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Review

Mucosal immunity in liver autoimmunity: A comprehensive review

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ABSTRACT

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) all nestle within the umbrella term of autoimmune liver disease, in which the end result is immune-mediated hepatocellular or hepatobiliary injury. All three conditions are associated with gut inflammation; PSC and AIH being strongly linked to inflammatory bowel disease (IBD) and PBC to coeliac disease. This clinical observation has stimulated several intriguing pathogenic concepts in which gut commensals, pathogens and intestinal antigens are all implicated in causing liver injury. T_h17-cells have also been linked to AIH, PBC and more recently PSC. Given that the intestine is a key regulator of immunopathogenic T_h17 responses, this may underpin a common disease mechanism and open up novel treatment avenues based on rational targeting of immune pathways. Moreover, the discovery of long-lived mucosal memory T-cells being recruited to the liver in response to aberrantly expressed endothelial-cell adhesion molecules and chemokines, which are normally 'gut-restricted,' could plausibly explain why these diseases are associated with site-restricted tissue distributions and pave the way for therapeutic strategies based on modulating tissue specific lymphocyte homing. That particular gene-polymorphisms have been found which confer combined PSC/IBD susceptibility underscores the fundamental role of mucosal immunogenicity in disease pathogenesis. Mucosal lymphocytes may also play a pivotal role in graft versus host disease affecting the liver, and there is increasing evidence to support dysregulated mucosal immunity as being responsible for the hepatic manifestations of gluten-sensitive enteropathy, graft versus host disease, as wells as the pancreatobiliary manifestations of IgG4-related disease.

1. Introduction

In order to cope with the daily exposure to a vast array of nutrients and commensal microbes as well as potential pathogens, the mucosal immune system has evolved specific compartments to respond to pathogens whilst continuously monitoring and providing tolerance to harmless commensals and food-borne antigens. Nevertheless, microbes may penetrate intestinal defence mechanisms and enter the liver via the portal circulation where further levels of immune regulation operate.

In light of the close integration of the mucosal and hepatobiliary immune systems it is unsurprising that the liver can be affected by immune-mediated diseases primarily affecting the gut. The strong association between primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) has led to the hypothesis that liver disease is driven by lymphocytes generated in the intestine which enter the portal circulation and trigger hepatic inflammation upon reactivation. This enterohepatic pathway is facilitated by the aberrant expression of adhesion molecules and chemokines that under normal conditions are restricted to either the gut or liver. Clinical observations have also demonstrated a link between coeliac disease and all three major autoimmune liver diseases, the association being greatest with primary biliary cirrhosis (PBC). Disturbances in mucosal immunity may also be responsible for the hepatic manifestations of graft versus host disease (GVHD) and IgG4-associated autoimmune pancreatitis.

2. Organisation of the enteric immune system

2.1. The gut epithelial barrier

The first line of protection in the gut is composed of a mucus layer rich in anti-bacterial substances such as alpha-defensins and immunoglobulin A (IgA), as well as a large number of commensal microbes which greatly exceed the total number of eukaryotic cells within the human body [1,2]. Invasion by pathogens is further impeded by the barrier function of the epithelial monolayer, which

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expresses toll-like receptors and other pattern recognition receptors (PRR) that recognise cellular injury or damage. This means that the mucosal epithelium is more than just a barrier, and activation of this "epimmunome" links barrier function to innate and adaptive immune responses [3–5]. Mucosal epithelial cells express MHC class-II molecules; however, given the absence of appropriate co-stimulation, interactions with $CD4^+$ T-cells are biased towards tolerance rather than effector responses [6]. The ability of intestinal epithelial cells to secrete cytokines and chemokines in response to commensal bacteria, pathogens or injury allows them to play an active role in shaping the nature of the local immune response and modulate sub-epithelial dendritic cell (DC) and lymphocyte positioning and activation [5]. Under normal conditions molecules that promote T-regulatory and Type-2 responses such as IL-25 dominate to maintain an anti-inflammatory environment [7]. However, in response to epithelial damage or infection, activation of NFκB results in the secretion of mediators including IL-1, IL-6, TNF and CCL20 that shift the local differentiation toward proinflammatory Type-1 or Type-17 responses. Further regulation is provided through bidirectional paracrine interactions between epithelial cells and specialised subsets of tissue-associated T-cells [5]. For instance, IL-22 secreted by T_h22-cells has paracrine effects on the epithelium. Thus, synergistic interactions between the epithelial/stromal compartment and sub-epithelial DCs and lymphocytes maintain epithelial integrity and regulate first line responses to injury or infection.

2.2. Intraepithelial compartment

The gut epithelial barrier does not completely prevent luminal antigens from entering the tissues and antigens can cross the epithelial surface through breaks in tight junctions, perhaps at villous tips where epithelial cells are shed. As a result, the intestinal mucosa contains a large number of T-cells that reside either within the intestinal epithelium or the underlying lamina propria (LP). Intraepithelial lymphocytes (IELs) are primarily $CD8^+$ T-cells that include both γδ and αβ subsets and a population of $CD8\alpha\alpha^+$ T-cells. Intestinal CD8αα T-cells are a sub-population of $CD161^{hi}$ $CD8^+$ mucosal-associated invariant T-cells (see below) [8] and their development is independent of antigen presentation by major histocompatibility complex (MHC) molecules. In contrast, $CD4^+$ and CD8αβ T-cells localise to the intestinal mucosa after MHC-restricted activation in secondary lymphoid organs and include cytotoxic effector T-cells and $CD4^+$ T-cells that secrete TGFβ and suppress inflammation to maintain tissue integrity [9,10]. IELs express CCR9 and under normal conditions are attracted by epithelial CCL25 to the intraepithelial compartment, where they use CD103 to bind to E-cadherin at the epithelial zonula adherens. However, in response to inflammation, recruitment pathways involving CXCR3 and other chemokine receptors may be more pertinent [11].

2.3. Lamina propria

The sub-epithelial lamina propria (LP) contains numerous antigen-presenting, $CXC3CR1^+$ DCs which sample and process commensal and pathogenic bacteria from within the gut lumen [12]. These cells are able to receive antigen either from specialised microfold-cells (M-cells) or through dendritic processes which protrude between gut epithelial cells [10,13]. DCs, in particular those that express CD103, subsequently migrate to draining mesenteric lymph nodes (MLNs) or Peyer's patches where they activate naïve lymphocytes [14]. Gut myeloid DCs (mDCs) which are involved in taking up apoptotic enterocytes constantly 'traffic' to draining lymph nodes but in the absence of danger signals are not fully activated and thus maintain tolerance rather than stimulating effector responses [15]. However, following an inflammatory response to injury or extrinsic infection, specific signals drive maturation and activation of mDCs [16] that can stimulate the development of an immune response shaped by the nature of the activating stimulus [17]. In contrast, plasmacytoid DCs (pDCs) are recruited to inflamed tissues where they secrete Type-1 interferons and promote the local differentiation of immunosuppressive regulatory T-cells (T_{reg}) [18] which in conjunction with non-classical regulatory cells such as T_h3-cells, T_r1-cells and invariant NKT-cells, help control inflammation and maintain a tolerogenic immune response to food and self-antigens.

The outcome of immune activation in the LP is largely dependent on a balance between activation of IFNγ-secreting $CD4^+$ T-cells, which drive inflammatory responses, and immunosuppressive regulatory cells that suppress and restrain inflammation. The importance of this interrelationship is emphasised by murine studies in which T_{reg} depletion leads to fulminant colitis that can be reversed by reconstitution with T_{reg} [19]. B-cell blasts are also recruited to the lamina propria where they differentiate to become IgA-producing plasma cells. DCs that contain live bacteria induce IgA-producing plasma cells more effectively than DCs containing killed organisms and are prevented from reaching secondary lymphoid tissues in an effort to localise the induction of immune responses and prevent carriage of bacterial organisms to other sites [12,20]. The outcome of the immune response is dictated by DCs, the antigenic stimulus and the resulting cytokine microenvironment. T_h1 responses are driven by early secretion of IL-2, whereas IL-1, IL-6, and IL-23 are necessary for the induction of T_h17 responses. Leucocyte interactions with immature mDCs as well as some pDCs, or activation in the presence of IL-10 and TGFβ, preferentially leads to induction of T_{reg}.

2.4. MAIT-cells and innate lymphoid cells

Mucosal-associated invariant T (MAIT)-cells form a subset of non-conventional αβ T-cells whose T-cell receptor (TCR) consists of an invariant Vα chain (iVα7.2-Jα33) combined with limited conserved Vβ chains and are restricted to the evolutionarily conserved MHC-related molecule MR1 [21]. In humans, MAIT-cells develop in the thymus and following birth rapidly expand and populate the periphery [22]. MAIT-cells are present in human blood but use CCR6 and CXCR6 to preferentially locate to the lamina propria and liver. They are phenotypically similar to NK-cells being characterised by the expression of CD161 and NKG2D, and are mostly $CD8\alpha\beta^{lo}$ (or double-negative) displaying an effector ($CD95^{hi}$ $CD62L^{lo}$ $CCR7^-$) memory ($CD27^+$ $CD45R0^+$ $CD45RA^{lo}$ $CD122^+$) phenotype [23]. Intestinal CD8αα T-cells are probably a sub-population of $CD161^{hi}$ $CD8^+$ mucosal-associated invariant T-cells sharing common cytokine expression patterns, chemokine receptor phenotype and transcriptional profiles with their counterpart $CD8\alpha\beta^+$ T-cells [8].

The enrichment of MAIT-cells within the intestine and liver suggests a close relationship with the host microbiome, and their rapid postnatal expansion and acquisition of memory markers is triggered by responses to colonising commensal flora; germ-free mice have no detectable MAIT-cells until reconstituted with commensal bacteria [24]. MAIT-cells display active anti-microbial functions *in vivo* [25] and react with MR1-expressing cells infected or co-cultured with selective bacteria and yeasts, but not viruses [25]. Recent reports suggest that vitamin B metabolites generated by unique bacterial and yeast biosynthetic pathways are ligands for MR1 [26]. However, it is unclear how MAIT-cells mediate their antimicrobial functions and which particular cytokines are necessary for their continued proliferation. It has been postulated that in the presence of an intact mucosal barrier and an absence of