IL-15

Interleukin 15: its role in intestinal inflammation

D A van Heel

Interleukin 15 may have a central role in diverse intestinal inflammatory diseases, such as coeliac disease and inflammatory bowel disease, and hence manipulation of the IL-15 pathway may have therapeutic possibilities in these conditions

The cytokine interleukin 15 (IL-15, a protein of 114 amino acids) was first discovered due to IL-2-like stimulatory actions on T cells.^{1,2} The heterotrimeric IL-15 receptor comprises the β and γ chains of the IL-2 receptor, with a unique α subunit. These shared receptor subunits most likely explain the similar T cell growth factor properties of both IL-2 and IL-15. Several cell types can produce IL-15, including macrophages, dendritic cells, and intestinal epithelial cells. The discovery that enterocytes can both produce and respond to IL-15,³ and that IL-15 potentially stimulates intraepithelial lymphocytes,⁴ has focused attention on its role in intestinal inflammation. IL-15 also has a number of other activities, including recruitment and activation of T cells, maintenance of T cell memory, stimulation of proliferation and immunoglobulin synthesis by B cells, natural killer (NK) cell proliferation, activation of neutrophils, and inhibition of apoptosis. Mice with a genetically disrupted IL-15 gene ("knockout") remain healthy under specific pathogen free conditions.⁵ However, they display marked reductions in numbers of thymic and peripheral NK T cells, memory phenotype CD8⁺ T cells, and distinct subpopulations of intestinal intraepithelial lymphocytes. IL-15 receptor deficient mice demonstrate a broadly similar phenotype.⁶ These defects are rescued in the IL-15 knockout mouse by exogenous IL-15 administration, and IL-15 is therefore critical to the development of these lymphoid lineages.

In inflammatory bowel disease, increased expression of IL-15 on peripheral blood leucocytes has been reported.⁷ Expression of IL-15 mRNA was found to be significantly increased in inflamed rectal mucosa of inflammatory bowel disease patients.⁸ IL-15 is produced by activated lamina propria macrophages in ileal biopsies from Crohn's disease patients and colonic biopsies from ulcerative colitis patients.⁹ Some care

does need to be taken in the interpretation of IL-15 studies, as regulation is mainly at the post-transcriptional level (rather than mRNA) and IL-15 is bioactive in both secreted and membrane-bound forms. Yoshihara and colleagues¹⁰, in a recent issue of *Gut*, studied dextran sulphate sodium (DSS) induced colitis, in both acute and chronic phases, in IL-15 knockout and control mice.¹⁰ In acute colitis (~1 week DSS), IL-15 knockout mice displayed lower lethality, weight loss, and clinical and histological scores. Knockout mice had reduced lamina propria CD8⁺ T cells and NK cells, and lower levels of lamina propria proinflammatory cytokines (interferon γ , tumour necrosis factor α , and IL-12p40). Similar findings were seen in a chronic colitis model when DSS was given intermittently over 30 days. These data suggest targeting of IL-15 may be a novel therapeutic mechanism in inflammatory bowel disease.

In coeliac disease, IL-15 is also critical in disease pathogenesis, and its role is much better understood. IL-15 is overexpressed in both the lamina propria and intestinal epithelium of patients with active untreated coeliac disease compared with controls and gluten free diet treated coeliac patients.¹¹ Mention and colleagues¹¹ found that IL-15 was presented at the enterocyte cell surface, rather than being secreted in coeliac disease, suggesting a role in regulating intraepithelial lymphocytes through cell-cell contact. In ex vivo cultured duodenal biopsies, IL-15 mimics most of the epithelial modifications induced by wheat gliadin in coeliac but not in control samples.¹² Recent work has suggested that a wheat gliadin peptide (A-gliadin p31–43 or p31–49), different to that recognised by T cells, might act directly to induce IL-15 production in the lamina propria and initiate epithelial apoptosis.¹³ This peptide induces expression of the stress molecule MICA on enterocytes, an effect mediated by IL-15.¹⁴ IL-15 also activates intraepithelial

lymphocytes, including upregulation of the NKG2D receptor, which can interact with MICA thus enabling direct lymphocyte mediated cytotoxicity to enterocytes.^{15,16}

Di Sabatino and colleagues,¹⁷ in this issue of *Gut*, confirm previous studies and extend our knowledge of IL-15 in coeliac disease (see page 469). IL-15 was expressed in untreated coeliac disease enterocytes and lamina propria mononuclear cells, but not in cells from treated coeliacs or healthy patients. Levels correlated with the degree of mucosal damage. Intraepithelial lymphocytes from untreated coeliac patients showed increased activation and granzyme/perforin dependent cytotoxicity against epithelial cells, and resistance to IL-15 induced apoptosis. Enhanced intraepithelial lymphocyte proliferation and apoptosis resistance might be responsible for the generation of T cell lymphoma in the coeliac disease mucosa. In contrast with previous studies (which used cell line monolayers), Sabatino *et al* found that IL-15 was secreted by primary human coeliac disease enterocytes as well as being presented on the cell surface. Overexpression of IL-15, specifically in intestinal epithelial cells, in a murine model has been shown to induce chronic inflammation limited to the small intestine, with a histological picture of villous atrophy and lamina propria lymphocyte infiltration.¹⁸ The lymphocyte infiltrate comprised mostly CD8⁺ T cells expressing an NK cell marker, which were resistant to activation induced cell death.¹⁸ Interestingly, human in vivo data has shown direct mucosal damage when wheat gliadin p31–49 peptide is instilled into the small intestine of patients with coeliac disease.¹⁹ Further research is necessary to understand the mechanisms of p31–49 signalling and its effects on intestinal mucosa, how this is linked to IL-15 production, and why these changes should only occur in coeliac disease.

A human monoclonal antibody targeting IL-15 (HuMax-IL15, Genmab) has been developed which blocks the epitope of IL-15 binding to the γ subunit of the IL-15 receptor. In a phase I/II clinical trial in rheumatoid arthritis, HuMax-IL15 was well tolerated with substantial improvements in disease activity.²⁰ These studies suggest that manipulation of the IL-15 pathway might have therapeutic possibilities in both coeliac disease and inflammatory bowel disease. IL-15 appears to be central to coeliac disease, and probably inflammatory bowel disease pathogenesis, and greater understanding of its role is likely to generate further insights into the underlying mechanisms of intestinal inflammation.

ACKNOWLEDGEMENTS

DAvH is supported by grants from the Wellcome Trust, Coeliac UK, and Hammersmith Hospitals Charitable Trustees.

Gut 2006;**55**:444–445.

doi: 10.1136/gut.2005.079335

Correspondence to: Dr David van Heel, Gastroenterology Section, Imperial College London (Hammersmith Campus), Du Cane Road, London W12 0NN, UK; d.vanheel@imperial.ac.uk

Conflict of interest: None declared.

REFERENCES

- Burton JD, Bamford RN, Peters C, *et al.* A lymphokine, provisionally designated interleukin T and produced by a human adult T-cell leukemia line, stimulates T-cell proliferation and the induction of lymphokine-activated killer cells. *Proc Natl Acad Sci U S A* 1994;**91**:4935–9.
- Carson WE, Giri JG, Lindemann MJ, *et al.* Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. *J Exp Med* 1994;**180**:1395–403.
- Reinecker HC, MacDermott RP, Mirau S, *et al.* Intestinal epithelial cells both express and respond to interleukin 15. *Gastroenterology* 1996;**111**:1706–13.
- Ebert EC. Interleukin 15 is a potent stimulant of intraepithelial lymphocytes. *Gastroenterology* 1998;**115**:1439–45.
- Kennedy MK, Glaccum M, Brown SN, *et al.* Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice. *J Exp Med* 2000;**191**:771–80.
- Lodolce JP, Boone DL, Chai S, *et al.* IL-15 receptor maintains lymphoid homeostasis by supporting lymphocyte homing and proliferation. *Immunity* 1998;**9**:669–76.
- Kirman I, Nielsen OH. Increased numbers of interleukin-15-expressing cells in active ulcerative colitis. *Am J Gastroenterol* 1996;**91**:1789–94.
- Sakai T, Kusugami K, Nishimura H, *et al.* Interleukin 15 activity in the rectal mucosa of inflammatory bowel disease. *Gastroenterology* 1998;**114**:1237–43.
- Liu Z, Geboes K, Colpaert S, *et al.* IL-15 is highly expressed in inflammatory bowel disease and regulates local T cell-dependent cytokine production. *J Immunol* 2000;**164**:3608–15.
- Yoshihara K, Yajima T, Kubo C, *et al.* The role of interleukin 15 in colitis induced by dextran sulphate sodium in mice. *Gut* 2006;**55**:334–41.
- Mention JJ, Ben Ahmed M, Begue B, *et al.* Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology* 2003;**125**:730–45.
- Maiuri L, Ciacci C, Auricchio S, *et al.* Interleukin 15 mediates epithelial changes in celiac disease. *Gastroenterology* 2000;**119**:996–1006.
- Maiuri L, Ciacci C, Ricciardelli I, *et al.* Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *Lancet* 2003;**362**:30–7.
- Hue S, Mention JJ, Monteiro RC, *et al.* A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. *Immunity* 2004;**21**:367–77.
- Meresse B, Chen Z, Ciszewski C, *et al.* Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. *Immunity* 2004;**21**:357–66.
- Kinoshita N, Hiroi T, Ohta N, *et al.* Autocrine IL-15 mediates intestinal epithelial cell death via the activation of neighboring intraepithelial NK cells. *J Immunol* 2002;**169**:6187–92.
- Di Sabatino A, Cicciocioppo R, Cupelli F, *et al.* Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease. *Gut* 2006;**55**:469–77.
- Ohta N, Hiroi T, Kweon MN, *et al.* IL-15-dependent activation-induced cell death-resistant Th1 type CD8 alpha beta+ NK1.1+ T cells for the development of small intestinal inflammation. *J Immunol* 2002;**169**:460–8.
- Sturgess R, Day P, Ellis HJ, *et al.* Wheat peptide challenge in coeliac disease. *Lancet* 1994;**343**:758–61.
- Baslund B, Tvede N, Danneskiold-Samsøe B, *et al.* Targeting interleukin-15 in patients with rheumatoid arthritis: A proof-of-concept study. *Arthritis Rheum* 2005;**52**:2686–92.

Histamine

Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies

J D Wood

There is altered expression of histamine H₁ and H₂ receptor subtypes in mucosal biopsies from the terminal ileum and large intestine of patients with symptoms of food allergy and/or irritable bowel syndrome

The research article by Sander and colleagues¹ in this issue of *Gut*, reports their results for expression of histamine receptor subtypes in the human intestinal tract from normal individuals and patients with symptoms of the irritable bowel syndrome (IBS) and/or food allergies (see page 498). Work of this nature was overdue because most of the available histological and functional data for histamine receptors in the small and large intestine were obtained from animal models. The authors' principal findings for the human bowel are in general agreement with the animal literature that reports on expression of the histamine H₁, H₂, and H₄ receptor subtypes in the enteric nervous system (ENS), intestinal musculature, mucosal epithelium, and

immune/inflammatory cells. In contrast, the finding by Sander and colleagues¹ that histamine H₃ receptors are not expressed in the human bowel was unexpected in view of the clearcut evidence for functional involvement of the H₃ receptor subtype in the nervous control of motility, secretion, and blood flow in guinea pig intestine, which serves as the primary animal model.^{2–5}

The authors' evidence for altered expression of histamine H₁ and H₂ receptor subtypes in mucosal biopsies from the terminal ileum and large intestine of patients with symptoms of food allergy and/or IBS is consistent with current concepts for the involvement of histamine release from enteric mast cells and its paracrine signalling function in the ENS as an underlying

factor in these two disorders.^{5–8} Histamine is not expressed by enteric neurones and is not a neurotransmitter in the ENS.⁹ Its signalling function is paracrine in nature through release from enteric mast cells and inflammatory granulocytes. Mastocytosis and presumably elevated availability of histamine are present in microscopic colitis, parasitic infections, IBS, and no doubt additional functional gastrointestinal disorders associated with symptoms of cramping abdominal pain, watery diarrhoea, and defecation urgency.^{6, 8, 10–17}

The appearance of histamine H₂ receptors in human myenteric ganglia is reminiscent of expression of the H₂ receptor subtype in the guinea pig ENS. Binding of histamine to H₂ receptors on enteric neuronal cell bodies in the guinea pig, either during exogenous application of histamine or by degranulation of neighbouring mast cells, elevates neuronal excitability characterised by firing of longlasting trains of nerve impulses.^{18–21} In the case of submucosal secretomotor neurones, elevated firing rates increase the volume of mucosal secretions of electrolytes and H₂O and thereby increase the liquidity of the intestinal contents, which in turn can underlie neurogenic secretory diarrhoea.²² For musculomotor neurones in the myenteric plexus, histamine H₂ evoked firing alters contractile behaviour of the muscularis externa that is coordinated with organised secretory patterns.^{23, 24} Similar outcomes for