

# Where do IgA plasma cells in the gut come from?

S J C Golby, J Spencer

The relationship between mucosal IgM and IgA has recently been addressed in murine systems to investigate how IgA secreting plasma cells localise in the intestine and to determine if switching from IgM to IgA occurs in the microenvironment of the gut mucosa

The gut is the major site of antibody production in humans. The most abundant isotype produced is IgA, but the importance of IgA has been questioned. On the one hand, in IgA deficient patients, IgM can compensate functionally<sup>1,2</sup>; on the other hand, it might be argued that such flexibility is an absolute requirement because the system is indispensable.<sup>3</sup> The relationship between IgM and IgA in humans has been studied by analysis of the immunoglobulin genes used by plasma cells. Such studies can give information on the history of the B cells that generated them because they contain a unique fingerprint acquired during B cell development that enables the identification of related cells. Investigations of human mucosal plasma cells have shown that in humans, clonally related IgM+ and IgA+ plasma cells that probably secrete antibody with the same specificity can occupy the same mucosal microenvironment.<sup>4-7</sup> In addition, immunoglobulin genes become mutated if the cell has been selected for the production of high affinity antibody. In the human gut, IgM is encoded by mutated genes<sup>4</sup> and is therefore associated with secondary immune responses, alongside IgA and IgG, and it is perhaps not surprising that it can compensate functionally in IgA deficiency.

In mice the situation appears to be quite different; cells expressing IgM appear to be more strictly the precursors of IgA secreting cells. In mice, approximately 50% of intestinal IgA plasma cells are derived from IgM expressing cells in the peritoneal cavity. These cells, known as B1 cells, are a self replenishing population, many of which express the CD5 antigen.<sup>8</sup> The remaining 50% of plasma cells are derived from B cells in the organised lymphoid tissue in the Peyer's patches and are known as B2 cells. Theoretically, the peritoneal precursors generate a rapid, although relatively low affinity response against potential pathogens while in contrast, Peyer's patches take longer to generate a plasma cell response, but this response is of high affinity and specificity.<sup>9</sup>

The relationship between mucosal IgM and IgA has recently been addressed

**Fagarasan S, Kinoshita K, Muramatsu M, et al.** In situ class switching and differentiation to IgA-producing cells in the gut lamina propria. *Nature* 2001;**413**:639-43.

**One of the front lines of the immune defence is the gut mucosa, where immunoglobulin-(IgA) is continuously produced to react with commensal bacteria and dietary antigens. It is generally accepted that, after antigenic stimulation in the Peyer's patches, IgA+ lymphoblasts (B220+IgA+) migrate through the lymph and blood circulation, and eventually home to the lamina propria of the intestine. Mice that lack activation-induced cytidine deaminase (AID) are defective in class switch recombination (CSR) and somatic hypermutation. CSR changes the immunoglobulin heavy chain constant region (CH) gene being expressed from Cmu to other CH genes, resulting in a switch of the immunoglobulin isotype from IgM to IgG, IgE or IgA. AID-/- mice also secrete large amounts of immunoglobulin-mu (IgM) into faeces, and accumulate B220-IgM+ plasma cells as well as B220+IgM+ cells in the gut. Here we show that lamina propria B220+IgA+ cells have just completed CSR, as they still express both AID and transcripts from circular DNA that has been "looped-out" during CSR. Lamina propria IgM+ B cells seem to be pre-committed to switching to IgA+ in vitro as well as in vivo. Culturing lamina propria IgM+ B cells together with lamina propria stromal cells enhances preferential switching and differentiation of B cells to IgA+ plasma cells. We conclude that IgA+ cells in the gut lamina propria are generated in situ from B220+IgM+ lymphocytes.**

in two murine systems in order to investigate how IgA secreting plasma cells localise in the intestine and to find out if switching from IgM to IgA occurs in the microenvironment of the gut mucosa.<sup>10,11</sup> The two reports have generated quite different answers and the likely explanation is that they have studied different populations of cells: the plasma cells derived from B1 cells and from B2 cells.

The first of these studies, by Fagarasan and colleagues<sup>10</sup> from Kyoto University in Japan, demonstrated that in mice, B cells are indeed able to undergo class switching from IgM production to IgA production in the intestinal lamina propria, in the absence of germinal centres or T cell help.

Mice that are deficient in the enzyme activation induced cytidine deaminase (AID) are defective in both class switch recombination and somatic hypermutation.<sup>12</sup> Fagarasan *et al* observed that these mice accumulate IgM+ cells in the lamina propria gut and excrete increasing amounts of IgM in their faeces with

age. This suggested that in normal mice, IgA+ cells might be generated in the lamina propria from IgM+ cells.

Isolation of lamina propria IgM+ cells from normal mice revealed that they express both AID and  $\alpha$ -germline transcripts, showing that they are ready to undergo class switch recombination. Lamina propria IgA+ cells also expressed transcripts from circular DNA that is excised during switching, indicating that at least some of them had very recently undergone class switch recombination. When cultured with lipopolysaccharide, interleukin 5, and transforming growth factor  $\beta$ , the lamina propria IgM+ cells generated IgA+ cells but the Peyer's patch IgM+ cells did not. Addition of lamina propria stromal cells preferentially enhanced switching to IgA and differentiation into plasma cells. The authors proposed that the switching is occurring in gut homing B1 cells derived from the peritoneum that had not previously passed through Peyer's patches.

The other recent study, from Bowman and colleagues,<sup>11</sup> focused on the homing

of bone marrow derived B2 cells to the murine intestine. These cells initially enter the Peyer's patches where they switch to expressing IgA, before returning to the blood and homing to the lamina propria. This report demonstrated that the thymus expressed chemokine (TECK), which is expressed in the lamina propria of the small intestine, selectively attracts IgA+ splenic B cells but not IgM+ splenic B cells. It remains to be seen whether the IgM+ B1 cells studied by Fagarasan *et al* are responsive to TECK.

Not much is known about the role of TECK in B cell migration in humans. TECK expression has been observed in the crypt epithelium of the human small intestine.<sup>13,14</sup> Only approximately 2% of freshly isolated peripheral blood CD19+ B cells migrate in vitro in response to TECK<sup>15</sup> but it would be interesting to see which isotype these cells express and whether they possess any gut homing markers such as  $\alpha 4\beta 7$  or  $\alpha E\beta 7$ .

It is not known whether B1 cells are involved in human mucosal antibody responses and it will be important to answer this question if we are to appreciate the level of relevance of these ground breaking observations in animal models to human physiology and disease. It is essential that we understand the different B cell homing and class switching mechanisms in humans because mucosal immunisation, for example, would be more difficult if a significant proportion of the effector

population produces antibody with low affinity and low specificity. Similarly, in inflammatory bowel disease, it would increase our understanding of the disease process if we knew why the profile of immunoglobulin isotypes secreted by lamina propria plasma cells is altered.

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#### Authors' affiliations

S J C Golby, J Spencer, Histopathology Department, Guy's, King's and St Thomas' School of Medicine, St Thomas' Campus, London SE1 7EH, UK

Correspondence to: J Spencer;  
jo.spencer@kcl.ac.uk

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