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SYNTHETIC PEPTIDES AS THE BASIS FOR ANTI-VIRAL VACCINES

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One of the exciting lines of investigation in immunology today is to establish whether synthetic peptides or their conjugates might replace the presently existing vaccines for providing protection against infectious diseases, including viral disease. In our early studies this approach was demonstrated to be feasible in the case of a model system, namely the bacteriophage MS-2. We demonstrated that a synthetic conjugate, containing a 20 amino acid residue peptide corresponding to a part of the phage's coat protein, elicited in rabbits antibodies with efficient anti-viral neutralizing activity (1). Furthermore, attachment of the synthetic adjuvant muramyl dipeptide to the above conjugate resulted in a completely synthetic anti-MS-2 vaccine with built-in adjuvanticity (2). Similar results were subsequently achieved in various laboratories with synthetic peptides corresponding to an antigenic determinant of diphtheria toxin (3), or to the immunizing fragment of M protein of Streptococcus pyogenes (4). The synthetic approach has been applied in the case of several animal viruses as well. Studies with hepatitis B, conducted by five different groups, all led to synthetic peptides which elicited antibodies reactive with the intact virus, in one case even inducing partial protective immunity in chimpanzees (5). In the case of foot and mouth disease virus, a 20 amino acid residue peptide of the VP_1 protein elicited neutralizing antibodies in guinea pigs that led to their protection against infection with the virus (6).

In our laboratory we have studied the system of the influenza virus. We have synthesized an 18-amino acid residues peptide corresponding to sequence 91-108 of the hemagglutinin of H3 influenza strains, and conjugated it to tetanus toxoid. This conjugate elicited in rabbits and mice anti-peptide antibodies that reacted also with the intact influenza virus of several A type H3 strains. Moreover, these antibodies were capable of inhibiting the hemagglutination activity of the relevant strains and to interfere with the *in vitro* growth of the virus in tissue culture. More importantly, mice immunized with the peptide-toxoid conjugate were partially protected against further challenge infection with several strains of influenza H3 virus (7). It should be noted that this particular sequence, which is common to at least twelve strains of influenza, comprises a folded region in the hemagglutinin peptide chain, which is adjacent to a proposed antigenic site. This could explain its cross-

strain protective effect. In this case as well MDP attached to the conjugate served as a built-in adjuvant (8).

More recent data are indicative of two other hemagglutinin synthetic peptides corresponding to the sequences 138-164 and 181-200 of the molecule, respectively, that also elicit protective immunity. One of these peptides comprises the ''loop'' region of the hemagglutinin (140-146) which is considered to form the entire antigenic site ''A'', and in addition a part of antigenic site ''B'' of the molecule. Conjugate of this peptide with tetanus toxoid induced in rabbits antibodies that cross-reacted with the intact virus. Furthermore, immunization of mice with this synthetic vaccine also resulted in partial protection against challenge infection (9). Conjugates containing the octapeptide 139-146 induced anti-peptide antibodies which did not recognize the virus even though anti-viral antibody reacted with the free peptides. The peptide 181-200 also elicited anti-influenza immune response with partial protection against infection. In the case of this peptide we could also demonstrate cellular immune response (10), which could be a significant factor in the future design of synthetic vaccines.

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