Ito Cells, Stellate Cells, and Myofibroblasts: New Actors in Antigen Presentation

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Winau et al. (2007) provide convincing evidence that liver stellate cells can be antigen-presenting cells. This paper raises the following question: what are the roles and importance of diverse antigen-presenting cells in different organs?

Investigations in the last several years indicate that each organ in the body is capable of regulating antigen processing and presentation. This regulation is heavily dependent on anatomical and physiological considerations such as: patterns of blood flow, barriers to vascular permeability, features of endothelial cells, organization of connective tissue, expression of adhesion molecules and chemokines, and, of course, the antigen-presenting cells (APC) of the tissue. The features of antigen presentation in the brain, with its tight control of vascular permeability and its barriers for lymphocyte entry, is very different from other organs such as liver, lungs, or pancreas. Although general rules apply, nevertheless each organ has a unique set of properties that influence and modulate how the innate and adaptive cellular systems interact with microbes and foreign proteins that invade them, and with self proteins, in case of autoimmunity.

Antigen presentation in each organ is dependent on the content and activity of their APC, which include the physiological, or “professional” ones, the dendritic cells (DC) and macrophages derived from bone marrow stem cells by way of the monocyte (see recent review of Reis e Sousa, 2006), APC may also include the B cells. An issue concerning antigen presentation among various organs is the extent to which cells other than the professional APC handle and present antigens. Such cells serving as APC may have a profound influence on presentation. This is the central issue raised in the paper by Winau et al. (2007). What are potential “nonprofessional” APC? These may include the major component cells of the organ that give it its individuality—hepatocytes, intestinal epithelial cells, thymocytes, nerve cells, and so forth. In general, these cells have a limited role in initiating T cell activation: most do not express the molecules required for presentation including class II MHC molecules, and the expression of class I is limiting in many of them. However, the claim was raised early on that upon inflammation, and in response to cytokines, tissue cells may aberrantly express MHC molecules, and in this way present autologous antigens (Bottazzo et al., 1983). The extent to which this effect takes place has still to be determined. A second cellular component in organs is their stroma with its content of vessels and connective tissue cells. More attention to the stromal cellular elements seems justified as a result of the findings by Winau et al. (2007).

Winau et al. (2007) examined hepatic stellate cells or Ito cells (named for the Japanese anatomist that described them). These cells have been of major interest for those studying liver pathology (Geerts, 2001) but have not been the subject of much attention by the immunology community. Ito cells, which comprise about 5%–8% of total cells in the liver, are located at a strategic site in the space of Disse (Figure 1). The liver sinusoid contains a layer of fenestrated endothelial cells that separate the lumen of the sinusoid from the hepatocytes. The space of Disse is situated between the endothelial layer and the hepatocytes, and in it are situated the Ito cells. On the other hand, Kupffer cells, which represent in number the major APC in liver, and DC face the lumen.

Stellate cells are not confined to the liver but are found in many tissues and organs where they have been examined in the context of inflammation and fibrosis. These cells show a number of distinguishing features: they are contractile and phagocytic and display extensive dendrites and lipid droplets; they express vimentin, the intermediate filament protein glial fibrillary acidic protein (GFAP), usually found in neural cells; and they are the major reservoir for vitamin A in the body. Importantly in the context of liver fibrosis, upon their activation stellate cells produce extracellular matrix proteins including collagen (Geerts, 2001). Stellate cells will transdifferentiate to myofibroblasts upon stimulation by cytokines, particularly TGF-β. Myofibroblasts show features of smooth muscle cells expressing α-smooth muscle actin and responding to environmental signals by releasing extracellular matrix proteins (Powell et al., 1999; Tomasek et al., 2002). Stellate cells and myofibroblasts are important in wound healing, in control of local blood flow during inflammation, and in tissue repair processes. Stellate cells have been claimed to be of mesenchymal or endodermal origin, but this needs to be definitely established (Geerts, 2004; Ogawa et al., 2006).

Winau et al. (2007) carried out an extensive series of experiments in which Ito cells isolated from either human or murine livers were examined for several parameters of presentation. Ito cells displayed CD1d molecules and were highly effective in activating NKT cells. NKT cells recognize glycolipid antigens from self proteins and from microbes and are known to be
enriched in liver. Ito cells secreted IL-15, an important cytokine that regulates NK and NKT cells, and expressed the costimulatory molecule CD86. When injected intravenously into CD1d null mice, Ito cells induced NKT cell proliferation. Winau went on to show that not only did Ito cells present antigens via CD1d, but also by class I and II MHC pathways. Indeed, mice injected with Ito cells infected with *Listeria monocytogenes* expressing the protein ovalbumin developed protective immunity to *Listeria ovalbumin* and activated ovalbumin-specific CD8+ T cells. Thus, Ito cells can process intracellular bacteria and are effective in crosspresentation. This study encourages an examination of the potential role in infection of stellate cells. In sum, the extensive analysis by Winau et al. (2007) makes a strong case for Ito cells as fully capable APC.

A previous study also documented some antigen-presenting features of human liver stellate cells (Viñas et al., 2003), although it did not investigate antigen presentation except in the limited context of an allogeneic reaction. Viñas et al.’s indicated that human stellate cells expressed MHC molecules and responded to cytokines by expressing costimulatory molecules.

What is the relative contribution of antigen presentation by stellate cells compared to other cells of the liver parenchyma such as Kupffer, DC, and sinusoidal endothelial cells (Figure 1)? Although Winau et al. (2007) show that injection of Ito cells plus antigen are effective in activating T cells, this approach does not establish the relative contribution of the various APC, an issue that is difficult to determine. Along these lines, a recent report (Schmeig et al., 2005) indicated that mice depleted of CD11c+ cells lost NKT cells in spleen but not in the liver despite depletion of DC in both organs. When mice were injected with chloroquine-containing liposomes, which targets phagocytic cells and depletes both Kupffer cells and DC, liver but not spleen NKT cells were affected. They concluded that the major APC responsible for activation of NKT cells differed between liver and spleen. Because Ito cells, as Winau et al. (2007) discuss in their paper, are phagocytic, it needs to be determined whether the chlordanate treatment also targeted them. This is unlikely, given the anatomical situation around the GFAP+ Ito cells. Thus, the relative contribution of stellate cells as APC, their unique responses as part of immunological interactions warrants a critical examination. APC-T cell interactions not only result in activation of T cells, but also of the presenting cell. In the scenario of the stellate cell interacting with T cells, the stellate cell response in terms of fibrogenesis and control of blood flow could be of major importance.

**REFERENCES**


**Figure 1. Cells of the Liver Sinusoids**

The Ito or stellate cells are located in the space of Disse, which is separated from the lumen by the fenestrated endothelium. Kupffer cells and DC face the lumen.