

The role of BCG in prevention of tuberculosis and the strategies to improve its immunogenicity

Rola BCG w zapobieganiu gruźlicy i strategię prowadzące do zwiększenia jej immunogenności

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Summary

Tuberculosis (TB) remains a major public health problem and the main cause of death from the infectious diseases worldwide. *Mycobacterium tuberculosis* (Mtb), a causative agent of tuberculosis, is the oldest known human pathogen. The only available TB vaccine, BCG, was first administered in 1921 and has remained the only protecting tool against TB since then. Yet, its efficacy is limited and there is an urgent need to design and produce a novel vaccine that will protect against this deadly disease in the era of emerging problems with resistance to antibiotics. In this review a current, global TB situation is outlined and the characteristics of BCG are presented. Finally, the strategies leading to generation of BCG variants providing improved protecting efficacy are shortly described.

Key words: tuberculosis, vaccine, BCG, *Mycobacterium tuberculosis*

Introduction

Tuberculosis (TB) is caused by a slow-growing bacterium, *Mycobacterium tuberculosis* (Mtb), first described by Robert Koch in 1882 [1]. Analyses indicate that mycobacteria emerged about 70 000 years ago and expanded among modern humans during the Neolithic period [2]. Nowadays, TB is still a major public health problem with over 10 million people getting sick and nearly 2 million dying from TB every year [3]. The average TB incidence rate in Europe in 2013 was 51 per 100 000, while rates in some chosen countries were as follows (per 100 000 inhabitants): 27 in Poland, 123 in Romania, 226 in Moldova, 17 in the UK and 3.8 in Iceland [4]. As estimated one third of human population is infected with Mtb and most of infected people remain latently infected and are never sick. Nevertheless, an active TB disease develops in 5–15% of them [5]. Moreover, Mtb is highly contagious and even one transmitted bacterium is able to infect a new host organism [6]. Available antibiotic treatment allows us to control the infection fairly well with nearly 90% success rate for newly diagnosed TB cases [5]. Yet, the availability of diagnostic tools is insufficient and the access to antibiotics is

limited in some parts of the world. Moreover, Mtb strains resistant to several antibiotics pose a major problem. Multi-drug resistant (MDR) Mtb strains are resistant to at least rifampicin and isoniazid, while extensively drug resistant (XDR) strains are MDR with additional resistance to at least fluoroquinolone and an injectable second line drug, such as amikacin, capreomycin or kanamycin [7]. As estimated, only about 50% of MDR TB patients is successfully treated and the number of MDR and XDR cases increases annually by over 20% [7]. Thus, an efficient vaccine that could mount lasting immune response to mycobacteria and prevent the pathogen spread would greatly help to overcome the TB crisis.

BCG

Bacille Calmette-Guerin (BCG) is a live, attenuated vaccine based on *Mycobacterium bovis* (*M. bovis*), the causative agent of bovine TB, that can also be transmitted to humans [8]. BCG was developed by Albert Calmette and Camille Guerin in 1921 and presently it is the only approved TB vaccine [9]. BCG was developed by repeated passaging of *M. bovis*, which caused the loss of some genes. Sequencing of bacterial genome revealed several groups of genes that are present in virulent Mtb, while lacking in BCG [10]. Such groups were named Regions of Difference (RD) and it is thought that a loss of RD1, coding

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for ESX-1 secretion system, was a primary event during the attenuation process [11, 12]. BCG protecting efficacy against pulmonary tuberculosis is variable and depends on genetic and environmental characteristics of the vaccinated population, TB prevalence in the region, exposure to non-tuberculous mycobacteria as well as on the BCG strain variation [13]. While in some settings BCG protective efficacy reached 80% over 15 years, other studies reported lower or no protection [13–15]. Nevertheless, BCG displays a significant efficacy in protecting children against tuberculous meningitis and miliary TB [16, 17]. Immune response mounted by BCG declines with time and usually lasts up to 20 years [8]. Interestingly, repeating vaccination does not give any further protection, so it is not recommended to re-vaccinate people with BCG [8]. WHO recommends BCG vaccination of neonates in the countries with a high incidence of TB, whereas the countries with low TB incidence may choose to vaccinate children from the risk groups, including those who are directly in contact with TB patients [18]. Presently, BCG vaccination of neonates is not obligatory in the Northern Europe and in most of Western European countries, Czech Republic and Slovak Republic. Some countries however, including Canada and Italy, recommend vaccination of children from the risk groups. A current situation of the BCG policies may be found using the BCG World Atlas [19].

It is noteworthy however, that BCG is mounting an immune response also to non-mycobacterial antigens. Kleinnijenhuis *et al.* demonstrated that monocytes isolated one year after BCG vaccination of the healthy individuals had increased levels of pattern recognition receptors, including TLR4 and mannose receptor, which was accompanied by a robust pro-inflammatory cytokine production triggered by lipopolysaccharide, a ligand of TLR4 [20]. Clinical study from West Africa showed that BCG vaccination was associated with decreased child mortality unrelated to TB and that administration of another vaccine, namely diphtheria-tetanus-pertussis vaccine, did not result in a similar protection [21]. That suggests that BCG administration may have some TB-unspecific and beneficial outcomes [21]. Indeed, immunostimulatory properties of BCG have been employed in the cancer treatment. Intravesical BCG instillation is recommended in patients suffering from non-muscle invasive bladder cancer [22]. Such an immunotherapy, causing T cell recruitment to the bladder, decreases the risk of recurrence and progression of the cancer of the intermediate- and high-risk patients [23, 24].

Nevertheless, BCG administration as TB vaccine as well as in the course of the bladder cancer treatment may result in some adverse effects. BCG is administered intradermally which requires a skilled and well-trained personnel and sometimes errors in BCG deposition result in formation of subcutaneous abscesses [25]. The most serious complication of BCG vaccination comprises systemic BCG infection with high morbidity and mortality, yet it is worth mentioning that such a serious condition develops more frequently in immunocompromised children

[26]. Similarly, systemic BCG infections were sporadically recorded in the course of treatment of the bladder cancer patients [27, 28].

Novel vaccine candidates and animal models for vaccine candidate testing

BCG with its limited efficacy against pulmonary TB, the most contagious form of TB, is not able to stop the global epidemics. Therefore, there is a strong need to develop a novel vaccine to replace BCG and to improve the control over TB. The ideal vaccine should elicit the polyfunctional T cell response supported by the release of Mtb-specific antibodies, which together will allow controlling Mtb spread within infected host. The novel vaccine could be prophylactic and/or therapeutic. A prophylactic vaccine should prevent the infection, primary disease and development or reactivation of latent infection. A role for the therapeutic vaccine, on the other hand, would comprise of shortening the course of illness and improving the outcome of antibiotic treatment [29]. Several novel vaccines are in pre-clinical and clinical trials and huge efforts are made in order to identify new potential vaccine antigens, suitable mycobacterial vaccine strains, novel delivery systems and to define correlates of protection which will help to assess the magnitude of the immune response mounted by the tested vaccine candidates [30].

Preclinical testing of new vaccine candidates is complicated given a complex nature of Mtb infection. None of the animal models fully reflects characteristics of human TB, yet each one delivers important information to assess the safety and efficacy of tested vaccine candidates [31]. The most suitable model is non-human primates, whose response to Mtb resembles that of humans fairly well, but the ethical and economic constraints limit the use of this model to vaccine candidates, which have already shown a good efficacy among small animal models [32]. Mice model is the most popular one, given its relatively low cost and great sets of data and tools available to study the murine immune response to infections. Nonetheless, mice exhibit limited pathological profile, that does not correspond to human immune response to Mtb, therefore they are mostly used in the pre-screening studies [31]. Recently, guinea pigs have been more widely used. Unlike mice, their immune response to Mtb is exaggerated and has characteristics of the allergic response. At the same time, guinea pigs are a good model to study immune response to lipid antigens because they express a full range of CD1 proteins, lipid-presenting molecules [31, 33]. Other models, such as rabbits, rats as well as cows and goats are also used in TB vaccine studies, yet their role is limited and the data is not abundant [31].

Current vaccine testing relies on demonstration that a given vaccine candidates are more efficient than BCG, but the precise correlates of protection are not defined. Moreover, a study design measuring prevention of infection rather than prevention of disease among humans would be very beneficial, but defining an

asymptomatic infection with Mtb is not easy with the currently available diagnostic tools [32]. Therefore, more clinical studies are necessary to establish correlates of protection which could be used in the vaccine candidate screening approaches.

Vaccine candidates based on BCG

BCG is very well characterized and used in clinics for almost a century, therefore it became a natural base for the next generation TB vaccine. It has been proposed to improve BCG immunogenicity by a number of ways, including insertion of Mtb antigens and increasing their antigen presentation capacities, addition of adjuvants derived from bacterial toxins and insertion of human cytokine genes to trigger more vigorous immune response towards Mtb [8].

There are 16 RDs missing in BCG, yet some of them may be present in certain BCG substrains [34]. As a result, genes from those regions are a natural target in searching for Mtb virulence factors as well as potential antigens that could be re-incorporated into BCG to improve its immunogenicity. Such a strategy was employed to design vaccine candidates based on BCG and additionally expressing proteins of the virulent mycobacterial strains. For instance, proteins encoded by RD1 are called an immunogenicity island and several of them, including ESAT-6 and CFP-10, have been included in the vaccine design strategy. Addition of ESAT-6 in a recombinant BCG and DNA vaccine prime-boost approach triggered stronger IFN- γ responses than BCG alone, yet its efficacy during the Mtb challenge in guinea pigs was not improved [35]. Several studies tested the addition of other Mtb antigens or its combination in order to improve the immune response triggered by those immunization strategies.

In parallel, another approach was employed. The strategy relies on removing from BCG genes that code for proteins engaged in the attenuation of the immune response to mycobacteria. For instance, mycobacterial virulence gene *zmp1*, a putative zinc metalloproteinase, is known to inhibit inflammasome activation and IL-1 β processing [36]. BCG lacking this gene has been generated and obtained results demonstrated augmented antigen presentation and increased mycobacteria-specific CD4 and CD8 T cell responses [36]. Additionally, promising results have been obtained on the bovine model [37].

Furthermore, improved BCG immunogenicity could be achieved by preparing vaccines expressing human immunomodulatory proteins, such as IFN- γ , GM-CSF, IL-18 and IL-2. Several candidates have been tested but the ability to influence the cytokine profile triggered by BCG did not result in improved protective efficacy of such vaccine candidates [8].

Finally, immunogenicity of BCG may be increased by addition to the vaccine toxins derived from other pathogens. The ability of bacterial toxins to mount an immune response is often associated with a considerable toxicity for the organisms. As a result, the use of bacterial toxins in combination with BCG re-

quires a thorough investigation that can guarantee that a certain toxin or its derivative is safe to use on humans [8]. Nascimento *et al.* demonstrated that BCG expressing low levels of LTAK63, a non-toxic derivative of *Escherichia coli* heat labile enterotoxin, triggered higher Th1 and IL-17 cytokine secretion in the lungs of immunised mice [38]. Moreover, immunized mice challenged intratracheally with Mtb had significantly reduced bacterial burden in the lungs [38].

Other approaches

There is an urgent need for a novel TB vaccine, therefore searching for suitable candidates is not limited to BCG-based approaches. Some strategies comprise using virulent Mtb as a base for creating non-pathogenic mycobacterial strains that are mounting a robust immune response but at the same time, they are safe and non-toxic. MTBVAC is one of the promising candidates that entered clinical trials. It is a live, attenuated Mtb strain aiming to replace BCG as a TB preventive vaccine and at the moment it generates promising results, demonstrating improved protective efficacy [39]. Yet, more efficacy trials are necessary to progress further with this TB vaccine candidate [39].

Additionally, whole bacterial cells that are inactivated are tested as potential vaccine candidates, which may be also used as a boost with prior BCG vaccination. DAR-901 is a heat inactivated, non-tuberculous *Mycobacterium obuense*, which used as a booster after BCG, generated better protection against Mtb in mice than BCG alone [40]. Furthermore, human clinical trials demonstrated that such a strategy was safe and mounted cellular and humoral immune responses to mycobacterial antigens and DAR-901 entered the efficacy trials [41].

Also, subunit vaccines are in the vaccine pipeline. In general, they are generated to be used as booster in combination with BCG, used to prime the immune response. Subunit vaccines may comprise of a single mycobacterial antigen or be used in combination, they can be formulated with adjuvants or expressed by the viral vectors [9]. MVA85A, a recombinant modified vaccinia Ankara vector expressing mycobacterial antigen 85A, was one of the most advanced vaccine candidates but failed to demonstrate improved protection in phase IIb clinical trial [42]. Similarly, subsequent testing of MVA85A as a prime vaccination in HIV-exposed newborns did not show spectacular efficacy [43]. Yet, other subunit candidates are still in the pipeline and great efforts are undertaken in order to identify the most promising candidates [9, 30].

Summary

BCG, a nearly 100 year-old vaccine, is the only TB vaccine available today. It protects the infants from the most serious forms of Mtb infection but its efficacy in protecting adults from TB is questionable. BCG vaccination is still recommended in

the countries with a high TB incidence whereas most of low-incidence countries stopped BCG programs or reduced the vaccination to newborns from the risk groups. It is therefore clear that BCG is not able to stop TB epidemics, especially when the emergence of multi-drug resistant Mtb strains poses a major problem, and the antibiotic treatment coverage is not optimal. The need for the novel, more effective prevention strategy protecting from pulmonary TB, the most common form of disease, is evident. Great efforts are engaged into developing new vaccine candidates, yet at the moment no new TB vaccine is ready to be introduced to the clinics.

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Streszczenie

Gruźlica pozostaje ważnym problemem zdrowia publicznego i jest główną przyczyną zgonów z powodu chorób zakaźnych na całym świecie. *Mycobacterium tuberculosis* (Mtb), bakteria wywołująca gruźlicę, jest najstarszym znanym ludzkim patogenem. Jedyną dostępną szczepionką przeciwgruźliczą, BCG, po raz pierwszy zastosowano już w 1921 r. i od tego czasu pozostaje ona jedynym narzędziem zapobiegającym gruźlicy. Jej skuteczność jest jednak ograniczona i istnieje pilna potrzeba zaprojektowania i wyprodukowania nowej szczepionki, która chroni przed tą śmiertelnością chorobą, szczególnie w dobie pojawiających się problemów z antybiotykoopornością Mtb. W niniejszej pracy przeglądowej opisano aktualną, globalną sytuację epidemiologiczną dotyczącą gruźlicy i przedstawiono charakterystykę BCG. Opisano także strategie prowadzące do wytworzenia wariantów BCG zapewniających lepszą ochronę przeciwgruźliczą.

Słowa kluczowe: gruźlica, szczepionka, BCG, *Mycobacterium tuberculosis*
