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Review

Innate T cell responses in human gut

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ABSTRACT

One arm of the gut-associated immune system is represented by a vast collection of T lymphocytes which participate in the subtle interplay between innate and adaptive immune mechanisms and maintain homeostasis at the main body external surface. Mounting data are providing exciting new insight into the innate-like mechanisms which enable intestinal T cells to rapidly sense local conditions and which broaden the spectrum of their functions and regulation at this strategic location. Herein we discuss how innate-like T cell recognition by unconventional T cell subsets and expression of innate NK receptors might modulate immune T cell responses in the human normal or diseased intestine.

1. Introduction

In mammals, intestinal homeostasis is controlled by the interplay between innate and adaptive mechanisms which regulate a dialogue between epithelial cells and immune cells and adjust the host response to the daily charge of antigens derived from the microbiota and food proteins and to the periodic attacks by pathogens. One arm of the gut-associated immune system is represented by a vast collection of T lymphocytes organized in two functionally distinct compartments: the mucosal inductive sites represented by specialized lymphoid organs, Peyer's patches (PP), isolated follicles and mesenteric lymph nodes (MLN) – where adaptive immune responses can be initiated following sampling of intraluminal antigens – and the mucosal effector sites. In PP and MLN, mucosal dendritic cells present MHC/peptide complexes and deliver the costimulatory signals necessary for the activation of blood-derived naive αβ T lymphocytes (TL). They simultaneously induce membrane receptors enabling adherence to the mucosal endothelium and thereby imprint gut homing specificity. This step initiates the generation of specific effector/memory and regulatory TL which migrate back into the mucosa after a 4–7 days hemolymphatic cycle. At the intestinal effector site, primed CD4+ TL distribute mainly into *the lamina propria* while CD8+ TL migrate electively into the epithelium, and both subsets coordinate host local responses to intraluminal antigens. It is however now clear that T cell contribution to intestinal homeostasis does not rely only on conventional adaptive T cell responses but also involve innate-like mechanisms mediated by subsets of unconventional TL or by non-polymorphic receptors that can sense local conditions in the tissue and broaden the spectrum of T cell function and regulation at this strategic location. Thus, γδ TL which represent a minor T cell component in most lymphoid compartments are, in humans as in mice, preferentially associated with the intestinal epithelium. Due to their characteristics more similar to those of innate than adaptive immune effectors, they are thought to act as sentinels enabling immediate host responses to danger signals and more generally immunosurveillance of epithelial injury and transformation. In addition, a large and variable proportion of intestinal TL, particularly in the epithelium, express non-polymorphic receptors initially described as the attribute of natural killer lymphocytes. Natural killer receptors (NKRs) enable their recognition of ligands modulated during tissue injury and participate to their activation via both T cell receptor (TCR) dependent and independent pathways. Herein, we will discuss how innate-like T cell recognition by unconventional T cell subsets and expression of innate NKRs might modulate immune responses in the human normal or diseased intestine.

2. Innate-like recognition by the T cell receptor of intestinal unconventional T cells

2.1. Intestinal γδ TL

In humans, approximately 15% of small intestinal and 40% of colonic IEL are γδ TL, compared to 5% among TL in *lamina propria* and peripheral blood. γδ TL have a much more restricted TCR V region repertoire than conventional αβ TL and use mainly three Vδ and at most 6 Vγ chains to make their TCRs [1,2]. While 80–90% of γδ TL in adult peripheral human blood express Vδ2 paired to Vγ9 chains, a large proportion of intestinal γδ T-IEL use the Vδ1 or more

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rarely the Vδ3 chain paired with different Vγ chains [1,3–5]. Molecular analysis of TCRδ junctional regions indicates that intestinal γδ TL have a polyclonal repertoire at birth, which becomes oligoclonal within the second decade irrespective of the V region usage [6]. In individual adult subjects, identical TCRδ transcripts can be found at multiple intestinal sites and this repertoire is relatively constant over 1–2-year periods. This repertoire is however unique to each individual and, notably, is distinct between monozygotic twins concordant for celiac disease, a small intestinal disease associated with a massive expansion of intraepithelial γδ TL [7] (see below). Moreover no overlap was observed between the TcRδ repertoire in the intestine and blood of the same individuals. These findings are best explained by a model in which γδ TL randomly selected for by a limited set of ligands in the intestinal tract, can expand locally, recirculate and home back throughout the whole intestinal length [1].

The nature of the ligands and the rules for antigen recognition by γδ TL are not fully delineated. The CDR3 loops of TCRα and β chains are nearly identical in length and show constrained length distributions, which may reflect the necessity for αβ TCRs to contact both MHC molecules and peptides. In contrast, the CDR3 lengths of TCRδ chains are highly variable in length, while those of TCRγ chains are short and constrained [8]. These characteristics, reminiscent of the CDR3 structure of immunoglobulins, suggest that, alike B cells, γδ TL recognize the conformational shape of intact antigens and point to an important contribution of δ CDR3 to antigen recognition [8]. The antigens recognized by intestinal γδ TL remain poorly defined (Table 1). Vγ9Vδ2 TL, which predominate in the periphery but can represent a sizeable fraction of normal γδ T-IEL, are thought to discriminate between normal versus altered self via the recognition of phosphorylated compounds produced through the isoprenoid biosynthetic pathways. One weak agonist of Vγ9Vδ2 TL is isopentenyl pyrophosphate (IPP) synthesized in the mevalonate pathway of mammalian cells. This pathway, essential for sterol synthesis, cell growth and membrane integrity, leads to overproduction of IPP by transformed and infected cells. In addition, a strong agonist of Vγ9Vδ2 TL, HDMAPP, can be generated by microorganisms using the '1-deoxy-D-xylulose-5-phosphate' metabolic pathway in cells infected by intracellular bacteria [2,9]. Other data indicate that Vγ9Vδ2 TL may recognize self proteins up-regulated during cellular stress and/or transformation, notably a complex between apolipoprotein A1 and adenosine triphosphate synthetase which is normally found in the inner membrane of mitochondria but is translocated at the surface of some tumor cells [10], the heat shock protein HSP60 and the human mutS homolog 2 (hMSH2) also found at the surface of some tumor cells [11]. The extensive structural diversity of Vδ1 and Vδ3 TCRs suggests the recognition of a highly diverse set of antigens. Yet, the antigens recognized are even more ill defined and very few cognate interactions have been demonstrated so far. One possible ligand for TCRδ1 is the stress-inducible MHC class I chain-related gene A (MICA), an antigen expressed at low level by normal colonic epithelial cells and up-regulated in many epithelial tumors as well as in small intestinal enterocytes in coeliac disease. Groh et al showed that Vδ1 T-cell clones isolated from an intestinal epithelial tumor recognized MICA+ tumor cells and MICA-transfected target cells in a TCR dependent manner [12,13] and confirmed direct binding of the Vδ1-CDR3 region to MICA by surface plasmon resonance analysis. This interaction was however of very low affinity [14]. Since MICA is also a ligand for NKG2D, an activating NKR receptor expressed by γδ TL (see below), stimulation of Vδ1 T cells by MICA likely relies on a dual signal implicating both the TCR and NKG2D. Other studies have identified the non-polymorphic MHC class Ib molecule CD1c as a possible ligand for Vδ1 TL [15] and suggested the presence of CD1-restricted Vδ1 TL in the human duodenal mucosa [16]. In one study, Vδ1 T cell clones recognized CD1c independently of the presence of bacterial compounds although their expansion was obtained by stimulating peripheral T-cells with *Mycobacterium tuberculosis* extract in the presence of CD1-expressing autologous dendritic cells (DCs). Since CD1c is up-regulated in DCs by bacteria and inflammatory products, CD1c could in turn favor the expansion of self-reactive Vδ1 TL. In a more recent study, duodenal T Vδ1 T cell clones were activated by CD1a, c or d either alone or in the presence of exogenous phospholipids [16]. This mechanism of activation may perhaps operate *in situ* since CD1d has been detected at the surface of human enterocytes [17,18] and since CD1c can be expressed by activated dendritic cells. The frequency of Vδ1 T cells specific for either MIC or CD1 has not been assessed but is presumably low and, in most instances, the antigens recognized by their TCR remain unknown. Expansion of Vδ1 TL has however been observed in several infectious contexts involving intracellular bacteria and viruses [2]. Observations discussed above support the idea that Vδ1 TL recognize self-antigens up-regulated in response to stress, malignant transformation or infection. This concept is further supported by analyzing antigen recognition by the Vδ1 and Vδ3 cells that undergo massive clonal expansions during CMV infections in immunosuppressed hosts [19,20]. A large number of Vδ1 and Vδ3 T cell clones derived from these patients reacted against fibroblasts infected by CMV but not other herpes viruses. Moreover, these clones reacted against colonic tumor cell lines but not against normal intestinal epithelial cells or transformed cell lines of hematopoietic origin. Recognition was TCR-dependent but CD1c- and MICA-independent. Therefore CMV-reactive γδ T-cell clones may recognize specific-CMV epitope(s) resembling self-antigens expressed by transformed epithelial cells or more likely self-antigen(s) selectively induced in CMV-infected cells and epithelial tumor cells. Since a fraction of Vδ1 TL present in the blood of CMV-infected patients expressed intestinal homing receptors, it was suggested that expansion of Vδ1 cells takes place in the intestinal mucosa, a frequent site of CMV multiplication [20]. Along the same line, expansion in Vδ1 TL was observed both in the blood and colonic mucosa of patients infected with HIV. Yet, there was no overlap between the Vδ1 CDR3 regions in the blood and intestinal compartments and the expression of mucosal homing receptors on circulating Vδ1 cells was only modestly increased, suggesting that expansion occurs independently in each compartment. Notably Vδ1 expansion persisted after antiviral therapy, also pleading against the recognition of an exogenous virus-derived determinant [21].

The functions of human intestinal γδ TL remain largely elusive. The nature of the recognized antigens, their mode of recognition independent of antigen-processing and their phenotype of effector/memory cells suggest that they may act as sentinels rapidly mobilized during infection by intracellular pathogens or upon transformation of epithelial cells. Accordingly, Vδ1 T clones derived from CMV-infected patients can kill CMV-infected target cells and produce IFN-γ that inhibits *in vitro* propagation of CMV [20]. CD1c reactive Vδ1 TL can exert perforin- and Fas-dependent cytotoxicity and produce granulysin, a potent anti-microbial protein [15]. Vδ1 TLs found in intestinal (as well as extraintestinal) epithelial tumors can kill tumors cells [12]. In keeping with the possible role of epithelial γδ TL in the immunosurveillance against tumors, TCR δ−/− deficient mice showed lower resistance to the induction of chemically induced epidermal tumors [22]. γδ TL may serve other functions. *In vitro*, γδ TL helped initiating adaptive responses, either indirectly by stimulating the maturation of dendritic cells (Vδ1 TL) [23,24] or even directly via processing and presentation of soluble antigens to αβ T-cells (Vδ2 TL) [25]. Whether γδ TL can exert such innate-like immune functions *in vivo* in the intestine remain however to be demonstrated. Studies in mice have also suggested roles for intestinal γδ TL in tissue repair [26,27] and in local immunoregulation [1,28]. The later function has also been proposed for human intestinal γδ T-cells on the basis of observations in celiac disease.