 08-May-2023, DOI: 10.4172/2476-2024.1000216

Citation: Ivanyi J (2023) Detrimental Role of 'Decoy' Constituents in Tuberculosis Vaccination. Diagn Pathol Open 8: 216.

is reflected by the finding, that an immune-dominant CD8-T cell recognized epitope can block the T cell line mediated inhibition of infection in macrophages. Bactericidal Th1 action can be inhibited also by 'alternative' activation of non-mycobactericidal macrophages, resulting in the necrosis, rather than apoptosis of infected macrophages. Shifting the T cell response from Th1 to Th2 phenotype by BCG may explain also the abrogation of protection to vaccination, using the mycobacterial wall lipase LipY as adjuvant and the lack of protection despite enhanced T cell responses following recombinant influenza A vaccine vaccination [3].

Discussion

The key importance of the sequence of exposure with two different mycobacterial antigenic stimuli was demonstrated by the finding that vaccination with various mycobacterial antigens was poorly protective in Mtb pre-infected mice and that Ag85A-coding DNA protected mice when administered before, but not after BCG. These findings can be interpreted along the 'Original Antigenic Sin' (OAS) phenomenon, which was discovered in respect to vaccination with Influenza viruses. The OAS specifies the predominant impact of immunity to the first antigen following sequential immunization, which overrides the booster antigen's antigenic specificity. The OAS also explains the preferential responses to *M. avium* antigens after pre-exposure to environmental mycobacteria, the poor protection by antigen challenge in BCG primed macaques and the failure of BCG protection following prior exposure to environmental species of mycobacteria in mice and also in human populations. The epitope recognition mechanism of OAS has been attributed to T helper cell mediated cross reactivity between related antigens, though its wider impact could involve also non-reciprocal immunodominant versus cryptic epitopes and even 'mimicry' between taxonomically unrelated antigens. Thus, when using the BCG-prime/heterologous boost vaccine regimen, BCG priming, including the undesirable decoy antigens, may override specificity and phenotype of T cell response to the potentially protective boosting subunit vaccine.

Reactivation of Mtb infection is considered a feature of pathogenic strains of tubercle Bacilli. However, it was observed also following non-sterilizing chemotherapy using the 'Cornell' model in mice, following intravenous BCG Pasteur strain infection [4]. Notably, the need for starting chemotherapy at least three weeks post infection suggested that the constituents, inducing a host adaptive response essential for the relapse, are present within the Pasteur strain of BCG. However, the assumption, that BCG pre-infection would condition hosts toward latent Mtb infection with a potential for reactivation, is yet to be evaluated experimentally. In order to eliminate the reactivation supportive constituents, it has been proposed to test new vaccine candidates in experimental animals (e.g. Cornell model) for protection against reactivation of Mtb infection. When choosing suitable stimuli for reactivation, in addition to immunosuppression, 'decoy' immune activation by proinflammatory agents and coinfection need to be considered [5]. Moreover, the role of neuro endocrine stimulation of the hypothalamic pituitary adrenal axis is supported by the demonstrated reactivation of Mtb infection by physical exertion of mice and the finding of different corticosteroid levels between active and latent TB [6].

Conclusion

In conclusion, immune mechanisms can be unfavourable to Mtb infected hosts, due to mycobacterial 'decoy' constituents. 'Decoy' related mechanisms may be involved also when using BCG priming or using mycobacterial genetic constructs for testing candidate vaccine subunits for vaccination against TB. The 'decoy' constituents probably evolved to support the successful evasion from destruction and effective transmission of Mtb by a minority of infectious cases who reactivate from long term latency. Having retained some of the relevant 'decoy' constituents by BCG, their impact during priming by BCG may be detrimental to the testing of mycobacterial subunit vaccine candidates or modified BCG for protection against TB. Considering the key pathogenic role of recrudescence from dormancy, it is mandatory to test new vaccine candidate for protection in models involving the reactivation of infection.

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