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Review

BCG immunomodulation: From the 'hygiene hypothesis' to COVID-19

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ABSTRACT

The century-old tuberculosis vaccine BCG has been the focus of renewed interest due to its well-documented ability to protect against various non-TB pathogens. Much of these broad spectrum protective effects are attributed to trained immunity, the epigenetic and metabolic reprogramming of innate immune cells. As BCG vaccine is safe, cheap, widely available, amendable to use as a recombinant vector, and immunogenic, it has immense potential for use as an immunotherapeutic agent for various conditions including autoimmune, allergic, neurodegenerative, and neoplastic diseases as well as a preventive measure against infectious agents. Of particular interest is the use of BCG vaccination to counteract the increasing prevalence of autoimmune and allergic conditions in industrialized countries attributable to reduced infectious burden as described by the 'hygiene hypothesis.' Furthermore, BCG vaccination has been proposed as a potential therapy to mitigate spread and disease burden of COVID-19 as a bridge to development of a specific vaccine and recombinant BCG expression vectors may prove useful for the introduction of SARS-CoV-2 antigens (rBCG-SARS-CoV-2) to induce long-term immunity. Understanding the immunomodulatory effects of BCG vaccine in these disease contexts is therefore critical. To that end, we review here BCG-induced immunomodulation focusing specifically on BCG-induced trained immunity and how it relates to the 'hygiene hypothesis' and COVID-19.

1. Pleiotropic protective effects of BCG vaccine

Developed in 1921, the live vaccine Bacille Calmette-Guerin (BCG) is used clinically for prevention of tuberculous (TB) meningitis and disseminated TB disease in infants, as well as an adjunct immunotherapy for non-muscle invasive bladder cancer (Kaufmann et al., 2010; Colditz et al., 1994; Ottenhoff and Kaufmann, 2012). Since its introduction, BCG vaccination has been reported to reduce the occurrence, severity, and mortality of various non-TB infections, reflecting robust pleiotropic and broad-spectrum protective effects. Indeed, BCG vaccination reduced non-TB acute lower respiratory tract infections among children (Stensballe et al., 2005), hospitalizations due to non-TB respiratory infections (Castro, 2015), as well as first-year mortality by three-fold amongst newborns (Aaby et al., 2011). Furthermore, BCG-vaccination reduced mortality due to malaria and unclassified fever amongst children in Guinea-Bissau (Roth et al., 2005), as well as mortality attributed to malaria, sepsis, respiratory infections, and leprosy by >40% in West Africa (Aaby et al., 2011; Roth et al., 2005; Biering-Sørensen et al., 2012; Ponnighaus et al., 1992; Garly et al., 2003). BCG vaccination also reduced incidence of respiratory syncytial virus (RSV) infection in Guinea-Bissau (Stensballe et al., 2005), respiratory tract infections in older patients in Indonesia (Wardhana et al., 2011), protected against pneumonia in tuberculin-negative elderly in Japan (Takashi et al., 2005), and reduced respiratory tract infections by as much 70% amongst adolescents in South Africa (Hawkridge et al., 2008). Similar evidence has been reported from BCG-vaccinated cohorts in the United Kingdom, South Asia, India, and Haiti (Shann, 2010; Higgins et al., 2016). Importantly, clinical trials have also failed to demonstrate a protective effect of BCG vaccination. For example, BCG vaccination at birth had no effect on infection rates in Danish children by 15 months (Stensballe et al., 2019), suggesting that the mechanisms of BCG-induced immunomodulation may be more complicated and dependent on various extrinsic and host factors including gestational age, caesarean delivery, and maternal BCG vaccination status. Identification of the immunological mediators of this non-specific protection is therefore critical for the effective clinical application of this agent.

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2. BCG-induced immunomodulation

BCG-induced immunomodulation appears multifaceted, with effects on both the innate and adaptive immune systems. One of the central mechanisms is trained immunity, which can be conceptualized as the strengthening of the innate immune system such that subsequent responses are enhanced, thus representing a form of innate immunological memory (Mulder et al., 2019; Netea and van der Meer, 2017) (Fig. 1). This non-specific enhancement of innate immune responses is attributed with the ability of BCG vaccination to protect against a range of non-TB infections, supported by experimental findings. BCG-vaccination of severe-combined immunodeficient (SCID) mice reduces infectious burden from disseminated candidiasis (Kleinnijenhuis et al., 2012), suggesting the protective effect resides in the innate immune system. BCG vaccination also reduces viral load of influenza A virus (Spencer et al., 1977)and protects against herpes simplex virus type 2 (HSV2) (Starr et al., 1976). Furthermore, subcutaneous administration of muramyl dipeptide (MDP), a mycobacterial cell wall compound, protects against vaccinia virus and HSV2 infection, mediated by peritoneal macrophages (Ikeda et al., 1985). BCG vaccination also reduces viremia following vaccination with the live-attenuated yellow fever vaccine, mediated by upregulated monocyte IL-1β production (Arts et al., 2018). Various innate immune cells isolated from BCG-vaccinated patients display increased pro-inflammatory cytokine production (e.g. IL-1β, TNF-α, IL-6) upon *ex-vivo* re-stimulation with various pathogens (Kandasamy et al., 2016; Kaveh et al., 2014; Kleinnijenhuis et al., 2014, 2012). For example, isolated peripheral blood mononuclear cells (PBMCs) produce increased TNF-α and IL-1β when re-stimulated with *Staphylococcus aureus* and *Candida albicans* (Kleinnijenhuis et al., 2012) and isolated natural killer (NK) cells have enhanced pro-inflammatory cytokine production when stimulated with various pathogens (Kleinnijenhuis et al., 2014). Furthermore, isolated innate immune cells from BCG vaccinated individuals produce increased levels of the CXCR3 ligands CXCL9, CXCL10, and CXCL11 (Joosten and Krista, 2018). Importantly, CXCR3 receptor blockage leads to mycobacterial overgrowth, implicating these innate chemokines in BCG-induced immune protection (Joosten and Krista, 2018). Interestingly, these BCG-induced innate immune effects appear to be long-lived. For example, LPS-induced TNF-α and IL-1β remain elevated up to 1 year post-vaccination (Kleinnijenhuis et al., 2014), PBMC-derived TNF-α and IL-1β levels remain elevated up to 3 months (Kleinnijenhuis et al., 2012), and clinical protective effects attributed to trained immunity have been

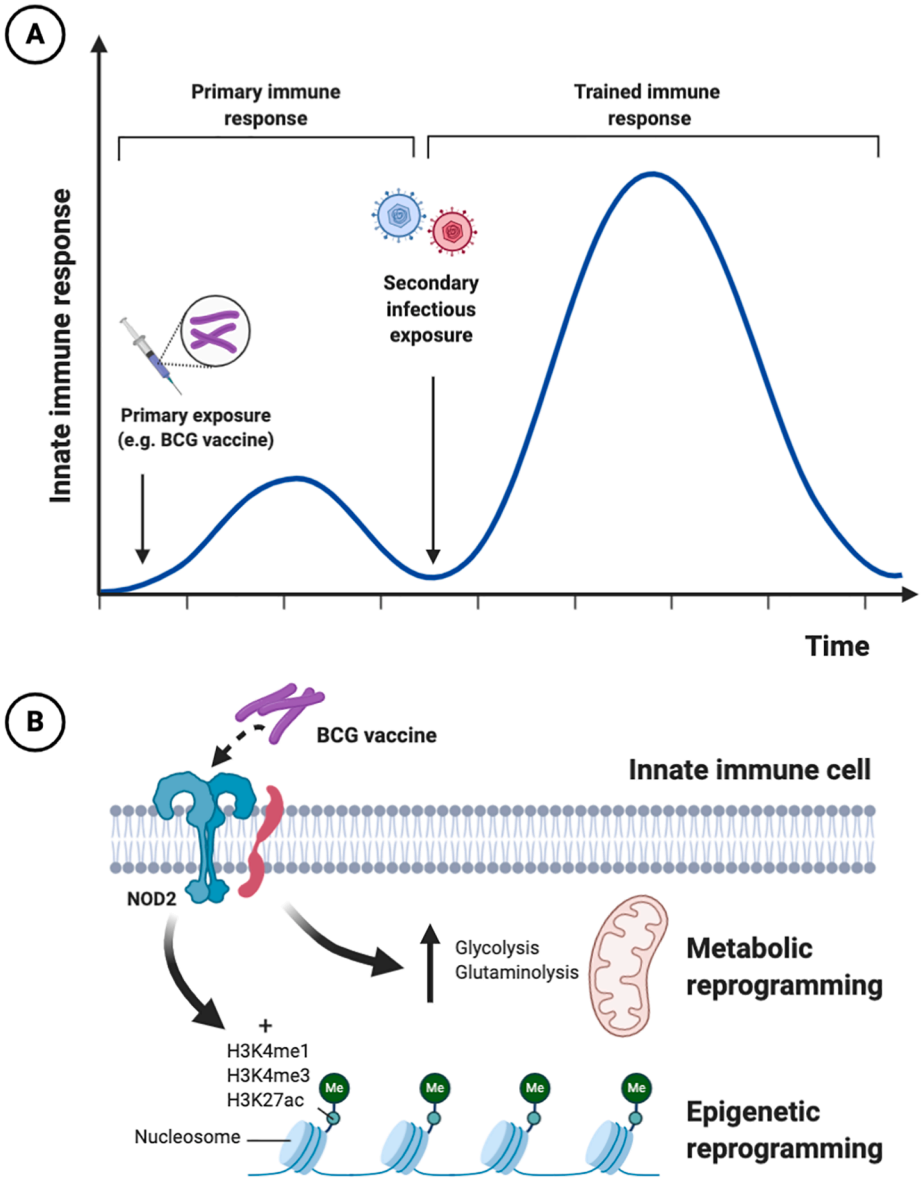

Fig. 1. BCG-induced trained immunity. A) Trained immunity is the enhancement of innate immune responses following an initial exposure such that subsequent responses are increased, representing a form of innate immunological memory. B) Mechanisms of BCG-induced trained immunity include the metabolic and epigenetic reprogramming of innate immune cells (e.g. macrophages, monocytes, dendritic cells) that enhances pro-inflammatory and antimicrobial effects, mediated through stimulation of various intracellular signaling pathways. Figure created with BioRender.com.

reported to last up to a year in different cohorts of healthy patients (Kleinnijenhuis et al., 2014). This is particularly interesting considering that monocytes typically have a lifespan of only a few days (Yona et al., 2013). The answer to this paradox may lie in the bone marrow. Indeed, BCG vaccine delivered to the bone marrow increases populations of myeloid-based progenitor cells and long-term haematopoietic stem cells (LT-HSCs) (Mitroulis et al., 2018), potentially mediated through an IL-1β and granulocyte macrophage colony-stimulating factor (GM-CSF)-dependent upregulation of key cell proliferative pathways (Kaufmann et al., 2018). Whether systemic administration of BCG vaccine has similar training effects on bone marrow cell populations remains unknown. BCG-induced trained immunity is thought to be mediated, at least in part, by epigenetic reprogramming of innate immune cells that enhance anti-microbial and pro-inflammatory capacity (Arts et al., 2016; Kleinnijenhuis et al., 2012; Saeed et al., 2014). Indeed, BCG vaccination increases H3K4 trimethylation at promoter sites of pro-inflammatory and anti-microbial genes in circulating monocytes (Kleinnijenhuis et al., 2012), as well as histone H3 lysine 4 monomethylation (H3K4me1), trimethylation (H3K4me3), and H3 lysine 27 acetylation (H3K27ac) via a nucleotide-binding oligomerization domain-containing protein 2 (NOD2)-dependent pathway at anti-microbial gene promoters in cultured human monocytes (Cheng et al., 2014; Mulder et al., 2019). BCG-vaccination has also been shown to metabolically reprogram innate immune cells, including the selective alteration of metabolic regulators of histone modifying enzymes. For example, BCG vaccination induces a metabolic switch to glycolysis in dendritic cells, polarization of monocytes to a glycolytic-dependent pro-inflammatory phenotype, and induces glutaminolysis in innate immune cells, resulting in the accumulation of fumarate and inhibition of KDM5 histone demethylases (Uthayakumar et al., 2018; Arts et al., 2016). Importantly, *in vitro* inhibition of this metabolic switch prevents BCG-induced epigenetic changes and cytokine upregulation upon re-stimulation. For example, blocking mTOR-dependent glycolysis with metformin diminished cytokine and lactate production from isolated innate immune cells (Arts et al., 2016)and inhibition of the Akt/mTOR pathway reduces *ex-vivo* glucose consumption and lactate production (Uthayakumar et al., 2018; Cheng et al., 2014), highlighting the importance of this metabolic pathway for the BCG-induced effects. Trained immunity responses in myeloid progenitor cells have also been associated with induced activation of cholesterol biosynthesis, an effect attributed to the capacity of cells to remodel the physiochemical properties of their membranes and the lateral organization of cellular and lipid-protein signaling capacity (Mitroulis et al., 2018). Indeed, the cholesterol metabolite mevalonate has been shown to induce trained immunity via IGF1-R and mTOR-dependent histone modifications of pro-inflammatory genes (Bekkering et al., 2018). In addition to the reprogramming of innate immune cells, the non-specific protective effects of BCG vaccination may be mediated by several other mechanisms. For example, cross-reactivity from vaccine-primed T-cells may protect against unrelated pathogens due to structural similarity between epitopes or T-cell receptor cross-recognition (de Bree et al., 2018; Frankild et al., 2008), as seen with other infectious agents. For example, Epstein-Barr virus-specific T-cells cross-react with influenza A epitopes (Cornberg et al., 2010) and CD8+ T-cell cross-reactivity between hepatitis C virus and influenzae neuraminidase sequences has been reported (Urbani et al., 2005). Importantly, evidence suggests that this cross-reactivity may be involved in BCG-induced protection. Indeed, *ex-vivo* stimulation of PBMCs isolated from BCG-vaccinated patients induce long-lasting heterologous T_H1/T_H17 responses that protect against unrelated pathogens (Kleinnijenhuis et al., 2014), BCG-induced protection from vaccinia virus in murine models is associated with enhanced CD4+ and CD8+ T-cell responses and lost following CD4 + T-cell depletion (Mathurin et al., 2009), and non-mycobacterial stimulation of BCG-vaccinated individuals induce heterologous T_H1/T_H17 cytokines for up to 1 year post-vaccination (Kleinnijenhuis et al., 2014). These findings may be explained by a population of BCG-induced antigen-specific memory cells (e.g. memory T cells and NK cells) that undergo heterologous or 'bystander' activation when challenged with an unrelated pathogen. Indeed, memory cells require less signal to be activated upon a second stimulus and thus would be more responsive upon re-stimulation (Uthayakumar et al., 2018). Therefore, the non-specific protective effect of BCG vaccination may be partly attributed to bystander activation of BCG-induced polyclonal effector T-cell populations by subsequent infectious challenge (Uthayakumar et al., 2018). Indeed, recently it has been shown that BCG immunotherapy for bladder cancer induces CD4+ T-cell-dependent tumor-specific immunity through tumor cell-intrinsic IFN-γ signaling (Antonelli et al., 2020). Another possibility is that BCG vaccination creates a cytokine and immunological milieu that promotes antibody generation by memory B-cells, thus conveying generalized protection against various pathogens (Uthayakumar et al., 2018). Indeed, general enhancement of antibodies is thought to explain the ability of live-attenuated vaccines to stimulate T-follicular helper (T_{fh}) cell polarization, which promotes B-cell maturation and memory cell formation (Ugolini et al., 2018). For example, BCG-derived RNA PAMPs activate TLR-8 signaling on monocytes and dendritic cells, inducing IL-12p40 production and stimulation of T_{fh} development in lymph nodes (Ugolini et al., 2018), an effect not observed by inactivated or non-live vaccines (Uthayakumar et al., 2018). Epidemiological studies have also shown that hypermorphic TLR8 polymorphisms enhance BCG-induced protection (Uthayakumar et al., 2018), lending support to this theory. B-cells may also play a role in BCG-induced immunomodulation. Indeed, mice deficient in B-cells display diminished BCG-induced T_H1 responses (Dockrell and Smith, 2017; Tanner et al., 2019). This may be due to the IL-17-dependent regulatory role that BCG-induced B-cells have over neutrophilia, which if excessive can impair dendritic cell migration to lymph nodes and thus compromise CD4+ T-cell priming (Kozakiewicz et al., 2013). Fig. 2.

3. BCG vaccine and the 'hygiene hypothesis'

The majority of human immune system evolution has been characterized by recurrent infection with numerous non-pathogenic microbes, a consequence of exposure to micro-organism-rich environments (e.g. farms, animals, untreated water sources, etc.) (Bach, 2018; Guarner et al., 2006). The effective elimination of these 'microbial allies' from industrialized populations due to improved hygiene and medical care has been robustly associated with a dramatic rise in autoimmune and allergic conditions, as described by the 'hygiene hypothesis' (Strachan, 1989; Guarner et al., 2006; Bach, 2018). Indeed, over the past four decades rates of autoimmune and allergic conditions have increased significantly in industrialized countries (Kotz et al., 2011) and have begun affecting patients at younger ages (Patterson et al., 1996; Karvonen et al., 1999), reflecting increased disease severity. Extensive research has revealed the remarkable capacity of microbial species to manipulate human immune responses (White and Artavanis-Tsakonas, 2012; Harn et al., 2009; Zakeri et al., 2018), however even more interesting is the finding that microbial stimulation appears critical to the proper development and function of the immune system (Bach and Chatenoud, 2012; Gent et al., 1994; Guarner et al., 2006). Understanding this relationship requires consideration of the equilibrium model of immune function, which conceptualizes the immune system as a dynamically regulated entity that maintains balance between antagonistic responses through cross-repressive mechanisms (Sansonetti, 2004; Sansonetti and Di Santo, 2007; Eberl, 2016). When one arm of the immune system is stimulated, competing responses are cross-repressed by various mechanisms, including type-specific regulatory T-cells (T_{regs}) (Eberl, 2016; Guarner et al., 2006). Consideration of the 'hygiene hypothesis' within this framework is important for therapeutic development. For example, induction of T_H1 responses could protect against viral infections or reduce tumor growth, accomplished by either direct stimulation or indirectly through suppression of T_H2 responses and

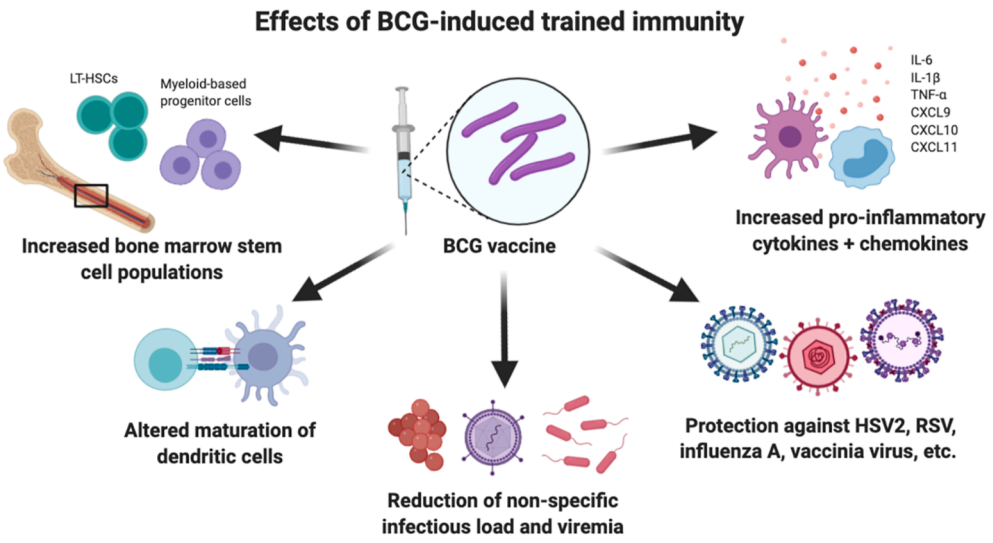

Fig. 2. Effects of BCG-induced trained immunity. BCG vaccination results in increased production of pro-inflammatory cytokines (e.g. IL-6, IL-1β, TNF-α) and chemokines (e.g. CXCL9, CXCL10, CXCL11) by innate immune cells, conveys protection against various viral infections (e.g. HSV-2, RSV, influenza A, vaccinia virus), reduces non-specific infectious load and viremia following infectious challenge, promotes alternative maturation states of dendritic cells that alter polarization of naïve T-cells, and increases populations of bone marrow stem cells, including long-term hematopoietic stem cells (LT-HSCs) and myeloid-based progenitor cells, attributed with the longevity of the effects. Figure created with BioRender.com.

release of cross-repression (Eberl, 2016). Indeed, the historic use of *Streptococcus pyogenes* as a cancer therapy and the current use of BCG vaccine for non-invasive bladder cancer exploit this principle (Buffen et al., 2014; Ikeda et al., 2002; Silverstein, 1974). A similar approach could be used to attenuate autoimmune and/or allergic conditions, such as type-1 diabetes mellitus (T1DM) or multiple sclerosis (MS). This approach has the theoretical advantage over the current use of anti-inflammatory medications as it restores immune balance and strengthens immune function, in contrast to the suppression of immune effector molecules (e.g. histamine, TNF-α) (Eberl, 2016). For example, administration of T_H1-inducing microbes could be used to suppress pro-allergic T_H2 responses or type 3-driven autoimmune conditions. This approach has been extensively studied using helminth-derived products (HDPs) (Finlay et al., 2014; Gause and Maizels, 2016; Harn et al., 2009; Zakeri et al., 2018). BCG vaccination could be a form of this therapy as it has been reported to reduce the incidence of allergic and autoimmune conditions (Bilenki et al., 2010; Gouveia et al., 2017). Indeed, BCG vaccination induces a robust T_H1/T_H17 response (Soares et al., 2008; Kleinnijenhuis et al., 2014; Kagina et al., 2010; Smith et al., 2017), thus could be an effective means of promoting cross-repression of pro-allergic and/or autoimmune responses (Eberl, 2016; Guarner et al., 2006), potentially mediated through the training of dendritic cells. Alternative maturation states of dendritic cells will preferentially drive naïve T-cells to different effector phenotypes (e.g. T_H1, T_H2, T_H17 cells), thus shaping the subsequent adaptive immune response (Carvalho et al., 2009). For example, helminth parasites and HDPs have been shown to induce tolerogenic dendritic cells, characterized by reduced expression of classic maturation markers (e.g. CD-40, CD-80, CD-86, MHC-II) and reduced pro-inflammatory responses to LPS provocation (Carvalho et al., 2009; Zakeri et al., 2018; Maizels et al., 2004). Importantly, these tolerogenic cells demonstrate a propensity to drive T_{reg} differentiation when exposed to naïve T-cells (Aranzamendi et al., 2012; Falcón et al., 2010). As BCG vaccine is cheap, widely available, and safe, it would be an ideal therapeutic candidate for mimicking this effect in conditions of immune dysregulation. Indeed, mycobacterial components protect against autoimmune conditions in mouse models via TLR-dependent activation of dendritic cells (Bilenki et al., 2010; Gouveia et al., 2017; Akbari et al., 2001), BCG vaccination alters dendritic cell cytokine production and migration (Chen et al., 2009; Ritz et al., 2008), and mucosal BCG vaccination confers protection in the lung parenchyma by inducing tissue resident memory T-cells via conditioning of dendritic cells (Sharpe et al., 2016). Importantly, intravesical administration of BCG vaccine for bladder cancer has been reported to enhance T_{regs} (Fenner, 2018; Chevalier et al., 2018) and *in vitro* administration of BCG induces T_{reg} marker expression in cultured human PBMCs (Boer et al., 2014). Non-PRR mechanisms of dendritic cell activation are also likely involved. For example, the receptor protein Programmed Death-1 (PD-1 or CD-279) and its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) are important regulators of dendritic cell and naïve T-cell interactions (Keir et al., 2008; Gouveia et al., 2017). Interestingly, *M. tuberculosis* induces T_{reg} differentiation via a PD-1-dependent mechanism (Periasamy et al., 2011; Trinath et al., 2012). BCG-induced metabolic reprogramming of dendritic cells may also be involved. Indeed, metabolic shifts in innate immune cells are implicated in the BCG-induced suppression of inflammation in autoimmune conditions (Ristori et al., 2018). BCG vaccination has also been shown to induce apoptosis of autoreactive T-cells in an IFN-γ-dependent manner (Dalton et al., 2000) as well as promote B-cell IL-10 secretion and suppression of autoimmune responses (Lampropoulou et al., 2008). Despite these findings, more investigation is required to interrogate the effects of BCG on autoimmune and allergic conditions. Assessment of BCG-conditioned dendritic cells, including expression of various maturation markers, cytokine production, and gene expression changes followed by a series of adoptive transfer experiments in established animal models of autoimmune conditions (e.g. NOD, EAE mice) could reveal important mechanistic details of the immunomodulatory capacity of BCG.

4. BCG vaccination and COVID-19

In addition to a role in autoimmune and allergic conditions, BCG vaccine has gained significant attention as a potential agent in the global fight against COVID-19 (O'Neill and Netea, 2020; Redelman-Sidi, 2020; O'Connor et al., 2020). As mentioned previously, BCG vaccination has been shown to protect against a variety of non-TB infections, including several respiratory viruses (e.g. RSV, influenza A, HSV2) (Stensballe et al., 2005; Wardhana et al., 2011; Takashi et al., 2005), attributed at least in part to training of innate immune cells (Buffen et al., 2014; Kleinnijenhuis et al., 2014; Arts et al., 2018). Furthermore, a recent randomized trial demonstrated an 80% reduction of respiratory tract infections in BCG vaccinated elderly patients (Giamarellos-Bourboulis et al., 2020). Based on this, BCG vaccination has been proposed as a potential preventative measure against SARS-CoV-2 infection and a means of reducing the morbidity and mortality of COVID-19 (O'Neill and Netea, 2020; Redelman-Sidi, 2020; Netea et al., 2020; Gursel and Gursel, 2020). In theory, inducing trained immunity in healthy individuals should boost anti-microbial defence, inhibit viral replication, reduce viral load, lower systemic inflammation, and thus reduce severity, duration, morbidity, and mortality associated with SARS-CoV-

2 infection (O'Neill and Netea, 2020; Gursel and Gursel, 2020). Intriguingly, preliminary epidemiological studies on the pandemic have reported lower infection rates and mortality in BCG-vaccinated populations (Miller et al., 2020; Gursel and Gursel, 2020; Hegarty et al., 2020). Importantly, these studies suffer from several inherent biases related to differences in case reporting, public health measures, and diagnostic criteria between regions and thus need to be considered carefully (O'Connor et al., 2020; O'Neill and Netea, 2020). BCG vaccine is widely available, safe, relatively cheap, immunogenic and it has immense potential for rapid clinical translation as a bridging therapy until a specific vaccine can be developed. To that end there are currently more than 15 randomized clinical trials currently ongoing around the globe to assess BCG vaccination as a potential therapy for COVID-19. Importantly, this protection should not be limited to the BCG vaccine, as any inducer of trained immunity should be effective. These include the oral polio vaccine, the newly developed BCG-based VPM1002 vaccine, the live-attenuated MTBVAC vaccine, and the MMR vaccine, all of which may be important options for bridging therapy to a specific COVID-19 vaccine (Franklin et al., 2020; O'Neill and Netea, 2020; Netea et al., 2020). Indeed, a recent report claimed that MMR vaccination may provide protection from COVID-19, attributed to non-specific protective effects (Franklin et al., 2020). Despite the promise, there are several important issues that must be investigated prior to widespread administration of BCG vaccine, which are being addressed by the clinical trials currently underway. In addition to bridging therapy, another potential use of BCG vaccine is as a recombinant vector for the introduction of immunogenic viral antigens. BCG has several advantages in this regard including safety of administration, relative ease and low cost of production, temperature stability, and self-adjuvant activity (Dockrell and Smith, 2017; Kilpeläinen et al., 2018; Covián et al., 2019). Indeed, several recombinant BCG strains (rBCG) expressing heterologous viral antigens have been developed. For example, administration of rBCG vaccine expressing a nucleocapsid protein of measles virus (rBCG-MV) significantly reduced viral titres in brain homogenates and mortality in a mouse model of measles-induced encephalitis, as well as enhanced proliferation of antigen-specific T-cells *in vitro* (Fennelly et al., 1995). Moreover, administration of rBCG-MV in macaque monkeys reduced lung pathology and induced paracortical lymph node hyperplasia after viral challenge, suggesting a T-cell-mediated effect (Zhu et al., 1997). Similar approaches have been attempted with HIV antigens in preclinical mouse models. For example, a rBCG vaccine expressing the Env capsid protein of HIV induced a T_H1 response, however failed to promote HIV-specific antibody production (Yu et al., 2007), a rBCG vaccine expressing HIV viral antigens in combination with a viral vector elicited HIV-specific T-cell responses (Chapman et al., 2013), and rBCG-HIVA, expressing the H and P epitopes of the Env capsid protein and viral polymerase of HIV, induced activation of HIV-specific T-cells (Hopkins et al., 2011a, 2011b). Interestingly, combining rBCG-HIVA with a recombinant viral vector induced a robust T-cell response against HIV and *M. tuberculosis* (Hopkins et al., 2011a, 2011b). rBCG vaccines have also been developed to express antigens from human metapneumovirus (hMPV), a major cause of acute lower respiratory tract infections in children and the elderly (Lay et al., 2015). For example, a rBCG vaccine expressing the phosphoprotein of hMPV (rBCG-P-hMPV) induced humoral and T_H1 immune responses, reduced viral load in the lung parenchyma, (Soto et al., 2018; Céspedes et al., 2017), blocked T-cell infiltration, and conferred protection against hMPV in mouse models (Palavecino et al., 2014). rBCG vaccines have also been developed for human respiratory syncytial virus (hRSV) infections, one of the leading causes of acute lower respiratory tract infections and hospitalizations in children under 5 years of age (Shi et al., 2017; Mazur et al., 2018). A rBCG vaccine expressing the nucleoprotein (N) of hRSV (rBCG-N-hRSV) protects against hRSV in mouse models, reducing pathological damage and lung neutrophil infiltration (Soto et al., 2018; Céspedes et al., 2017). Interestingly, the vaccine induces secretion of viral-specific neutralizing antibodies, correlated with reduced lung viral titres (Soto et al., 2018; Céspedes et al., 2017). Furthermore, administration of rBCG-N-rRSV to mice induces a T_H1/T_H17 memory response that mediates virus clearance and reduces lung tissue damage (Céspedes et al., 2017). Therefore, rBCG vaccines represent a novel preventative approach for viral respiratory infections. Importantly, it remains unclear if rBCG vaccines convey the same broad spectrum protective effects as the unaltered strain (Covián et al., 2019). Furthermore, the lack of clinical trial data poses a major hurdle to the rapid clinical translation of any potential findings. Despite these limitations however, the development of a rBCG-SARS-CoV-2 vaccine combining the innate immunological boost of BCG vaccine for short-term protection with SARS-CoV-2 antigens for induction of a specific adaptive immune response for long-term immunity should theoretically convey increased protection, thus represents an intriguing area for further research.

5. Immunotherapeutic potential of BCG vaccination

Therapeutic utilization of microbe-induced immunomodulation could be a viable approach for conditions of immune dysregulation attributable to reduced infectious burden by mimicking the 'natural' exposure that has been removed from development. Indeed, evidence from clinical trials supports this assertion. For example, the prevalence of atopy is increased following helminthiases treatment (LYNCH et al., 1993) and *S. pneumoniae* vaccination (Klugman et al., 2003), the occurrence of atopic dermatitis is reduced by probiotic administration to pregnant women and newborns (Pelucchi et al., 2012; Kalliomäki et al., 2001, 2003), and disease progression of MS is attenuated by infection with *Trichuris suis* (Fleming et al., 2011; Correale and Farez, 2013). Exploiting the immunomodulatory capacity of BCG vaccine holds great promise as an immunotherapy (Mulder et al., 2019). Indeed, BCG vaccine is currently used as an immunotherapy for non-muscle invasive bladder cancer, with potential application for other malignancies (Sokal et al., 1974; Silverstein, 1974; Morton et al., 1974; Mulder et al., 2019). BCG vaccinated newborns have reduced rates of melanoma (Pfahlberg et al., 2002)and childhood leukemia (Morra et al., 2017), childhood BCG vaccination is associated with reduced risk of lung cancer in American Indigenous and Alaskan native populations (Usher et al., 2019), BCG induces tumor regression in non-invasive urothelial carcinoma (Herr et al., 1988; Herr and Morales, 2008), and direct injection of BCG vaccine induces regression of melanoma nodules (Morton et al., 1974). This anti-cancer effect has been attributed to trained immunity. Indeed, BCG induces the transcriptional reprogramming of tumoral macrophages that enhances pro-inflammatory responses and increased T-cell infiltration into the tumor (Lardone et al., 2017), thought to oppose the cancer-induced anti-inflammatory state (Prescott et al., 1992; de Boer et al., 1991; Böhle et al., 1990). Interestingly, BCG vaccine also induces bladder tumor cells to express antigen-presenting and co-stimulatory molecules, thus making them more visible to immune cells (Ikeda et al., 2002). In addition to cancer, BCG vaccination has been proposed as an immunotherapeutic for autoimmune conditions (Covián et al., 2019). Initial trials of BCG vaccine in type-1 diabetes mellitus (T1DM) patients reported disease remission when administered within the first month of diagnosis (Shehadeh et al., 1994). However, a subsequent trial reported no change in hemoglobin A1c (HbA1c) levels (a measure of blood glucose) or endogenous insulin production (Allen et al., 1999). In a phase 1 clinical trial, multiple doses of BCG vaccine in patients with long-term T1DM reduced HbA1c levels and promoted death of insulin autoreactive T-cells, associated with a systemic glycolytic shift in metabolism (Faustman et al., 2012). Similarly, BCG vaccination in long-term T1DM patients was reported to stabilize HbA1c levels without an increase in hypoglycemia, an effect that persisted for up to 8 years post-vaccination (Kühtreiber et al., 2018). Furthermore, in non-obese diabetic (NOD) mouse models of T1DM, BCG vaccination reduced insulitis and disease progression (Sadelain et al., 1990), mediated by TNF-α-induced destruction of insulin autoreactive T-cells (Kodama et al.,

2003). BCG vaccination has also been proposed as a treatment for multiple sclerosis (MS), a disease characterized by neurological dysfunction due to autoimmune-mediated CNS demyelination. Interestingly, BCG vaccination reduced frequency of active lesions (Ristori et al., 1999) and 5 year risk of developing clinical disease when administered following the first demyelinating episode (Brenner et al., 2014). In the MS mouse model of experimental autoimmune encephalitis (EAE), injection of extended freeze-dried (EFD) BCG attenuates disease severity, reduces spinal cord infiltration of CD45+ cells, and reduces T_{regs} in secondary lymphoid organs, consistent with attenuated disease severity (Lippens et al., 2018). BCG vaccine has also been proposed as an immunotherapeutic for use in neurodegenerative diseases, predominately Alzheimer's dementia (AD) (Gofrit et al., 2019a, 2019b). Indeed, bladder cancer patients treated with intravesical BCG vaccine are less likely to develop AD as compared to those not administered BCG therapy (Gofrit et al., 2019), attributed to induction of T_{regs} that suppress neuroinflammation (Gofrit et al., 2019) through IL-10 production (Kinney et al., 2018). Furthermore, there is an observed inverse correlation between BCG vaccination and AD/dementia in epidemiological studies (Gofrit et al., 2019) and BCG vaccination improves brain pathology and cognitive performance in the APP/PS1 mouse model of AD (Zuo et al., 2017). Further prospective data will be needed to unravel this intriguing connection.

6. Conclusion

Despite being introduced more than a century ago BCG vaccine remains highly relevant today. Exploitation of BCG-induced immunomodulation has widespread therapeutic potential, including the mitigation of autoimmune and allergic conditions attributed to reduced infectious exposure, the treatment of several types of cancers and neurodegenerative conditions, and in the prevention of the spread of SARS-CoV-2 infection and COVID-19 disease. Only further research will reveal the true potential of this multi-faceted immunomodulatory agent.

Author Contributions

A.J.M and Y.A.G. were involved in the conception and writing of the manuscript. Both authors contributed to critical revision and editing of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imbio.2020.152052.

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