

REVIEW

Human mucosal T-lymphocyte and macrophage subpopulations in normal and inflamed intestine

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The intestinal immune system is responsible for protecting the host against intestinal pathogens, whilst preventing harmful hypersensitivity reactions against normal dietary constituents. These demands are reflected in the extent and complexity of gut-associated lymphoid tissue (GALT), which is only now beginning to be understood. GALT is just one component of a common mucosal immune system which encompasses all mucosal sites including respiratory and urogenital tracts, mammary and salivary glands [1]. The intestinal immune system is either confined to organized compartments, such as Peyer's patches, isolated lymphoid follicles and draining lymph nodes, or exists as a diffuse cell population scattered throughout the mucosa.

Dysfunction of mucosal immunity has been implicated in intestinal disease including coeliac disease and inflammatory bowel disease [2,3]. One approach to understanding the mechanisms underlying such dysfunction has been to make use of a wide panel of monoclonal antibodies in extensive analyses of the phenotype of normal mucosal lymphoid cells compared with those of inflamed tissue. This review will focus upon the phenotype of both T lymphocytes and cells of the monocyte/macrophage lineage in both the normal and inflamed intestine.

Intraepithelial lymphocytes

Intraepithelial lymphocytes (IELs) probably represent the most extensively studied component of diffuse intestinal lymphoid tissue and have been the subject of several reviews [4–6]. IELs were first demonstrated to be T cells with a T cell specific polyclonal antiserum [7]. Numerous studies confirmed this finding and revealed that between 70 to 90% of human IELs are CD3⁺/CD8⁺, a phenotype consistent with suppressor/cytotoxic function [8–12]. In the small bowel the ratio of CD8 to CD4 positive helper T cells is approximately 4:1, in the colon a higher percent-

age of CD4⁺ IELs occur [12]. Human IELs express a specific membrane receptor defined by the monoclonal antibody HMLI (Fig. 1) [13]. HMLI also identifies the majority of IELs in bronchial and mammary epithelium; the precise nature of the receptor remains to be defined [13].

Human IELs have the phenotype of memory T cells

Early phenotypic studies found that human IELs lacked the classical markers of T cell activation such as MHC class II, CD35 and the IL-2 receptor (CD25, 14, 15). However, there is now evidence that the majority of IELs represent the so-called memory population of T cells. CD7, which has been shown on the majority of colonic and small intestinal IELs [10,12,16] is a 40 kD antigen belonging to the Ig supergene family and is expressed by prothymocytes and retained and expressed by activated T lymphocytes [17,18]. In general CD7 appears accepted as a T cell activation marker [16].

More recently, it has been demonstrated that at least a proportion of colonic and small bowel IELs express the low molecular weight LCA molecule (CD45RO) identified by the monoclonal antibody UCHL1 [16,19]. Activation of resting or naive T cells is now well known to induce a switch in expression from high molecular weight (220 kD) CD45RA to CD45RO expression [20]. It is interesting that peripheral blood lymphocytes can be induced to express HMLI following PHA stimulation. Thus HMLI expression by IELs may reflect T cell activation rather than representing a unique marker of mucosal T cells [3,21]. The observation that IELs bear the β_1 integrins, VLA-1 and VLA-4 also implies a role as memory T cells [22].

Function of human IELs

Intraepithelial lymphocytes are clearly an unusual cell population showing marked differences in both phenotype and function to peripheral blood T cells. CD8⁺ IELs, lack CD5 and CD6 [10,23,25]. Both CD5 and CD6

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are normally associated with 'helper' T cell function supporting the concept that IELs are suppressor or cytotoxic in function [25]. *In vitro* studies have shown that human IELs cannot directly mediate specific cytotoxicity, although non-specific cytotoxicity has been described [26]. Interestingly, isolated IELs from mice and guinea-pigs can mediate both specific and non-specific cell mediated cytotoxicity: one of several differences between human and rodent [27–29]. Isolated human IELs do not exhibit NK activity and this cannot be induced by either IFN γ or IL-2 [30]. In line with functional studies IELs lack H366, a putative marker of MHC restricted cytotoxic T cells, HNK-1, leu7 and leu11, surface molecules characteristic of NK cells [11,12,14,31,32].

Recently Smart *et al.* [16] showed that IELs do not regulate mucosal Ig synthesis. However, classical studies in humans and rats have demonstrated that antigen presentation by MHC class II positive epithelial cells results in the selective induction of CD8⁺ suppressor T cells and a down-regulation of the immune response [33,34]. Moreover, human IELs secrete a factor (probably IFN γ) which induces MHC class II on epithelial cells [35]. The conjecture that MHC class II positive epithelial cells present antigen to previously sensitized CD8⁺ IELs thereby providing a mechanism for oral tolerance has been proposed on several occasions [3,36]. As yet, there is no unequivocal evidence for the role of IELs in the maintenance of oral tolerance but their phenotype and proximity to both epithelial cells and the underlying mucosal immune system make them likely candidates.

The T cell receptor of IELs

In man the majority of mature T cells express a T cell receptor composed of two disulphide linked polypeptides α and β each of 40 to 50 kD molecular weight [37]. The search for genes encoding the TCR α chain led Tonegawa *et al.* to a novel group of T cell specific rearranging genes which were subsequently found to form part of a second TCR heterodimer, $\gamma\delta$ TCR [38,39]. Studies suggest that two separate ontological pathways exist giving rise to T cells which express either the $\alpha\beta$ or $\gamma\delta$ heterodimer [40,41]. In the human, three distinct forms of $\gamma\delta$ TCR have been described, two of which are non-disulphide linked and one which is disulphide linked [42]. The small number of V region genes available limits the potential repertoire of T cells bearing the $\gamma\delta$ TCR, thus $\gamma\delta$ T cells have been regarded as part of a primitive immune response in terms of ontogeny [43].

Expression of the $\gamma\delta$ TCR by murine and avian IELs

In mice and birds, T cells at epithelial surfaces, including dendritic epidermal lymphocytes, intestinal IELs and a population of murine pulmonary T cells, predominantly

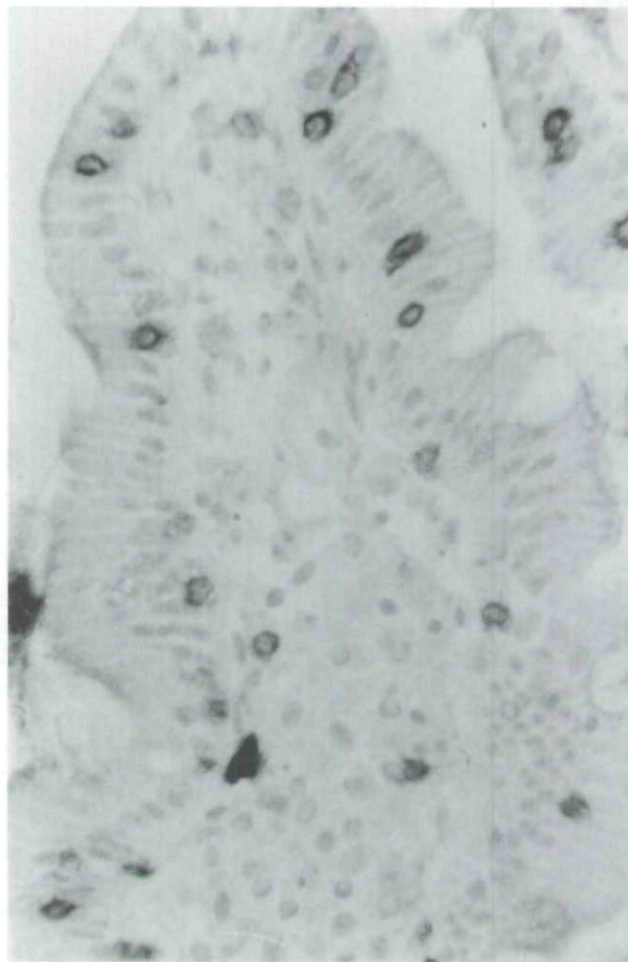


Fig. 1. Frozen section taken from a normal human jejunal biopsy stained using an indirect immunoperoxidase technique with the monoclonal antibody HML1. This antibody recognizes the majority of human IELs and a proportion of lamina propria T-cells (magnification $\times 400$).

express the $\gamma\delta$ TCR [44–46]. This apparent tropism for epithelial surfaces by murine and avian $\gamma\delta$ ⁺ T cells led to the hypothesis that these cells provide a defence system at this site [47]. It was speculated that the $\gamma\delta$ cells could destroy damaged or infected epithelial cells possibly via recognition of autologous stress proteins [48]. Later studies in the mouse however, demonstrated that a substantial fraction of (Thy-1⁺) IELs in normal mice utilize the conventional $\alpha\beta$ TCR [49,50]. It is of particular interest that IELs present in athymic mice exclusively express the $\gamma\delta$ TCR suggesting that in mice at least a proportion of $\gamma\delta$ ⁺ IELs are independent of the thymus for their differentiation.

Expression of the $\gamma\delta$ TCR by human IELs

The early observation that murine and avian T cells bearing the $\gamma\delta$ TCR have an apparent tropism for

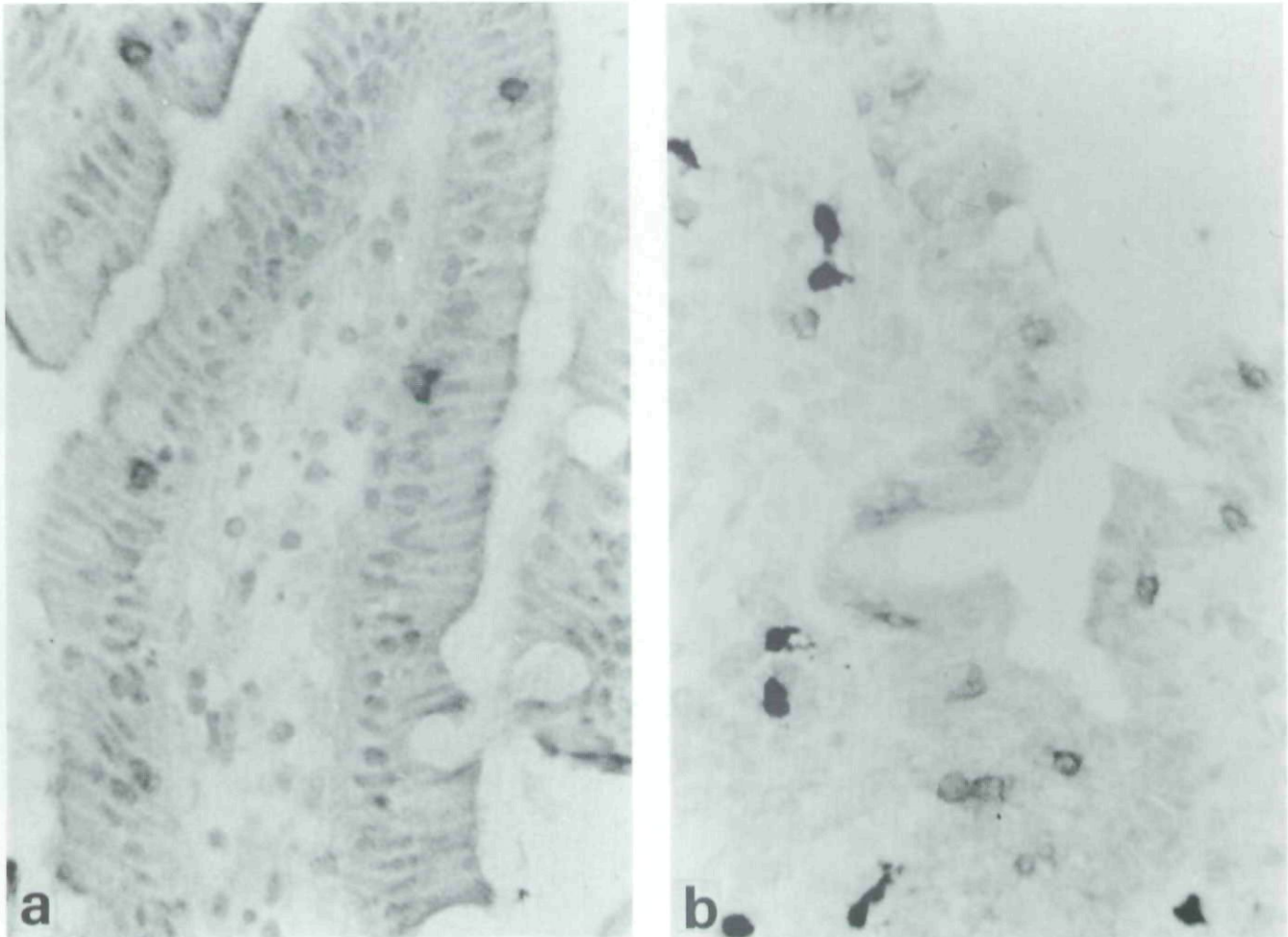


Fig. 2. (a) Reactivity of the monoclonal antibody TCR- γ -1 which recognizes a framework determinant on the T-cell receptor γ chain within the normal human small intestine. Between 1 and 15% of IELs bear the $\gamma\delta$ TCR, whilst $\gamma\delta$ positive lamina propria T-cells are very rare (magnification $\times 250$). (b) Frozen section taken from a jejunal biopsy from a patient with untreated coeliac disease. In contrast with (a), the inflamed mucosa in coeliac disease is characterized by an increased proportion of IELs bearing $\gamma\delta$ TCR (see Table 1) (magnification $\times 400$).

epithelial surfaces prompted several groups to establish the TCR status of IELs populating the human gut [44,45,51,52]. Preliminary findings based on the reactivity of the monoclonal antibody δ TCSI revealed that approximately 2% of normal human IELs expressed the $\gamma\delta$ TCR [53]. However, δ TCSI is only expressed by a unique $V_{\delta 1}/I_{\delta 1}$ rearrangement and does not show panreactivity for all TCR $\gamma\delta$ subpopulations [54]. Similarly early studies by Cerf-Bensussan *et al.* revealed that up to 85% of IELs expressed the marker WT31 which characterizes T cells expressing the conventional $\alpha\beta$ TCR [55].

Analysis of TCR expression by human IELs using framework antibodies has revealed that approximately 1–15% express the $\gamma\delta$ TCR whilst the majority bear the $\alpha\beta$ TCR (Fig. 2(a)) [3,25,56]. A higher percentage of $\gamma\delta$ T

cells has been reported in the colon than in the small bowel [25]. In fact, Groh *et al.* (56) have demonstrated that between 1–15% of all lymphoid populations are composed of T cells bearing the $\gamma\delta$ TCR.

Evidence is accumulating to suggest that $\gamma\delta^+$ IELs are a unique and heterogeneous population. Whereas in peripheral blood the disulphide linked form of $\gamma\delta$ TCR is prevalent, the $\gamma\delta$ TCR of human IELs is predominantly a non-disulphide linked molecule [57]. IELs present in the fetal intestine bear the disulphide linked $\gamma\delta$ TCR indicating that luminal antigen may affect TCR status [57]. In the mouse the $\gamma\delta$ TCR expressed by IELs has been shown to be structurally diverse, encoded by a $V_{\gamma 7}$ gene which can pair with one of four V_{δ} genes [58]. Murine IELs also co-express CD8 in contrast with $\gamma\delta$ T cells at other sites which

are mainly CD8⁺, CD4⁺ [44]. Human IELs bearing the $\gamma\delta$ TCR are approximately 50% CD8⁺, CD4⁺; the remainder express CD8 (25). Since T cells bearing the $\gamma\delta$ TCR appear during intrathymic development and migrate into peripheral blood as a CD4⁺, CD8⁺ population it has been suggested that CD8 expression may be induced in the epithelium [25,48]. Whilst this may be true for murine IELs, 30% of human peripheral blood and 50% of splenic $\gamma\delta$ T cells co-express CD8 indicating a more general role for CD8 in the function of the human $\gamma\delta$ T cell subset [59].

Function of T cells bearing the $\gamma\delta$ TCR

A precise role for T cells bearing the $\gamma\delta$ TCR remains to be defined. Functional studies have demonstrated that $\gamma\delta$ T cells isolated from peripheral blood act as broadly reactive cytotoxic T cells able to lyse various tumour cells [60]. In the mouse at least there is evidence that freshly isolated $\gamma\delta$ positive IELs are constitutively cytolytic *in vitro*, suggesting that they are actively cytotoxic in the intestine [61]. Analysis of potential gene usage of the $\gamma\delta$ T cell receptor has revealed far greater diversity than originally thought. The TCR γ gene allows more potential junctional diversity than any other TCR genes [62]. TCR $\gamma\delta$ cells can also recognize conventional MHC class I and II molecules as well as MHC class Ib proteins [43].

A ligand for the $\gamma\delta$ TCR remains uncertain. However, it is becoming clear that in common with the $\alpha\beta$ TCR, the $\gamma\delta$ TCR can recognize antigen in an MHC restricted manner [60]. $\gamma\delta$ cells can recognize conventional mycobacterial antigens [62]. This phenomenon could simply represent a cross-reaction with autologous stress proteins or alternatively, $\gamma\delta$ T cells which originally arose to recognize stress proteins could have evolved greater diversity to include mycobacterial antigens [62]. The observation that the murine $\gamma\delta$ TCR is structurally diverse combined with evidence that the $\gamma\delta$ TCR can show conventional MHC restriction favours the view that at least a proportion of $\gamma\delta$ IELs serve to enhance the repertoire of the $\alpha\beta$ TCR bearing IEL population [43,56,58].

Lamina propria T cells

The lamina propria contains a variety of lymphoid and accessory cells, including B and T lymphocytes, plasma cells, eosinophils, macrophages, basophils and mast cells [63]. Lamina propria T cells, unlike IELs are predominantly of the CD3⁺/CD4⁺ helper phenotype [8,11,12,14]. The ratio of CD4:CD8 lamina propria T cells closely resembles that of peripheral blood [23]. As with IELs, an absence of NK associated antigens is characteristic of lamina propria T cells [11,64]. Lamina propria T cells

generally lack the classical T cell activation markers MHC class II, CD25 and transferrin receptors [10,13,15]. Approximately 50% of human lamina propria T cells express HMLI, although virtually none bear the $\gamma\delta$ form of TCR [25].

The predominant function of human lamina propria T cells is immunological help [65,66]. Lamina propria T cells help B cells in a PWM-driven immunoglobulin synthesis system. Indeed, colonic lamina propria T cells may represent a prestimulated IgA-specific helper T cell population [16]. Functional evidence for helper activity is supported by phenotypic data; thus the majority of lamina propria T cells express CD5, a molecule thought to be important in helper function [24]. Although the majority of human LP T cells are mature helper T cells, colonic CD8⁺ LP T cells capable of non-MHC restricted anti-CD3 triggered cytotoxicity occur [67]. Thus, in the normal mucosa, a balance appears to be maintained between helper and suppressor mechanisms presumably to provide specific responsiveness to pathogens, whilst avoiding over reactivity.

Intestinal mononuclear accessory cells

Mononuclear accessory cells are frequently subdivided into non-phagocytic dendritic cells which show constitutive expression of MHC class II and mononuclear phagocytes which are involved in ingestion of debris, microbial killing and exhibit facultative MHC class II expression [68,69]. The cell-mediated immune response is dependent upon both groups, the former as antigen-presenting cells and the latter as effector cells [70].

Within the intestinal mucosa two major types of dendritic accessory cell may be found. Follicular dendritic cells (FDCs) facilitate B cell responses and occur within germinal centres of lymphoid follicles and Peyer's patches (PP) [71]. Interdigitating reticulum cells (IDRC) facilitate T cell responses and occur diffusely throughout the lamina propria, within parafollicular regions and beneath the dome epithelium of lymphoid follicles and PP [63,72]. Diffuse lamina propria IDRC or type II accessory cells are known to occur with greater frequency in the small bowel than in the colon [12]. The phenotype of these cells is RFDI, CD11c, CD68 and MHC class II positive [73,74]. The observation that type II cells may occasionally be seen with dendritic processes extending into the villus epithelium has led to the suggestion that these cells may have a role in sampling incoming luminal antigen [12,73]. Antigen presentation by these superficial accessory cells may mediate local division of lamina propria B cells into IgA secreting plasma cells [73,75]. The high level of dietary antigen in the small bowel is claimed to account for the numerous antigen presenting cells at this site [12,73].

As with IDRC, classical or type I macrophages are present throughout the lamina propria, as well as within PP and are particularly abundant in the colon [12,14]. Within the colon, type I macrophages occur as a continuous band in the subepithelial zone and a major proportion are activated or 'angry' [12,14,73]. The phenotype of this population is consistent with a population of active scavenger-type macrophages: they express RFD7, KiM8 FcRI (CD64) and have strong acid phosphatase and non-specific esterase activity [14,73,74]. The large bacterial flora present in the colon is thought to account for the high level of activated macrophages present; the small bowel contains significantly fewer bacteria [14,76].

Peyer's patches

The PP plays a vital role in the uptake and entrapment of luminal antigen resulting in the priming of follicular lymphocytes. The epithelium overlying the PP (follicle-associated epithelium, FAE) contains specialized M cells which exhibit unique features allowing the uptake of macromolecules, bacteria and viruses [77-79]. The events following antigen uptake are thought to totally depend upon an inherent balance between the suppressor and helper elements of the mucosal immune response [80]. Thus, M cells transfer antigen to the so-called dome region macrophages. These cells differ from morphologically similar cells in the adjacent lamina propria in that they contain S100 protein, but lack lysozyme [81]. Dome macrophages do however exhibit acid phosphatase activity [82]. Within the parafollicular regions of lymphoid follicles are numerous CD4 positive helper T cells. It has been suggested dome macrophages can either present antigen to these cells, directly phagocytose antigen to prevent further entry, or transfer degraded antigen to IDRCs which in turn present antigen to the follicular T lymphocytes [83].

The presence of T suppressor cells also within parafollicular regions may be important in the suppression of IgM, IgG and IgE production [84]. These suppressor cells migrate from the gut to the peripheral immune system where they mediate antigen-specific systemic hyporesponsiveness or oral tolerance [83]. The predominant local response as described is the generation of helper T cells which select for IgA secreting B cells [80]. T cells cloned from murine Peyer's patches have been shown to cause a switch in B cells expressing surface IgM to IgA [85]. The importance of such preferential selection of IgA as the predominant mucosal antibody is that IgA can bind micro-organisms, preventing their attachment to epithelial cells. IgA is selectively transported across the epithelium by a secretory component, and unlike IgG or

IgM does not fix complement, and so cannot initiate damaging inflammatory reactions within the mucosa.

Antigen processed in the Peyer's patch generates systemic hyporesponsiveness and a predominantly IgA mediated immune response in the mucosa. B and T lymphoblasts primed in the Peyer's patch migrate via mesenteric lymph nodes and enter the systemic circulation via the thoracic duct. Lymphocytes then selectively extravasate from the blood at mucosal sites by adhering to high endothelial venules (HEV) present in the PP or lamina propria [86].

Homing receptors and vascular addressins

It is clear that once activated at specific sites in the body lymphocytes exhibit remarkable selective migration back to the tissues where they originally encountered antigen [87]. Human lamina propria T cells bear homing receptors which bind selectively to mucosal HEV. Binding is mediated via an 85-95 kD lymphocyte glycoprotein (gp 90, Hermes) defined by monoclonal antibodies of the Hermes series [88]. Recently PgP-1, a polymorphic glycoprotein and CD44 have been shown to recognize the same structure and belong to the same supergene family as the Hermes antigens [89]. The mouse equivalent of gp 90 Hermes is a molecule LPAM, an $\alpha\beta$ heterodimer, with an α chain which has been shown to be homologous to the VLA-4 α chain [90]. In fact the LPAM α chain can associate with either the β_1 integrin β chain (LPAM-1) or a novel β chain β_p (LPAM-2) [91] and both LPAM-1 and LPAM-2 are involved in adhesion of lymphocytes to PP HEV. The observation that both IELs and LP T cells express the β_1 integrin VLA-4 in the human may be important in homing of mucosal lymphocytes [22].

The ligands for recirculating lymphocytes are displayed on the surface of endothelial cells and are located in a tissue-specific manner. These molecules have been termed vascular addressins [92]. Such molecules belong to a further supergene family and include the molecule MECA-367 present on murine PP HEV [87]. The precise homing properties of IELs remains to be defined, although a proportion of murine IELs have been shown to be derived from precursors in the PP which migrate via the MLN back into mucosal sites [93]. More recent evidence that IELs undergo specific homing arises from the observation that rotavirus specific cytotoxic IELs appear 6 days after oral inoculation with rotavirus [94].

Coeliac disease

The mucosal damage characteristic of coeliac disease, which is triggered by the ingestion of gluten is thought to involve an abnormal immune response. Evidence to

support a primary role for the immune system includes: the presence of splenic atrophy; mesenteric lymph node degeneration; plasma cell infiltration of the lamina propria; presence of a high level of anti-gliadin serum antibody, elevated serum soluble IL-2 receptor and complement activation within the mucosa [95–100]. *In vitro* studies also indicate that both the humoral and cell-mediated arms of the immune response show specific activation to gluten in coeliac disease. For example, the increased IgA and IgM secretion by cultured biopsies from patients with coeliac disease can be attributed to antigliadin antibody synthesis [97,101]. A leucocyte migration inhibition factor is secreted by biopsies from coeliac patients in response to the addition of gluten providing evidence of cell-mediated immunity to gluten [102,103]. In mice, the rejection of allogeneic fetal intestine and the phenomenon of graft versus host reaction, both T cell mediated phenomena result in mucosal morphological changes akin to coeliac disease [104,105].

IELs in coeliac disease

It has long been considered likely that the dense IEL population characteristic of the flattened mucosa in coeliac disease has a primary role in pathogenesis [4]. Using morphometric analysis with the invariant muscularis mucosa as reference, it was first shown that there is no absolute increase in the number of crypt and surface IELs [31,106,107]. In coeliac disease, the apparent increase in IELs observed in histological sections reflects an increased IEL density within a reduced total epithelial volume [107]. A number of observations do, however, implicate IELs in the pathogenesis of coeliac disease: the chronically inflamed mucosa contains IELs with increased mitotic activity, blastoid transformation and

flux rate across the basal lamina [107]. Oral challenge with gluten results in a dose-dependent migration of lymphocytes into the epithelium in patients with coeliac disease [108]. In addition to morphometric studies, numerous phenotypic studies have revealed that the ratio of CD4 to CD8 positive IELs is unaltered in coeliac disease [8,14]. Since both CD4 and CD8 T cell subsets may be further subdivided into distinct, functionally important cell types, subsequent phenotypic studies have concentrated on detailed analyses of these subpopulations [10,12,109].

As seen from Table 1 the increase in IELs bearing the $\gamma\delta$ TCR has been confirmed by several groups (Fig. 2(b)). It is also relevant that the elevated $\gamma\delta$ TCR subset resides predominantly within the CD3⁺, CD8[−], CD4[−] subset [109]. Furthermore, the increases in both the $\gamma\delta$ TCR⁺ subset and in the CD3⁺, CD4[−]/CD8[−] subset are retained in patients on a gluten-free diet [109,110] implying that these changes reflect a fundamental immunological abnormality.

The role of $\gamma\delta$ TCR⁺, CD4[−], CD8[−] IELs in the pathogenesis of coeliac disease is unclear. The lack of CD8 expression has been taken as an indication that the double negative $\gamma\delta$ TCR⁺ IELs are a primitive population, perhaps capable of recognizing non-classical MHC molecules or stress proteins [60]. In the blood, the CD3⁺, CD4[−], CD8[−] subset is known to have non-specific cytolytic activity [111]. Based on our current understanding, the most likely role for $\gamma\delta$ TCR⁺ IELs in coeliac disease is in recognition and possible destruction of damaged epithelial cells. In two other inflammatory conditions, rheumatoid arthritis and leprosy, an increase in T cells bearing the $\gamma\delta$ TCR has been described [112,113]. $\gamma\delta$ TCR⁺ IELs are not increased in other intestinal disorders, including tropical sprue, cow's milk protein intolerance and Crohn's disease (T. MacDonald,

Table 1. Changes in IEL subpopulations in coeliac disease

IEL subpopulation	% of total IEL		References
	Normal	Coeliac disease	
CD3 ⁺ , CD45RO ⁺	42	69	Brandtzaeg <i>et al.</i> [3] Harvey, Jones & Wright [19]
$\gamma\delta$ TCR ⁺	1–15	20–30	Brandtzaeg <i>et al.</i> [3] Spencer <i>et al.</i> [57] Halstensen, Scott & Brandtzaeg [110]
CD3 ⁺ , CD4 [−] , CD8 [−]	6	28	Spencer <i>et al.</i> [109]
CD7 ⁺ , CD3 [−]	20	1.4	Spencer <i>et al.</i> [109]
CD7 ⁺ , CD4 ⁺	10–15	30	Malizia <i>et al.</i> [10]

pers. comm.). Therefore, epithelial damage *per se* is not sufficient to induce an increase in T cells bearing the $\gamma\delta$ TCR.

The increase in CD4⁺CD7⁺ IELs in coeliac disease indicates an increased level of helper T cell activity [10]. A change in balance between helper-inducer and suppressor/cytotoxic T cells may be responsible for the breakdown in oral tolerance to gluten [10]. Epithelial cells, which show elevated MHC class II expression in coeliac disease (probably as a result of cytokine release by CD45RO⁺ active T cells and macrophages), may preferentially stimulate CD4⁺ helper IELs and LP T cells [3], leading to increased local and systemic production of IgG a feature typical of active coeliac disease.

The initial activation of the mucosal immune system may occur via an abnormal response to antigen such as an infectious agent in the context of the MHC haplotypes, DR3, DR7 and DQW2, which have been shown to confer susceptibility to coeliac disease [114]. Recent studies by Kagnoff *et al.* [115] have revealed that gliadin shows amino acid sequence homology with an early region protein (E1b) of human adenovirus type 12 (Ad12) and also demonstrated that a significantly greater proportion of patients with coeliac disease had had prior infection with adenovirus compared with a disease control group. However, no persistent adenovirus DNA has been detected, neither can serum antibodies specific for E1b of AD12 be detected in blood from patients with coeliac disease [116,117]. The events required to trigger coeliac disease in MHC susceptible individuals remain unknown.

Enteropathy-associated T cell lymphoma (EATL)

Evidence suggests that the small intestinal lymphoma (EATL) which can complicate coeliac disease is derived from mucosal T cells. In 1988, Spencer *et al.* demonstrated tumour cells in eight cases of EATL expressed HMLI, presumably defining a state of activation. All other cases of extra-intestinal peripheral T cell lymphomas studied were HMLI negative [118]. Thus EATL clearly represents a unique peripheral lymphoma.

More recent investigations [119] suggest that HMLI is not uniquely expressed on EATL, but can be found on a proportion of other T-cell lymphomas. The precise relationship of EATL to coeliac disease remains unclear. Molecular investigations of a restricted number of patients showing florid intraepithelial lymphocytosis suggest that the lymphoma may exist in a low-grade form prior to its detection as an acute disease. These observations imply that a selected group of coeliac patients may, in fact, be at risk from the development of EATL [119,120].

Role of macrophages in Crohn's disease

The aetiology of Crohn's disease remains obscure [121]. Most workers agree that an antigen-specific immunoregulatory abnormality is responsible [2]. Unlike coeliac disease, studies of Crohn's disease have found no differences between T cells of the inflamed and normal bowel [23,122]. A higher proportion of lamina propria T cells express CD45RO in Crohn's disease, suggesting increased T cell activation in this condition [19]. Increased numbers of IgM and IgG secreting plasma cells also implicate abnormal humoral immunity in this condition [2].

MHC class II positive, scavenger type macrophages with acid phosphatase and non-specific esterase activity are increased in Crohn's disease [14]. These cells are found

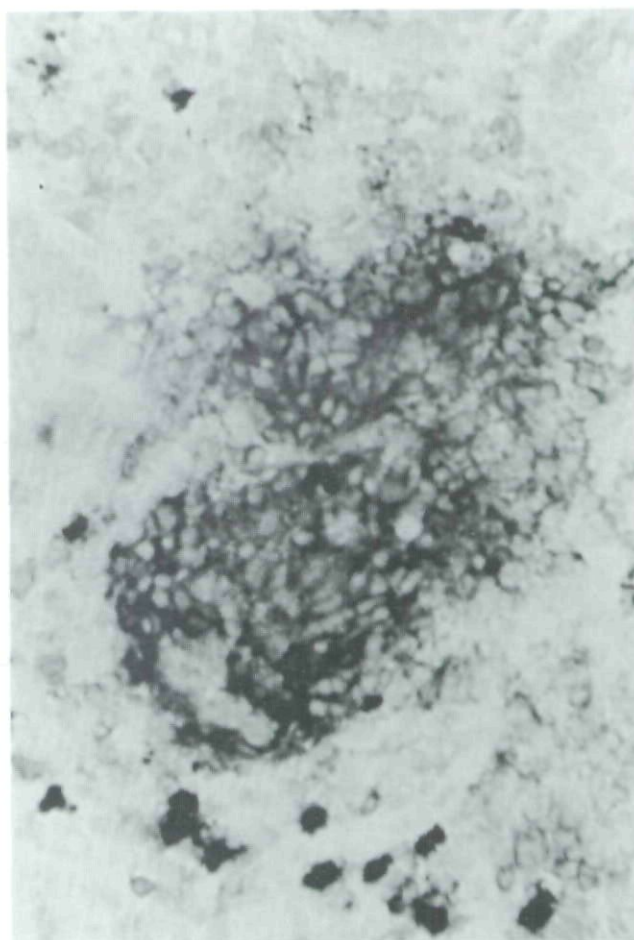


Fig. 3. Frozen section taken from a patient with colonic Crohn's disease showing a dense macrophage aggregate within the lamina propria. The macrophages are clustered at the site of a destroyed glandular crypt, presumably to intercept antigen which penetrates the damaged epithelium. The section is stained with the monoclonal antibody CD11c (3.9) (magnification $\times 250$).

around and within granulomas and at sites of ulceration [14,123,124] (Fig. 3). This altered distribution presumably reflects a higher than usual level of antigen stimulation due to epithelial damage [73,124]. Where the antigen persists granuloma formation occurs [125]. Furthermore, macrophages populating the inflamed mucosa are CD14 positive indicating recent recruitment from peripheral blood [123,126].

Macrophages show increased phenotypic heterogeneity in Crohn's disease, probably as a result of the mechanism outline above [73,123]. Similarly, dendritic-type accessory cells, usually rare in the large bowel are prominent [124]. These cells are particularly abundant adjacent to granulomas providing further evidence of exaggerated antigen handling in Crohn's disease. The appearance of RFD9 positive epithelioid-type cells represents the early stages of granuloma formation [73]. Although macrophages and dendritic cells are unlikely to be primarily responsible for the pathogenesis of Crohn's disease, they clearly provide a mechanism for tissue damage.

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