EPITOPE-BASED VACCINES: PROBLEMS AND PERSPECTIVES

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There is no doubt that the conceptual leap in understanding which led to the realization that one may use individual epitopes rather than whole microorganisms or its proteins antigens as vaccines has paved the way for more versatile and flexible strategies (1). Indeed this approach now offers the possibility of eventually circumventing hurdles posed by some of the more intractable pathogens with respect to eliciting protective immunity, thus the problem of antigenic variation (as in the case of HIV-1) may conceivably be tackled by using a cocktail of spectrum of epitope variants. Furthermore complications arising due to the presence of immunodominant decoy sequences or subdominance or masking of neutralization epitopes can potentially be eliminated with not be expected to have any of these attendant problems. However, despite the multifarious advantages that epitope-based strategies offer there are nevertheless some limitations that hamper their applicability. It is our opinion that the eventual success of this strategy will be contingent upon the successful resolution of these issues.

INDIVIDUAL EPITOPES

At the level of individual epitopes there are three principal drawbacks which dominate the issue. The first is that of genetic restriction. Because epitopes represent only a fraction of Th-cell determinants on pathogens it is likely that they will lack the ability to induce Th-cell activation in the context of a variety of MHC class II alleles. Since all vaccines are always intended for outbred populations this may pose a serious problem. However the recent discovery of **promiscuous** T cell epitopes offers a solution to the problem. The second hurdle is that of conformation. The overall determinants are described not only by primary amino acid sequence but also by secondary and, in many cases, tertiary structure of proteins. Thus a mimetic of a native epitope must represent not only the sequence but also the native conformation. This problem is an extremely daunting one and has not proved very easy to resolve. The third obstacle is that of immunogenicity. It is truism that smaller peptide sequences are less immunogenic that larger ones result of which epitope-based constructs are less likely to induce potent, long-lasting immune responses in the host. This is again not a trivial problem since any successful vaccine is expected to induce long-lasting immunity.

POLY-EPITOPE CONSTRUCTS AS VACCINES

Despite of what has been said earlier it must be realized that in many if not most cases immunization with a single epitope is unlikely to provide an effective immune cover for the host. This is especially true of multi-stage pathogens (eg. the malaria parasite *Plasmodium falciparum*) or pathogens showing a high degree of antigenic diversity (eg. HIV-1). The prospect of designing multiple-epitope constructs therefore needs to be considered. From a generic stand-point the problem poses it self as -How does one design such poly-epitope molecules in a manner that will be immunologically productive?. This again is not necessarily a trivial question since there are several potential problem which can complicate idealized immunological behavior, some of these are: (a) creation of irrelevant junctional epitopes, (b) fine specifity of antibody response, (c) selective immunodominance of B cell epitopes. Over the last few years our group has been engaged in systematically addressing these various issues, some successfully and some not so successfully (2-9). The presentation will summarize our efforts in this area and also attempt to delineate future directions.

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