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IgA Plasma Cell Development

Jo Spencer¹, Laurent Boursier¹, and Jonathan D. Edgeworth²

2.1. Introduction

Evolution in biological systems is rarely wasteful; it involves both adaptation and conservation of resources. In this context especially, the quantity of IgA secreted onto mucosal surfaces and the cellular processes that generate it are all the more remarkable. Approximately $10^{10}$ plasma cells per meter of gut are situated in the diffuse connective tissue stroma between the epithelium and the muscularis mucosa referred to as the lamina propria (Fig. 2.1) (Brandtzaeg et al., 1999; Brandtzaeg and Pabst, 2004). These produce antibody, most of which is immunoglobulin A (IgA), so that $\sim 3–5g$ of IgA is actively transported each day into the lumen of the human gut (Conley and Delacroix, 1987). This secreted

¹ Peter A. Gorer Department of Immunobiology, Kings College London School of Medicine at Guy’s King’s College and St. Thomas’ Hospitals, Guy’s Hospital, London, SE1 9RT, United Kingdom
² Department of Nephrology & Transplantation, Kings College London School of Medicine at Guy’s King’s College and St. Thomas’ Hospitals, Guy’s Hospital, London, SE1 9RT, United Kingdom
antibody has a critical role in maintaining homeostasis in an environment where the immune system and potentially proinflammatory bacterial stimuli are closely juxtaposed and separated by a single epithelial layer (Fagarasan et al., 2002). The aim of this chapter is to discuss the mechanisms that generate, diversify, and disseminate this extensive IgA-producing plasma cell population. There are considerable interspecies differences in mucosal lymphoid tissue that will be identified where relevant, but the final outcome in all species is the same: the production of the largest population of plasma cells in the body.

An early indication of local production of mucosal immunoglobulins was provided by Ogra and Karzon (1969), who noted specific antibody in secretions but not serum in response to human mucosal immunization with polio vaccine. The cellular basis for this partitioning of mucosal and systemic responses was identified by Gowans and Knight (1964), who described the “homing” of adoptively transferred and labeled immunoblasts from thoracic duct lymph of rats (which contains the lymphatic drainage from the gut), back to the gut. Craig and Cebra (1971) identified that commitment to IgA production was associated with the Peyer’s patch (PP) B-cells. Although the dynamics of the responses were debated to some degree, it was generally agreed from studies of animal models at the time that PPs are a source of precursors of IgA plasma cells that enter the blood via the lymphatics and subsequently home back to the gut and that might proliferate locally in response to local antigenic challenge before terminal differentiation (Husband, 1982; Husband and Gowans, 1978).

Analysis of human plasma cells and their precursors has been advanced by studies of the non-germline-encoded junctional regions of the immunoglobulin variable region (IgV) genes, which are unique for each cell (or clone of cells) of B lineage. Microdissection of cells from different zones of tissue sections combined with IgV gene analysis identified clonally related cells in the germinal centers of PPs and the adjacent lamina propria, indicating the origin of plasma

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**FIG. 2.1.** Paraffin sections of (a) colon and (b) ileum stained with antibody to IgA. IgA plasma cells are visible in the lamina propria. Under higher magnification (inset), single IgA plasma cells can be identified by abundant oval cytoplasm, eccentric round nucleus with characteristic condensation of chromatin that resembles a clock face.