Surface bacterial antigen CS31A as a tool to design new recombinants vaccines displaying heterologous antigenic determinants

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La capside des rotavirus est relativement complexe. Elle peut être représentée par un modèle de 3 couches concentriques. Elle est constituée de 4 protéines majeures (VP2, VP6, VP7, VP4) et de 2 protéines minoritaires (VP1, VP3). Chacune de ces protéines a été clonée et exprimée dans le système baculovirus–cellules d'insectes. L'expression de VP2 conduit à la formation de particules sphériques correspondant à la couche interne de la capside. La co-expression de VP2 et de diverses protéines structurales conduit à des pseudo particules stables (VLP : *virus like particles*) faciles à purifier. La co-expression de VP2 et VP6 permet d'obtenir des VLP2/6 qui sont morphologiquement identiques aux particules dont la couche externe a été solubilisée par chélation de calcium. De même, la co-expression des protéines VP2, VP6, VP7 (que VP4 soit co-exprimée ou non) conduit à des particules qui sont superposables en microscopie électronique aux particules virales complètes et infectieuses.

La stocchiométrie des différentes VLP coincide assez bien avec celle des particules virales infectieuses. Ces différentes VLP conservent aussi les caractéristiques antigéniques et fonctionnelles des virions authentiques. En particulier les VLP sont capables de fusionner avec des vésicules membranaires ou entrer en compétition avec des virus lors de mesure de l'attachement sur des cellules sensibles. Il est aussi possible d'obtenir des particules chimériques contenant des protéines provenant de souches virales appartenant à des sérotypes ou à des sérogroupes différents. Cette capacité des protéines virales de s'auto-assembler d'une façon précise (et cependant assez souple) permet d'aborder l'étude des interactions entre protéines de structure, le rôle de chaque protéine dans les différentes étapes de l'infection ou de la morphogenèse, et aussi les propriétés vaccinales de chaque protéine. Enfin ces VLP sont potentiellement utilisables pour vectoriser des antigènes (ou des drogues) et les cibler vers l'entérocyte.

Références

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Surface bacterial antigen CS31A as a tool to design new recombinant vaccines displaying heterologous antigenic determinants. C Martin, JP Girardeau, M Der Vartanian, MC Méchin, F Bousquet, Y Bertin, H Laude *, M Contrepois *(INRA-Theix, laboratoire de microbiologie, 63122 Saint-Genès-Champanelle; * INRA, laboratoire de virologie et immunologie moléculaires, domaine de Vilvert, 78352 Jouy-en-Josas cedex, France)*

New recombinant vaccines composed of a genetic fusion between an immunogenic bacterial protein and a foreign antigenic determinant (epitope) are currently under investigation. Such vaccines would present considerable advantages such as safety, low production cost, and ease of transport. The carrier proteins fimbriae have the advantage of being readily accesible to the host's immune system since

they are external to the bacteria. Furthermore, they are highly immunogenic and are present in great quantities on the cell surface. Consequently, a foreign epitope inserted into fimbriae would be introduced over the entire surface of the bacterial cell and, because of the polymeric structure of the pili, it would be repeated many times along its length. We therefore investigated the possibility of using the *Escherichia coli* polymeric surface antigen CS31A (Girardeau *et al*, 1988) as a vaccine candidate presenting viral epitopes. For this purpose, we introduced epitopes from different origins into 2 regions of ClpG, the major structural protein of CS31A. Epitopes from sites C and A of the porcine transmissible gastroenteritidis virus (TGEV) were introduced between amino acids –1 and +1 of the preprotein, and/or in the immunodominant V3 region (aa 190–aa 221). In the latter, epitopes from bovine rotavirus, poliovirus and FMDV were also introduced. These modifications of the ClpG sequence did not impede CS31A biogenesis, indicating that these regions are highly permissive to foreign insertions. Furthermore, the foreign epitopes were cell-surface-exposed and antigenic in their novel environment as observed by immunofluorescence or immunoelectron microscopy (Bousquet *et al*, 1994; Der Vartanian *et al*, 1994). Groups of mice were immunized intraperitoneally with recombinant bacteria synthesizing the various ClpG/viral epitope proteins or with purified recombinant ClpG/TGEV proteins emulsified in incomplete Freund's adjuvant. In the mice inoculated with the bacteria, an anti-foreign epitope antibody response was elicited in most cases in spite of the very complex immunogenic pattern of the bacterial cell surface. However, the antibody titers were low and the sera did not always recognize the viral particles. The amount of foreign epitope was probably too low to induce a high response (Bousquet *et al*, 1994). Purification of hybrid proteins allowed immunization with a known quantity of antigen (20 µg/injection). In these conditions, an early and high antibody response was elicited against the TGEV epitopes, especially when both epitopes were associated on the recombinant molecule. These sera recognized the virions and neutralized the cytopathic effect of TGEV on swine testis cell culture. Furthermore, anamnestic anti-TGEV antibody responses were observed when the mice were boosted with the recombinant protein or even with the virus itself 100 d following the priming. These experiments prove that CS31A is indeed a valuable tool for the exposure of foreign antigenic determinants in a vaccine design since high immunogenicity, immunological memory, and seroneutralization were demonstrated using 2 epitopes from the TGEV. Stimulation of the mucosal immunity by oral inoculation of recombinant bacterial strains or purified recombinant proteins associated with ISCOMs or cholera toxin is now under investigation.

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