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Mini Review

Measuring autophagy level along with vaccine reactive IFN–γ+CD4+ Th1 cells may be a promising approach to understand efficacy of anti TB vaccine(s)

Abstract

Autophagy is a homeostatic process in the eukaryotic cells which contributes towards degradation of unwanted cellular constituents, killing of the invading intracellular microbes and generation of cell mediated immunity (CMI). The professional antigen presenting cells (APCs) like: macrophages and dendritic cells, present microbial antigens (derived from engulfed and killed microbe) in combination with MHC-II to generate IFN-γ producing CD4+ Th1 cells. Over the years, inducing IFN-γ+ CD4+ Th1 mediated CMI has remained, predominantly, as the target for developing anti TB vaccine. In individuals, where Mycobacterium tuberculosis (MTB) bacilli invading the APCs evade induction of autophagy, anti TB vaccine may not be effective due to lack of presentation of MTB derived antigens to generate and re-stimulate vaccine generated memory CD4+ Th1 cells. On the other hand, induction of autophagy in the APCs kills the invading MTB bacilli and may sufficiently present microbial antigens to generate and re-stimulate vaccine generated IFN-γ producing CD4+ Th1 memory cells. The re-stimulated memory cells then differentiate to effector CD4+ Th1 cells to release IFN-γ which further takes part in activation of antimicrobial activity in APCs thereby leading to protection of the vaccinees and sustaining the vaccine generated CMI. Keeping all these points in view, a hypothesis has been described here, wherein it has been suggested that measuring autophagy activation status in combination with prevalence of IFN-γ producing memory/effector CD4+ Th1 cells against vaccine antigens may prove to be promising biomarkers for assessing protective efficacy of anti TB vaccine(s).

Review

Why anti TB Vaccine?

Tuberculosis(TB), a disease caused by Mycobacterium tuberculosis (MTB), is a big public health problem [1], as: (i) every year it causes deaths to the tune of about 1–3 million (as observed during the last decade) active cases of TB (ii) about one third of the world's population has latent TB infection (LTBI), a big reservoir for adding (through activation of latent infection) to active TB burden (iii) infection due to HIV makes the individuals more susceptible/prone to develop active TB and (iv) drug resistant {multi drug resistant (MDR), extensive drug resistant (XDR) and total drug resistant (TDR)}strains of MTB have emerged over the years. In such a scenario, availability of preventive vaccine(s) against tuberculosis can help a lot in TB control through reducing the development of new TB cases and thereby stopping MTB transmission in the communities. However, as of now, there is no sufficiently effective vaccine against TB. Hence, all these facts have made global TB control cumbersome and reinforce the urgency of having an acceptably effective anti TB vaccine for overpowering this disease.

Vaccine works through generation of memory

Briefly, a vaccine induces immunity through generation of memory immune cells in the host tissues and lymph nodes. The memory cells thus produced are common against the antigen(s) present in the vaccine as well as the targeted agent (pathogen). On transmission of the pathogen to the vaccinated host the memory cells encounter the vaccine homologous antigens present in the pathogen and get activated. This makes the memory cells to generate quick and efficient immune response where–after the disease development is prevented by elimination of the infecting pathogen. Thus, vaccination is intended to prime the host immune system against the antigens present in pathogen [2,3]. An effective anti TB vaccine would be the one by which invading MTB could be eliminated due to vaccine generated immunity and whereby could provide protection against developing TB.

Lack of efficient biomarker(s) for assessing the protective efficacy of anti TB vaccine(s)

During last one decade, tremendous progress has been made towards developing anti TB vaccine and as a result thereof more than a dozen of candidate vaccines are available for their further evaluation [4,5]. However, based on the, over the years, experiences with candidate vaccine failures an apprehension on the protective efficacy of anti TB vaccine has been prevailing in scientific community [5-8]. Hence, it is considered that availability of efficient human derived biomarker(s) reflecting the protective efficacy of anti TB vaccine can accelerate searching effective anti TB vaccine(s). Keeping this in view, several immunological and bacteriological investigations have been conducted, in the past, to find out some reliable biomarker(s) for assessing the protective efficacy of anti TB vaccine [9,10]. Unfortunately, no such biomarker(s) is available, as yet. Therefore, an urgent need for identifying biomarkers/ approaches to evaluate vaccine efficacy is strongly felt. Thus far, measuring IFN-γ producing CD4+ Th1 cells has, mostly, been considered to be prominent, but not sufficient, biomarker for assessing the protective efficacy of anti TB vaccine [6,10]. In this communication, a combinatorial platform (involving autophagy as well as IFN-γ producing CD4+ Th1 cells) has been discussed to be worthwhile for understanding the protective efficacy of anti TB vaccine.

Autophagy and IFN-γ+CD4+ Th1 as possible biomarkers for assessing the efficacy of anti TB vaccine

During MTB infection, the bacilli enter the lungs where they are phagocytosed by antigen presenting cells (APCs) such as macrophages and dendritic cells which thereafter get involved towards generating cell mediated immunity after entering the draining lymph nodes [11]. Mostly, protection from TB is considered to be dependent on generation of IFN-γ producing CD4+ Th1 memory cells [6,10-12]. However, there are reports describing that despite potential generation of IFN-γ+CD4+ Th1 cells, a vaccine fails in protecting the host [3,6,8]. In this context, it is speculated [3] that failure of such CD4+Th1 cells inducing vaccines in protecting the host could be due to inability of APCs towards killing of the invading MTB bacilli in the vaccinated hosts. This in turn could cause lack/insufficiency of presentation of MTB derived antigens in combination with MHC-II. Such an aberration at the level of APCs, may result in failure to re-stimulate vaccine generated IFN-γ+CD4+ Th1 memory cells to evoke antimicrobial activity in APCs. This eventually, may lead to failure of protective efficacy of vaccine, despite persistence of vaccine generated memory CD4+ Th1 cells.

Autophagy is a biological process by which dysfunctional and un-necessary cytoplasmic components including intracellular microbes, are degraded for their recycling and elimination from the cell [13]. Normally (when autophagy is not up-regulated), MTB replicates inside the APCs through inhibition of autophagy. However, induced autophagy may play a vital role towards killing and elimination of phagocytosed MTB by APCs [14,15]. In the context of improving the vaccine efficacy, it is worth mentioning that intermittent induction of autophagy in vaccinees can kill the invading phagocytosed MTB and thereby can enhance presentation of MTB derived antigens. This in turn, stimulate anti TB vaccine generated IFN-γ producing memory CD4+ Th1 cells to proliferate and differentiate into IFN-γ producing effector cells [16,17]. The IFN-γ produced by such stimulated cells may further be involved in generating anti-mycobacterial activity in APCs and thereby towards sustenance of vaccine generated CMI. In brief, IFN-γ+CD4+ Th1 inducing anti TB vaccine could be effective through prevalence of augmented autophagy in APCs and prevalence of memory IFN-γ+CD4+ Th1 cells in the vaccinees [18].

Conclusion

Over the years, assessing generation of IFN-γ producing CD4+ Th1 cells has been considered to reflect protective efficacy of anti TB vaccine in the vaccinees [6,10]. However, this approach alone is not sufficient. Keeping above described discussion in view, it is worthwhile suggesting that measuring elevation in autophagy levels in APCs along with vaccine specific memory and/or effector IFN-γ producing CD4+ Th1 cells may act as better reflectors of protective efficacy of anti TB vaccine. Though, the suggested approach appears to be logical and promising it deserves its exploration.

Acknowledgements

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