Can we say bye to BCG?

A recent report on the trial of BCG vaccines in South India for prevention of tuberculosis has indicated that BCG did not offer any protection against the adult form of bacillary pulmonary tuberculosis[1]. The study concluded that BCG cannot be expected to reduce the transmission due to tuberculosis. This observation of failure to protect, could not be attributed to defects in methodology, inadequate sample size, prior exposure to environmental mycobacteria or to the fact that mostly the disease was a result of exogenous reinfection. These unexpected results have posed the relevant question whether to continue BCG vaccination programmes in India. Earlier reports in this direction[2,3] also raise questions about the utility and efficacy of the BCG vaccine. The entire issue is very complex, thought provoking and needs critical evaluation and introspection.

The entire medical community in India, especially pediatricians and general practitioners are in a conflicting situation whether to use BCG vaccines. In this context we would like to present our views regarding immunological aspects of BCG vaccination and its role as Biological Response Modifier (BRM) which seems to protect individuals from autoimmune diseases especially type-I diabetes as well as from certain types of cancer. Immunologists caring for patients with autoimmune diseases need to establish organ specific immunological tolerance which is just as important as that facing transplant surgeons. In this context immunostimulation approach to prolong insulin production in the newly diagnosed diabetic is very promising. The strategy is based on the lower incidence of diabetes in NOD mice stimulated immunologically with bacillus Calmette-Guerin (BCG)[4] through stimulation and expansion of populations of T-cells making IL4 or IL10 (ref. 2) indicating upregulation of Th-2 wing. BCG vaccination is already known to be safe and immunogenic, and a preliminary human study has given some evidence about its benefits[5] and suggested that BCG vaccination may alter the natural history of the disease process in humans. A possible mechanism of the preventive effect of BCG against diabetes mellitus in NOD mice has also been reported[6]. Further, it has been shown that BCG injections prior to induction of diabetes in mice by low dose STZ injection depicting autoimmune diabetes have led to prevention of insulities[7] and thereby diabetes. All these reports indicate the beneficial effect of BCG vaccination in upregulating Th-2 wing and thus reducing the incidence of autoimmune diseases in general and type-I diabetes in particular.

Exposure to environmental pathogens can have a marked effect on the development of diabetes in disease-prone animals. Environmental stimulation of the immune system leads to a decrease in the proportion of animals that go on to develop clinical disease. Immunostimulation of disease-prone animals with agents such as complete Freund's adjuvant or the BCG vaccine blocks the development of diabetes in disease-prone NOD mice[5,8]. Immunostimulation with either of these agents blocks the development of disease both when administered early, that is, soon after weaning or quite late in the pathogenic process. Such immunostimulation does not inhibit the development of autoimmunity however, it does force the autoimmune response along a non-destructive pathway.

These observations emphasize the need to view the immune system as an integrated network regulated by both positive and negative influences. This positive and negative regulation of immune function is correlated with the nature of cytokine production in either destructive or non-destructive lesions[9]. Though the mechanism of adjuvant effect is not fully understood the fact that quite marked effects have been obtained in animal models using both complete Fruend's adjuvant and BCG vaccine has prompted clinical testing of BCG vaccination in newly diagnosed diabetic individuals. In addition, vaccination with autologous tumour cells accompanied with BCG as adjuvant has been shown to effectively prevent metastasis after successful surgery of colon cancer[10].

The reports cited here indicate the usefulness of BCG vaccine as immunostimulation to protect individuals from immunological disorders or from immune regulatory failures. Hence, we strongly propose continuation of BCG vaccination programme to prevent tubercular meningitis, if not bacillary pulmonary tuberculosis in India.

1. Narayanan, R. P., *Indian J. Med. Res.*, 1999, **110**, 56–69.
2. Maes, R. F., *Med. Hypotheses*, 1999, **53**, 33–39.
3. Sterne, J. A., Rodrigues, L. C. and Guedes, I. N., *Int. J. Tuberc. Lung Dis.*, 1998, **2**, 200–207.
4. Harada, M., Kishimoto, Y. and Makino, S., *Diabetes*, 1990, **8**, 85–99.
5. Shehadeh, N., Calcinaro, F., Bradley, B. J., Bruchlim, I., Vardi, P. and Lafferty, K. J., *Lancet*, 1994, **343**, 706–707.
6. Yagi, H., Matsumoto, M., Kishimoto, Y., Makino, S. and Harda, M., *Cell Immunol.*, 1991, **138**, 142–149.
7. Baik, S. H., *Diabetes Res. Clin. Pract.*, 1999, **46**, 91–97.
8. Sadelain, M. W. J., Qin, H-Y., Lauzon, J. and Singh, B., *Diabetes*, 1990, **39**, 583–589.
9. Shehadeh, N. N., LaRosa, F. and Lafferty, K. J., *J. Autoimmun.*, 1993, **6**, 291–300.
10. Tarasov, V. A., Filatov, M. V., Kisliakova *et al.*, *Hybridoma*, 1999, **18**, 99–102.

RAMESH BHONDE
PRADEEP PARAB

National Centre for Cell Science,
NCCS Complex,
Ganeshkhind,
Pune 411 007, India