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Immunotherapy

DNA vaccination during TB treatment generates super-protective immunity

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After tuberculosis, 'cured' individuals remain susceptible to disease, but not when cured with drugs plus DNA. This is the striking conclusion to be drawn from a study of DNA vaccination during chemotherapy of tuberculosis in mice described on pages 634–638 of this issue.[1] The implications are profound, both for practical control measures and for understanding the immunology of persistent infection.

Tuberculosis is a global emergency.[2,3] Yet, about 90% of people who become infected with *Mycobacterium tuberculosis* do not develop disease, do not become infectious and their immune response sooner or later eliminates the infection. They are not the problem. Tuberculosis occurs in the remaining 10% in whom the immune response is insufficient. Even in these individuals, the immune response usually arrests the initial bacterial growth and dispersal through the body before the disease develops. Bacterial numbers decline, but a few bacteria persist in a semidormant, nonculturable form in multiple locations, often for months and years, before growth resumes at one or more sites, usually in the lung. Devastating immunity-driven disease, bacterial dissemination and transmission ensue.

Thus, individuals in whom the immune response has been suboptimal and has then become disastrous are the cause of the global emergency. These are the patients who currently have to be cured by anti-tuberculosis drug chemotherapy and that is not easy in practice.

Chemotherapy has to be prolonged, for a minimum of 6–9 months with the currently available drug combinations, because of the persistence of the semidormant bacteria that are consequentially rather refractory to the drugs. In general, this period is too long and fully effective treatment is difficult to achieve in most of the regions and countries where tuberculosis is a major problem, so that relapse of 'cured' patients and an associated emergence of drug resistance are common. If treatment could be shortened, the benefit could be enormous. Adding on immunotherapy could be one way.

The study by Ha *et al* draws on growing evidence that DNA vaccination after infection can enhance protective immunity beyond the levels that BCG – the common vaccine for TB – or *M. tuberculosis* itself elicits, at least in mice. As they and others have shown, giving a DNA vaccine expressing one or two mycobacterial antigens during chemotherapy can eliminate the nonculturable bacteria that would otherwise reactivate and cause relapse. A vaccine or a derivative immunotherapeutic agent that does this in man might well be achievable and a good case can be made for early evaluation of even the existing prototype DNA vaccines as adjuncts to chemotherapy.

However, the study of Ha *et al* goes well beyond the impact on an established infection; the mice acquired long-lasting enhanced immunity to reinfection too. If this can be extrapolated to man, it means that cured patients would remain cured, against both reactivation and reinfection. Mixing the vaccine DNA with empty plasmid DNA showed that the effect was only partly dependent on antigen expression from the vaccine; clearly, the plasmid DNA backbone of the vaccine itself can modulate the ongoing immune response to the antigens that are being released from the dying bacteria into a more protective form. This effect might have been further enhanced when the plasmid did produce antigen, but only when the expression exceeded some threshold.

The described vaccine construction is novel in incorporating adenovirus tripartite leader sequence and herpes simplex virus glycoprotein signal sequence to enhance expression. This might help to explain the striking vaccine efficacy that was obtained, in contrast to the mixed results that others report. Nevertheless, a mixture of 50% vaccine DNA and 50% empty plasmid was no better than empty plasmid alone, implying that antigen production might still be close to the threshold. One wonders how much further manipulation of the vaccine to increase antigen production, processing and presentation could further enhance immunity. New ways of doing this are continually being devised.[4,5]

The limited immunological analysis in this study does not begin to indicate how DNA vaccines cause the stable step-change in immunity. However, they do add to the growing evidence that increases in antigen-specific T-cell production of interferon-γ are not sufficient and might even be unnecessary;[6] increased protection against reinfection did not correlate with increased frequency of those cells. Something else, perhaps the regulation of cytotoxic and bactericidal lymphocytes,[7,8] must have changed.

The implications of these findings extend to the development of prophylactic vaccines to replace BCG.[9] Such a replacement is sorely needed. To be superior to BCG, a replacement vaccine will have to raise immunity that extra step, beyond where BCG and natural infection reach. By succeeding in the therapeutic context and even protecting against reinfection, DNA vaccines will have demonstrated that they can do this and provide a valuable lead. ■

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