A Note on the Potential BCG Vaccination – COVID-19 Molecular Link

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Abstract: Objective: Our goal was to elucidate a potential molecular link between the past and current tuberculosis vaccine Bacillus Calmette-Guérin (BCG; a live attenuated strain of Mycobacterium bovis) immunization policies and COVID-19.

Methods: Our sequence homology analyses have demonstrated that there is an intriguing level of sequence homology between a few of the BCG and Sars-CoV-2 proteins.

Results: The data suggest that the BCG-specific memory B-cells that are preserved in BCG-vaccinated patients cross-recognize SARS-CoV-2 and that this cross-recognition may affect the virus proliferation and COVID-19 severity.

Conclusion: Our results can stimulate the sharply focused follow-up experimental studies.

Keywords: Covid-19, BCG vaccination, Sars-CoV-2 B-cell epitopes, bioinformatics analysis, tuberculosis vaccine, Mycobacterium bovis.

1. INTRODUCTION

The goal of our report is to stimulate the sharply focused follow-up experimental studies of the Bacillus Calmette-Guérin (BCG) - COVID-19 axis. The emerging data suggest that there is a previously unrecognized link between the past and current tuberculosis vaccine BCG (a live attenuated strain of Mycobacterium bovis) immunization policies (summarized in The BCG World Atlas, www.bcgatlas.org) and COVID-19. Mandatory BCG vaccination appears to alleviate the severity of SARS-CoV-2 pathology in infected patients [1]. Most probably, SARS-CoV-2, a beta-coronavirus originated from either bats and/or pangolins [2-5], is a causative agent of COVID-19 pandemic. The most recent studies using publicly available data of COVID-19 in 199 countries/regions suggested that BCG vaccination may have hindered the overall spread of the virus or clinical manifestation of the disease or both [6]. As of today, there is no plausible molecular explanation of this phenomenon. We hypothesized that, in addition to a general immunity boost caused by BCG vaccination, there is a level of sequence homology between the viral and BCG proteins and that this homology contributes to the disease alleviation in BCG-vaccinated patients relative to a non-immune cohort.

2. RESULTS

To elucidate a possible mechanism that links BCG vaccination with SARS-CoV-2, we determined the level of homology between the proteins encoded by the viral and BCG genomes using the blastx program. In contrast with other sequence regions of the bacteria and the virus, there was a substantial level of homology of the N-terminal region of M. bovis BCG lipoprotein lppD sequence (NAANTRL/HAG-GVAAADARAGGPELQRESTE 208-238, numbering starts from the N-end of Uniprot A0A0H3M501_MYCBP) with the NAANVYLHGGVAGALNTATNAMQVESDD sequence of macrolomain 1 (an ADP-ribosylhydrolase, PDB 6VXS; Fig. 1A, Fig. 2 left) [7, 8] of the SARS-CoV-2 orf1a,b/nsp3 (identical and similar residues are in bold and italics, respectively). An additional intriguing homology was recorded between the C-terminal NNAALVLPQGTTLPKGF (bat) or NNAATVLPQGTTLPKGF (human) region of the RNA-binding domain of the SARS-CoV-2 nucleocapsid N phosphoprotein; PDB 6VYO; Fig. 2 right) [9-11], which represents a recently identified SARS-CoV-2 B-cell epitope [12, 13], and the sequence regions from the three different proteins in M. bovis BCG. These regions are as follows: the ATVTLTPNKLPKL region of dehydrogenase/reductase, the ATVQLLPFE region of putative drug-transport integral membrane protein and the ATVQLRNLPRGT region of putative secreted protein (Fig. 1B). Partial overlap of these BCG sequences with the viral B-cell epitope implies that the BCG-specific memory B-cells may cross-recognize the viral proteins and that this cross-recognition may affect the virus proliferation and disease severity.

Because a 15-year long post-vaccination protection against tuberculosis is highly credible, this may explain a low clinical manifestation, if any, of COVID-19 in children in China, a country with universal and long-standing BCG vaccination, and, on the contrary, a higher clinical manifestation in certain European countries where BCG programs are no longer deployed. Accordingly, the vaccinated elderly with a low residual level of the cross-reactive memory B-cells may be more susceptible to the virus relative to the freshly vaccinated youth. On the other hand, the vaccinated elderly

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Fig. (1). (A) Sequence alignment of the N-terminal region of *M. bovis* BCG lipoprotein lppD (range 208-238) with the macrodomain 1 of the SARS-CoV-2 orf1a,b/nsp3. (B) Sequence alignment of the C-terminal region of the RNA-binding domain of the SARS-CoV-2 nucleocapsid N phosphoprotein (these two sequences differ by a single mutation in bats versus humans), representing the recently identified SARS-CoV-2 B-cell epitope [12], with the three sequences of *M. bovis* BCG proteins: dehydrogenase/reductase, the putative drug-transport integral membrane protein and the putative secreted protein.

Fig. (2). Potential epitopes in SAR-CoV-2. Left - Dimeric structure of the SARS-CoV-2 ADP-ribosylhydrolase 1025-1190 fragment (PDB 6VXS) with the NAANVYLKHGGGVAGALNKATNNAMQVESDD 1059-1089 epitope. Right - Structure of the SARS-CoV-2 nucleocapsid N phosphoprotein (PDB 6VYO) with the NNAIILQLPGTTLPGKF 153-171 epitope. Epitopes are in red.
is likely to be more resilient to SARS-CoV-2 than the non-vaccinated elderly of similar age. These associations support the notion that BCG vaccination may provide specific protection against SARS-CoV-2 and that the protection level may directly be proportional to the residual cross-reactive B-cells, in addition to the general immunity boost caused by BCG. Furthermore, we speculate that the administration of the Purified Protein Derivative (PPD)/the Mantoux tuberculin skin test normally used for the detection of M. tuberculosis infection may be feasible for screening patients at risk of COVID-19. The test results may then serve as a surrogate marker for the prediction of the viral disease morbidity and mortality as well as to generate valuable information for the subsequent epidemiological studies.

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CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

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