A Better Grip: T Cells Strengthen Our Hand against Influenza

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(See the article by Berthoud et al, on pages 1–7.)

Influenza A virus represents a major ongoing threat to public health owing to its propensity to evade immune control at the individual and population level. Infection can be prevented by pre-existing antibodies against the viral surface glycoproteins, hemagglutinin, and neuraminidase, but these are antigens that vary greatly within and between subtypes. Current immunization strategy relies heavily on the induction of strain-specific serologic immunity by trivalent inactivated vaccines that must be redesigned and produced annually to reflect circulating strains. As a consequence, we are perpetually at risk from new variants, including reassortant virus strains, with their attendant threat of pandemic influenza. Recent experience during the influenza H1N1 pandemic emphasized the enormous logistical challenge of generating and delivering new vaccines in a timely fashion.

Perhaps there is another way. The existence of antiviral cytotoxic T cell (CTL) immune responses has long been described and linked with amelioration of influenza. In mice, influenza-specific CTL can protect against otherwise lethal influenza [1]; in challenge studies involving humans, individuals with greater CTL responses experienced milder symptoms and reduced viral shedding [2]. As elegantly demonstrated by Townsend and McMichael [3], these responses tend to be directed not at the highly variable surface proteins but at epitopes within the conserved internal proteins of the virus.

The cross-reactivity of such T cell-mediated responses between subtypes is supported by theoretical, epidemiologic, and, latterly, in vitro immunologic analyses. Of note, Lee et al demonstrated T cell responses against H5N1 antigens in individuals without serologic evidence of ever having met this subtype of virus [4]. Cross-recognition was evident at polyclonal and clonal levels, in terms of cytotoxicity and cytokine production, and against both synthetic influenza peptides and vector-encoded whole viral antigens. Of importance, responses to 2 internal viral antigens, nucleoprotein and matrix protein 1, predominated and were also the most likely to cross-react between subtypes. Evidence suggests that influenza-specific CTL responses decay with a half-life of 2–3 years, however, presumably accounting for periodic re-infection in healthy adults [5]. This begs the question, could CTL immunity be boosted by suitable vaccination in vivo to provide heterosubtypic protection in time of need? Although an obvious candidate T cell immunogen would be the live attenuated influenza vaccine already in limited use, this showed a disappointing failure to boost cellular responses in healthy adults, despite apparently priming cell-mediated immunity in children [6].

In an important article in this issue, Berthoud et al [7] describe an alternative, vector-based strategy that results in reproducible boosting of influenza-specific T cell responses in healthy adults. Modified vaccinia virus Ankara (MVA) is a highly attenuated poxvirus that was derived by serial passage of vaccinia virus, can be engineered to express candidate antigens of interest, and has previously shown a favorable safety and immunogenicity profile [8]. Drawing on their extensive experience of MVA-based vaccine development for other infectious diseases, the authors engineered a vector expressing influenza A nucleoprotein and matrix protein 1 [7]. Adult volunteers were vaccinated once with either a high or a low dose of influenza-recombinant MVA, leading to a striking increase in the frequency of circulating influenza-specific effector T cells over the subsequent weeks that persisted for at least 6 months. CD8+ T cells predominated...
over CD4+ T cells and were polyfunctional, as assessed by their ability to produce cytokines (interferon-γ, interleukin-2, and/or tumor necrosis factor) and/or to degranulate on influenza peptide exposure. Of no surprise, this boosting effect was greatest in individuals who received the higher dose of MVA, albeit at the cost of significantly greater vaccine-related adverse effects.

These early phase clinical data offer proof of principle that boosting of T cell–mediated influenza immunity can be achieved and provide a strong rationale for the further studies that are planned. An early goal must be to define robust correlates of heterosubtypic protection, whether vaccine induced or naturally acquired; in particular, which aspects of CTL function are most protective? What is the effect on viral shedding? Is MVA really superior to live attenuated influenza vaccine or adjuvanted trivalent inactivated vaccines for the induction of cellular immunity and, if so, why? What is the duration of protection? Will antivector antibodies prove to be limiting for the maintenance of heterosubtypic protection by repeated vaccination? Answers to such questions will not only inform the development of a potentially important mass public health intervention, but also promise to advance our general understanding of antiviral immunity.

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References