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Pathogenesis and immunity in gonococcal infection.

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Studies on immunity to Neisseria gonorrhoea and the development of vaccines against gonorrhoea has been hampered by the multiple immune evasion mechanisms exhibited by gonococci and by the lack of a suitable animal model in which all aspects of the disease could be analysed. We have used the subcutaneous model of gonococcal infection which allows study of immune responses and protection as well as antigenic variation and inflammation. This model is not suitable however, for analysis of responses induced by the interaction of gonococci with the host mucosal system. Recently, we have developed a new mouse model of mucosal immunization to study immune responses at the mucosal level and systemic antibody and cellular responses following mucosal stimulation. Using the subcutaneous chambers model we have shown the crucial role of lipopolysaccharide (LPS) in virulence and particularly, the importance of LPS antigenic variation and in vivo sialylation as immune evasion mechanisms. We have demonstrated that infection with an attenuated aroA mutant induces a powerful immune response that results in protection against challenge in most animals. The antibody response is directed mainly to the proteins, but the precise identity of proteins eliciting a protective antibody response is not clear yet. We have lately obtained evidence of T cell responses following gonococcal infection. The cellular response detected is a TH1 response, is specific, and can be demonstrated in vitro using spleen T cells from guinea pigs or mice recently recovered from gonococcal infection, stimulated with a gonococcal whole cell lysate. In addition, using a new model, we have demonstrated that oral administration of live gonococci to mice results in production of specific IgA in the genital mucosa and systemic antibody and T cell responses.

The main clinical manifestation of gonorrhoea is the appearance of an acute inflammatory exudate containing mainly polymorphonuclear cells (PMN) some of which harbour large numbers of gonococci. The interaction of gonococci and phagocytic cells is complex and is not clear yet whether the restricted capacity of gonococci for invasion is due to the lack of capacity to invade on the part of the bacteria or to the efficiency of local non specific defence mechanisms like inflammation. The acute inflammatory cell infiltration may play an important part in the localization of gonococcal infection. In the guinea pig subcutaneous

chamber model, the inflammatory response remains acute with a majority of PMN and much fewer numbers of either macrophages or lymphocytes, even in prolonged infections lasting several weeks. The signals elicited by N. gonorrhoeae early during infection which stimulate this acute inflammatory response are still not fully characterised. Additionally, host processes which may prevent dissemination and are thus responsible for localization of infection are not known. We have shown the presence of the inflammatory cytokine TNFa in chamber fluid removed during infection with strain MS11 or LPS variants of strain GC40 in the guinea pig. We have studied the inflammatory response further, by measuring cytokines produced by human macrophages and PMN cells after in vitro stimulating with gonococci or their products and using Salmonella for comparison. The results indicate that gonococci induces a more prolonged release of IL-8 than Salmonella and that proteins as well as LPS are capable of stimulating inflammatory cytokine production.