7
Protection of Mucosal Epithelia by IgA: Intracellular Neutralization and Excretion of Antigens

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7.1. Introduction

Mucosal immunoglobulin A (IgA) antibodies are synthesized by local plasma cells in the lamina propria and are largely destined for export through the lining epithelium into the luminal secretions. Here, IgA antibodies can bind antigens and exclude them from the body, as has long been appreciated. It is becoming increasingly apparent, though, that passage through mucosal epithelium creates additional opportunities for IgA antibodies to function in host defense. For example, IgA antibodies against viruses can directly counter infections within mucosal epithelium, and immune complexes formed in the lamina propria containing locally produced IgA antibodies can pass through the epithelium via the same route and mechanism as free IgA. Thus, IgA antibodies might first encounter antigens in three anatomic compartments in relation to mucosal epithelium: in the lumen, in the epithelium itself, or in the lamina propria (Lamm, 1997). The nonclassical defense functions of IgA, in which IgA antibodies initially bind antigens in the lamina propria or inside the lining epithelial cells, are the focus of this chapter.

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7.2. Intraepithelial Cell Neutralization of Viruses by IgA Antibodies

Viruses are obligatory intracellular parasites, and IgA antibodies secreted by lamina propria plasma cells pass through the epithelial cells that cover the mucous membrane by receptor-mediated endocytosis and transcytosis in order to reach the lumen. These facts prompted the following question. What would happen if antivirus IgA antibodies were passing through an epithelial cell that happened to be infected by the same virus? Specifically, would the antibodies actually encounter viral antigens, and, if so, would the virus be inhibited? These issues have been explored in model systems both in vitro and in vivo.

Studies in vitro have taken advantage of the ability to grow polarized monolayers of epithelial cells that express the receptor for IgA, the polymeric Ig receptor (pIgR), on their basolateral surface (see Chapter 3). The cell often employed is the dog kidney epithelial cell line MDCK, transfected so that it expresses pIgR (Mostov and Deitcher, 1986; Tamer et al., 1995). This cell line has long been used by cell biologists for studying epithelial cell traffic because it grows easily in vitro and readily polarizes (i.e., forms monolayers in which the cells are attached to their neighbors by tight junctions and have apical and basolateral plasma membrane domains with different compositions, morphologies, and functions). Receptors for internalizing particular viruses may be preferentially expressed at the apical or basolateral side, and release of newly formed virus particles may be similarly polarized.

The original system used to demonstrate intraepithelial cell neutralization of virus by IgA antibody employed polarized monolayers of MDCK cells that expressed pIgR. The cells were grown in two-chambered transwells and infected via the apical surface with Sendai virus, a rodent paramyxovirus. Subsequently, IgA monoclonal antibodies to viral envelope protein were added to the lower chamber, from which they could be internalized by the pIgR. Assays for virus in the apical supernatant and cell lysate, together with appropriate controls, showed that the growth of virus had indeed been inhibited by the ability of the IgA antibody to bind viral protein intracellularly (Mazanec et al., 1992). Analogous model systems have since been used to demonstrate intracellular neutralization of a number of viruses belonging to different classes, including influenza virus (an orthomyxovirus) (Mazanec et al., 1995), measles virus (a paramyxovirus) (Yan et al., 2002), rotavirus (a reovirus) (Corthésy et al., 2006; Feng et al., 2002), and human immunodeficiency virus (HIV: a retrovirus) (Huang et al., 2005; Wright et al., 2006).

From the available studies collectively some tentative general conclusions can be drawn. One, the antiviral effect is mediated by IgA antibodies that are following the normal route of epithelial endocytosis and transcytosis. Thus, to be effective, IgA antibodies must be polymeric, and the epithelial cells must express pIgR at the basolateral surface. Two, IgA antibodies tend to be more effective when directed at antigens displayed on the surface of the virus as opposed to internal viral antigens. This result is thought to reflect that surface antigens