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Tuberculosis 2020

Massimo Amicosante

From the University of Rome "Tor Vergata", Division of Clinical Biochemistry and Clinical Molecular Biology, Department of Biomedicine and Prevention, Italy

Despite over 30 years of interventions and plans of the World Health Organization (WHO) and other Public Health Agencies to control tuberculosis (TB) diffusion, the United Nations' millennium development goal for TB to halve the global prevalence and death rate by 2015 compared to 1990 has not been reached and is still far from being tackled.[1]

TB continues to cause an outsized burden of morbidity and mortality, remaining one of the human infections with the highest prevalence worldwide.[2] Accordingly to the latest WHO report on TB on data of 2014,[2] together with the indication that about one third of world population is infected by the *Mycobacterium tuberculosis* (MTB, the bacteria determining TB), there are an estimated 8.6 million new cases every year worldwide of whom about 1/3 can transmit the disease (sputum smear-positive pulmonary TB) and 1.6 million who die because of late diagnosis or lack of access to treatment.[1-3]

In Sub-Saharan Countries and South East Asia, the lethal combination of TB and Human Immunodeficiency Virus (HIV) co-infection leads to high incidence and mortality.[2] In Europe and other developed countries, immigration from sub-Saharan Africa and the Indian sub-continent has led to a rise in the number of cases. Whilst in Eastern Europe, and especially in former states of the Soviet Union, multidrug and extensively drug resistant TB (MDR- and XDR-TB, respectively) has become a major threat to health.[2]

The incredible high numbers for this disease, together with the diffusion of MDR and XDR MTB-strains, call for efficient measures of prevention and control. These are passing by (i) an efficient preventive vaccine to block the inter-human transmission of the MTB and (ii) the rapid identification of subjects with active-TB capable to transmit the bacillus.

Among different preventive strategies vaccination is potentially the most cost-effective in the long term to block the inter-human transmission of MTB. It is already available one vaccine for TB and it is the most widely used vaccine in the world.[4] The Bacillus Calmette-Guérin (BCG) vaccine – named after the French researchers who developed it by attenuating the *Mycobacterium bovis* (one mycobacteria belonging to the MTB-complex together with *Mycobacterium africanum, Mycobacterium microti* and *Mycobacterium canetti*) – was first used in people in 1921. BCG, though time tested, has major limitations. While BCG protects infants, it is relatively ineffective in older children and adults for multiple factors.[4] Therefore, in spite of the available vaccine there is a pressing need for a vaccine that will protect also older children and adults against TB.[4] The attempts to study new vaccines have hitherto been only partially successful or even completely unsuccessful, and in several case new vaccine product under study are not inducing better protection than BCG.[5,6] Disappointing results of recent clinical trials point to bottlenecks in identifying a large number of new viable candidate vaccines, as well as a suitable strategy for the evaluation of significant risks of failure at relatively late stages of the development process.[6] Currently, there are over 20 candidates at different stages of the clinical trial pipeline both for pre- and/or post-exposure TB preventing vaccines, but none of these candidates has completed yet immunogenicity/efficacy clinical trial.[7] Recently, one of the most promising preventive TB vaccine candidate (MVA85A) fails in phase 2b trial for absence of any protection.[6-7] Among the different reasons for this vaccine candidate failure, two critical aspects are playing a major role. First, the absence of appropriate markers of protection after MTB infection, and (ii) the almost exclusive target of the T-cell response against MTB induced by this vaccine.[5-7] Novel vaccine candidates targeting both T- and B-cell immune responses against MTB to promptly block MTB at the host entrance, might represent an efficient alternative for a novel vaccine development.[8]

Early identification of (i) active TB patients and (ii) subjects who will develop active TB after infection is essential to control TB transmission.[3,9] In this context, over 50% of the active-TB cases remain without any laboratory confirmation or with delay in diagnosis for unavailability or missing accessibility to efficient diagnostic tools[2,3] and about 10% of the prevalence cases are due to reactivation/relapse of the disease likely due to failure/not appropriateness of chemotherapy for missing access to appropriate tests.[2,3] However, current diagnostic tests for active-TB are affected by a large number of limitations due to reduced or suboptimal sensitivity (smear-test, and serological tests), time to obtain results (culture-based tests), or accessibility/instrumental needs and costs for efficient molecular assays.[3,9] In addition, tests for TB infection do not discriminate between those with latent TB infection (LTBI) who will not develop active-TB after contact (>90%), those who will go on to develop active disease and those with active and contagious TB.[3,9]

Therefore, there is an urgent need of efficient diagnostic tests for TB allowing the clear identification of (i) active-TB patients, (ii) infected subjects progressing to active TB that might benefit from preventive therapy, and (iii) the appropriate monitoring of therapy in active-TB patients.

However, due to the peculiar biology of MTB when interacting with the host, the definition of biomarkers efficiently targeting the various TB diagnostic issues is still far to come.[3,10] Only by combined studies tackling basic MTB biology and

immunological responses against MTB, will be possible to arrive at the definition of diagnostic systems for the accurate and personalized differential diagnosis of the various TB infectious stages.[3, 8-10]

In conclusion, TB is still a tremendous public health issue worldwide. The target of TB control passes from the development of novel efficient vaccine(s) and diagnostic tools that can be efficiently used in central and peripheral laboratories. To reach these goals, reseaches must focus on the understanding the intimate mutual interaction of the MTB and host for identification of novel vaccine targets and biomarkers for diagnosis and monitoring vaccine effectiveness.

References

1. World Health Organization (WHO). Millennium Development Goals (MDGs). Fact sheet N°290. Updated May 2015. Available from: http://www.who.int/mediacentre/factsheets/fs290/en/
2. World Health Organization (WHO). Global tuberculosis report 2015. Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1
3. Kunnath-Velayudhan S, Gennaro ML. Immunodiagnosis of tuberculosis: a dynamic view of biomarker discovery. Clin Microbiol Rev. 2011; 24(4):792-805.
4. Bourzac K. Infectious disease: Beating the big three. Nature. 2014 Mar 6;507(7490):S4-7.
5. Parida SK, Kaufmann SH. Novel tuberculosis vaccines on the horizon. Curr Opin Immunol. 2010 Jun;22(3):374-84.
6. Bishai W, Sullivan Z, Bloom BR, Andersen P. Bettering BCG: a tough task for a TB vaccine? Nat Med. 2013 Apr;19(4):410-1.
7. Kaufmann SH, Lange C, Rao M, Balaji KN, Lotze M, Schito M, Zumla AI, Maeurer M. Progress in tuberculosis vaccine development and host-directed therapies – a state of the art review. Lancet Respir Med. 2014 Apr;2(4):301-20.
8. Bavaro T, Piubelli L, Amicosante M, Terreni M. From new diagnostic targets to recombinant proteins and semi-synthetic protein-based vaccines. Current Organic Chem; 2016; 20(11): 1150-68.
9. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, Metcalfe JZ, Cattamanchi A, Dowdy DW, Dheda K, Banaei N. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014 Jan; 27(1): 3-20.
10. Nikolova M, Markova R, Drenska R, Muhtarova M, Todorova Y, Dimitrov V, Taskov H, Saltini C, Amicosante M. Antigen-specific CD4- and CD8-positive signatures in different phases of Mycobacterium tuberculosis infection. Diagn Microbiol Infect Dis. 2013 Mar; 75 (3): 277-81.