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Editorial

Searching Anti Leprosy Vaccine: Views to go Forward

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Abstract

A preventive anti leprosy vaccine can contribute considerably towards global control and even elimination of leprosy. However, there is no successful vaccine available as yet. *M.leprae* is known to evade/subvert the antimicrobial activity of the invaded antigen presenting cells (APCs; macrophages and dendritic cells). Therefore, the cause for failure towards developing anti leprosy vaccine could be lack of presentation of *M leprae* antigens to re-stimulate the candidate vaccine generated $CD4^+$Th1 type of memory cells against *M.leprae*. Since, autophagy is known to kill *M.leprae* and present its antigens, intermittent induction of autophagy might help in improving vaccine efficacy by re-stimulation of vaccine induced memory cells and thereby persistence of vaccine generated immunity. On the other hand, T cell subsets other than $CD4^+$Th1 are also known to be protective in leprosy. A strategy involving such immune cells towards formulating anti leprosy vaccine may also prove to be advantageous. Hence, investigations on these aforementioned approaches are worthwhile exploring.

Keywords: Leprosy; Vaccine; Autophagy; Multiplex; Immunity; T subsets

Editorial

Leprosy is a chronic contagious disease caused by infection with *Mycobacterium leprae* (*M.leprae*), an obligate intracellular microbe which harbours, primarily, macrophages and Schwann cells. During this disease, mainly, skin and nerves are affected where immunological complications can result in nerve damage and thereby neuropathy leading to disabilities [1]. Over the years, despite remarkable global decrease in leprosy cases the new case detection rates have not changed much. The data from 106 countries documented occurrence of 210758 new cases during 2015. Of these, 22 countries have been reported to be high burdened [2]. Though Multi Drug Therapy (MDT) has brought down the global number of leprosy patients, persistence of new cases could be due to limitations of MDT and/or due to prevalence of undetected leprosy cases [2,3]. The existing scenario points-out that leprosy infection is still going on in community and for many countries it is still an important public health problem. Though, leprosy has been controlled significantly; nevertheless, its further control and finally, elimination can be boosted by anti *M.leprae* vaccine. As yet, no efficient anti leprosy vaccine is available for its use for prevention of occurrence of leprosy. Hence, efforts towards searching better vaccine are underway in several laboratories [4]. Through this communication, an attempt has been made to share views to further refine research on developing anti leprosy vaccine.

During early stage of *M.leprae* infection, innate immunity acts as a first checkpoint to defend the non-immune host. Individuals who are resistant to leprosy eliminate invading *M.leprae* after their destruction by Antigen Presenting Cells (APCs), particularly macrophages. On evasion of this check point *M.leprae* persists in the host and induces adaptive type of immunity [Humoral (HI) or Cell Mediated Immunity (CMI)] which is considered to be the primary determinant for manifestation of the disease as a spectrum where two polar forms viz: Lepromatous Leprosy (LL) and Tuberculoid Leprosy(TT) lie at two opposite ends of the spectrum [5]. Humoral immunity to *M.leprae* antigens is highest in LL form and on the other hand, CMI to *M.leprae* antigens is highest in TT. Likewise, *M.leprae* load is highest in LL but lowest in TT type of leprosy. Other than these two polar forms, there exist sub-polar but immunologically unstable forms which are known as Borderline Lepromatous (BL), Borderline-Borderline (BB) and Borderline Tuberculoid (BT) type of leprosy. Among these sub-polar forms of leprosy HI to *M.leprae* antigens and *M.leprae* load are lower (in a graded manner from BL to BB to BT form) when compared to LL form. Similarly, CMI to *M.leprae* antigens and *M.leprae* load increases, again, in a graded manner from BL to BB to BT leprosy. All these phenomena indicate that LL is most susceptible (due to inadequate CMI to *M.leprae* antigens) type of leprosy which has disseminated infection. Contrarily, TT is most resistant (due to good CMI to *M.leprae* antigens) form of leprosy where infection with *M.leprae* remains restricted. Thus, CMI is considered to be involved in defending the host against *M.leprae* infection.

A large body of literature has described that the CMI generated by $CD4^+$ Th1 cells provides protection against *M.leprae* infection. However, for induction of this type of immunity, *M.leprae* antigens need to be presented (in combination with MHC-II) by antigen presenting cells viz. Macrophages, Dendritic cells and Langerhan's cells [6]. A $CD4^+$Th1 based anti leprosy vaccine could be successful if vaccine generated $CD4^+$ Th1 type of memory cells are re-stimulated, by invading *M.leprae*, to give rise to effecter cells to protect the vaccinees. Occurrence of such a phenomenon can take place only when antigens derived from infecting *M.leprae* are processed and presented by APCs. However, *M.leprae* has been reported to impair antigen presenting process in APCs from leprosy patients [6-9]. This reflects that, probably, APCs from leprosy prone individuals may also fail in presentation of *M.leprae* antigens. This in turn may result in failure to re-stimulate vaccine generated $CD4^+$ Th1 memory cells and thereby towards maintaining the persistence of vaccine generated immunity. Hence, it may give rise to an apprehension about the efficacy of anti leprosy vaccine [10], particularly in *M.leprae* infected individuals who are prone to progress towards lepromatous type of

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leprosy. This all could be due to inability to generate sufficient CMI against *M.leprae* antigens. Taking stock of the forging discussion, it is worthwhile to improve the performance of anti leprosy vaccine by focusing on (i) modulation at the level of APCs to improve *M.leprae* antigen presentation and/or (ii) broadening of vaccine generated immunity by multiplexed formulation of vaccine.

Primary goal of a vaccine remains generation of immune response to contain growth of invading pathogen at the initial step of the insult (when bacterial number per invading cell may be scant) leading to prevention of development of disease and thereby spread to other members in the community. Among various APCs, for induction of Th1 mediated CMI, macrophages are found in abundant. To overcome hurdle at the level of antigen presentation for developing effective anti leprosy vaccine, probably, induction of autophagy in macrophages may help in improving the vaccine performance. Normally, *M.leprae* is known to be destroyed by autophagy [11], however, in leprosy prone individuals it may evade/subvert this line of defence [12] leading to progressive growth of leprosy bacilli and thereby disease. Autophagy is also known to be involved in antigen presentation in combination with MHC-II to stimulate $CD4^+$ Th1 mediated CMI. Moreover, autophagy may also contribute towards generation of CMI through production of IL1-β [13,14]. Hence, intermittent induction of autophagy might prove to be a promising platform for re-stimulation of vaccine induced memory cells in *M.leprae* encountering leprosy prone individuals and thereby for maintenance and persistence of vaccine generated CMI. Otherwise, vaccination without coupling with intermittent induction of autophagy may not protect individuals on their exposure to *M.leprae* [10]. Feasibility of such an approach has already been described in context of anti TB vaccine [14,15]. Hence, investigations on suitable autophagy inducing agents/strategies need to be explored keeping their safety and optimal frequency in view for intermittent induction of autophagy. Hopefully, this strategy may improve vaccine efficacy.

Multiplexing approach involving more than one immune components as well as potent antigens might also help in improving the vaccine efficacy. Thus far, various types of immune cells including CD4 (Th1 and Th17), CD8, natural killer (NK) cells, γδT cells [6,16-18] and several *M.leprae* antigens [4] have been reported to be involved in protective immune response against *M.leprae* infection. Over the years, efforts on developing anti leprosy vaccine have, largely, remained focused on inducing $CD4^+$ Th1 cell mediated immunity against *M.leprae* [4]. Keeping in view the diversity at the levels of protective immune components as well as *M.leprae* antigens, it is worth suggesting that a multiplex vaccine considering various relevant immune cells and potent *M.leprae* derived antigens may prove to be more effective. This all could be due to enhanced immunogenicity and broadening of vaccine generated immunity against *M.leprae*. Though tempting (but challenging) such a formulation needs to be well analyzed in terms of immunological behaviors of candidate immune cells and *M.leprae* antigens in combination. Only those combinations which would show additive effects regarding protection could be considered as desirable candidates for anti leprosy vaccine. It would be interesting to combine this approach with autophagy enhancing platform to further improve the vaccine efficacy. Though promising for developing a potential vaccine, making efforts on these lines are worthwhile.

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References

1. Britton WJ, Lockwood DN. Leprosy. Lancet. 2004; 363: 1209-1219.
2. World Health Organization. Global leprosy update, 2015: time for action, accountability and inclusion. Wkly Epidemiol Record. 2016; 91: 405-420.
3. Prasad P, Kaviarasan PK. Leprosy therapy, past and present: 90. Can we hope to eliminate it? Indian J Dermatol. 2010; 55: 316-324.
4. Duthie MS, Gillis TP, Reed SG. Gillis TP, Reed SG. Advances and hurdles on the way toward a leprosy vaccine. Hum Vaccine. 2011; 7: 1172-1183.
5. Parkash O. Classification of leprosy into multibacillary and paucibacillary groups: an analysis. FEMS Immunol Med Microbiol. 2009; 55: 1-5.
6. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev. 2006; 19: 338-381.
7. Hirschberg H. The role of macrophages in the lymph proliferative response to Mycobacterium leprae *in vitro*. Clin. Exp. Immunol. 1978; 34: 46-51.
8. Holzer, TJ, Nelson KE, Schauf V, Crispen RG and Andersen BR. Mycobacterium leprae fails to stimulate phagocytic cell superoxide anion generation. Infect. Immun. 1986; 51: 514-520.
9. Sibley LD, Franzblau SG and Krahenbuhl JL. Intracellular fate of Mycobacterium leprae in normal and activated macrophages. Infect. Immun. 1987; 55: 680-685.
10. Parkash O. Antileprosy vaccines: an apprehension. Int. J. Lep. 1995; 63: 572-573.
11. Ma Y, Zhang L, Lu J, Shui T, Chen J, Yang J, et al. A Negative Feedback Loop Between Autophagy and Immune Responses in Mycobacterium leprae Infection. DNA Cell Biol. 2017; 36: 1-9.
12. Yang D, Chen J, Shi C, Jing Z and Song N. Autophagy gene polymorphism is associated with susceptibility to leprosy by affecting inflammatory cytokines. Inflammation. 2014; 37: 593-598.
13. Dupont N, Jiang S, Pilli M, Ornatowski W, Bhattacharya D, Deretic V. Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1β. EMBO J. 2011; 30: 4701-4711.
14. Ben-Sasson SZ, Hu-Li J, Quiel J, Cauchetaux S, Ratner M, et al. IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci USA. 2009; 106: 7119-7124.
15. Parkash O. Anti Tuberculosis Vaccine and Autophagy: A Possible Platform to Improve the Performance of Vaccine. J Infect Pulm Dis. 2015; 1.
16. Jagannath C, Bakhru P. Rapamycin-induced enhancement of vaccine efficacy in mice. Methods Mol Biol. 2012; 821: 295-303.
17. Sieling PA, Ochoa MT, Jullien D, Leslie DS, Sabet S, Rosat JP, et al. Evidence for human CD^+ T cells in the CDl-restricted repertoire: derivation of mycobacteria-reactive T cells from leprosy lesions. J. Immunol. 2000; 164: 4790-4796.
18. Saini C, Ramesh V, Nath I. $CD4^+$ Th17 cells discriminate clinical types and constitute a third subset of non Th1, Non Th2 T cells in human leprosy. PLoS Negl Trop Dis. 2013; 7: 2338.

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