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Vaccinia virus recombinants: potential vaccines

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Vaccinia virus was used extensively in the smallpox eradication campaign and has proved itself to be a very effective vaccine. This can be attributed to a number of factors, notably, the ease with which it can be administered to large numbers of people by semi-skilled personnel as a single dose, the low manufacturing costs, and the great stability of the vaccine in the freeze dried form. Several groups (Mackett et al., 1982; Panicali and Paoletti, 1982; Kieny et al., 1984; Boyle et al., 1985) have reported the construction of vaccinia virus recombinants that express protective antigens from pathogenic agents. Thus it is hoped that vaccination with vaccinia recombinants will protect against a wide range of pathogens by illiciting a protective immune response against the foreign gene product as well as vaccinia itself.

These recombinants have generally been made by a two step procedure. The first step involves assembling a plasmid which contains a chimaeric gene flanked by vaccinia virus DNA. The chimaeric gene consists of a vaccinia virus transcriptional start site and upstream regulatory sequences adjacent to the protein coding sequence of the foreign gene. When inserted into vaccinia virus the chimaeric gene should be transcribed from the normal vaccinia RNA site and the mRNA produced should be translated into the authentic foreign protein. The next stage is insertion of the chimaeric gene into vaccinia virus. Transfection of vaccinia virus infected cells with the constructed plasmid allows homologous recombination to occur between the sequences flanking the chimaeric gene and the corresponding sequences in virus genomic DNA. The result is that, at low frequency, the chimaeric gene is inserted into virus DNA which is packaged, yielding infections recombinant virus.

The recombinant viruses can then be detected by a variety of methods. The virus DNA that flanks the chimaeric gene determines the site at which the foreign gene is inserted. Obviously this site must be non-essential for virus growth in tissue culture and although a number of different sites have been used most genes have been inserted into the virus thymidine kinase (TK) locus. The

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reason for this is that recombinant viruses have a TK minus phenotype and can be selected by growth in the presence of BudR. It has also been reported that TK minus viruses are less virulent than the wild type TK positive parental virus (Buller et al., 1985).

The foreign proteins made by vaccinia virus recombinants are of the predicted size and undergo appropriate post-translational modifications. Glycosylation (Smith et al., 1983a; Mackett and Arrand, 1985), proteolytic cleavage (Rice et al., 1985) and γ carboxylation (de la Salle et al., 1985) of foreign genes have been reported. The foreign gene product is also transported normally and has been detected on the appropriate cell surface (Stephens et al., 1986) or excreted from infected cells (Smith et al., 1983). Several recombinant vaccinia viruses have induced immunological responses to the foreign gene products in vaccinated experimental animals. A case is also reported of accidental vaccination of a human with a recombinant vaccinia virus (Jones et al., 1986). Although previously vaccinated L. Jones produced antibody which reacted with the foreign gene. In many cases antibody responses have neutralised virus infectivity in vitro and more importantly experimental animals have been protected against subsequent challenge with the appropriate virus. So far experimental animals have been protectively immunized against influenza virus (Smith et al., 1983b; Small et al., 1985), hepatitis B virus (Moss et al., 1984), herpes simplex virus types 1 and 2 (Paoletti et al., 1984; Cremer et al., 1985), Rabies virus (Kieny et al., 1984; Wiktor et al., 1984) and vesicular stomatitis virus (Mackett et al., 1985).

Cell mediated immune responses directed against the foreign gene products expressed by vaccinia have been detected (Bennink et al., 1984; Yewdell et al., 1985; McMichael et al., 1986). Cytotoxic T lymphocytes that recognise the haemagluttinin or nucleoprotein of influenza virus were induced by recombinant vaccinia viruses expressing these genes.

The ability of these live recombinant viruses to stimulate both cell mediated and humoral immune responses against the foreign gene product enhances the potential of these viruses as live vaccines. However, this approach is not without its problems. Many of the diseases against which recombinant vaccinias may be turned are chronic infections with large human or animal reservoirs and therefore control or eradication pose greater problems than that of smallpox. Serious adverse reactions to vaccinia possibly as high as 1 in 50,000 vaccinations (Lane et al., 1969) were sufficient cause for concern to encourage the development of attenuated vaccinia virus strains in the late 1960's and early 1970's. TK minus recombinant viruses are attenuated (Buller et al., 1985) and this may well be sufficient to reduce complication rates. Other problems may be encountered due to previous vaccination against smallpox, or even vaccination with a recombinant virus. Immunity to vaccinia may prevent sufficient replication of a recombinant virus and hence decrease the immune response to the foreign gene. As vaccination against smallpox has ceased in most parts of the world for as long

as 10 years, significant numbers of children have not been vaccinated and many adults' immunity to vaccinia is low. If this approach is widely adopted, then careful consideration of who to vaccinate against what may be required.

The large capacity (25 Kb or more) of vaccinia for foreign DNA (Smith and Moss, 1983) permits simultaneous expression of multiple foreign antigens creating polyvalent vaccines (Perkus et al., 1985). Polyvalent vaccines could be designed to fit needs of a particular geographical area, for example, a vaccine that simultaneously immunized against EBV, HBV, poliovirus and several haemorrhagic fevers would be highly desirable in Southern China. The potential advantages of immunization against diseases causing high morbidity and mortality such as HBV or Malaria seem to greatly outweigh the rare adverse complications especially if polyvalent vaccines could be produced.

In summary, vaccinia virus recombinants are a very attractive alternative to the use of subunit vaccines and are especially suited to use in the third world.

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