

Commentary

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Interleukin-10 in the intestine

Cytokines are small glycoprotein mediators involved in communication between cells. Immunological responses are, to a high degree, regulated and directed by specific cytokines. The simultaneous action of different cytokines, as well as their sequential interaction with target cells, seems to be of pivotal importance for an efficient host defence reaction. In inflammation, pro-inflammatory cytokines (that is, tumour necrosis factor- α (TNF- α), interleukin (IL)-1, IL-8, and IL-12) which initiate and perpetuate the activation of immune and non-immune cells are counterbalanced by contra-inflammatory mediators. According to this scheme, human T helper cells have also been functionally divided into those producing cytokines which augment immune activation (IL-2 and interferon- γ , which are attributed to type 1 T helper cells) and those secreting immunoregulatory interleukins (IL-4, IL-5, IL-10, and IL-13 by type 2 T helper cells).

Interleukin 10, previously named cytokine synthesis inhibitory factor (CSIF), has, like many other cytokines, multiple biological effects. Its main immunoregulatory function seems to be the inhibition of effector functions of activated phagocytes (monocytes, macrophages, granulocytes), T cells and non-immune cells. Human IL-10 down regulates transcription and secretion of IL-1 β , IL-6, IL-8, TNF- α , and G-CSF by activated monocytes and macrophages.^{1,2} IL-10 strongly inhibits production of interferon- γ and, to a lesser extent, IL-2 production by type 1 T helper cells,³ but not secretion of the type 2 T helper cell generated cytokines IL-4, IL-5 and IL-13.⁴ The inhibitory effect on T cells may be dependent on the presence of activated macrophages or dendritic cells.⁵ Recent studies also indicate an anti-proliferative effect of IL-10 on human intestinal lamina propria T cells.⁶ IL-10 knockout mice develop colitis, thereby indicating a potential role of IL-10 in maintaining normal non-inflammatory intestinal immunoregulation.⁷

In the mouse, IL-10 is produced by type 2 T helper cells and, in addition to other cells, by activated macrophages.⁸ In humans, activated monocytes and macrophages are thought to be one of the main sources of IL-10.⁸ However, T cell clones and Epstein Barr virus transformed lymphoblastoid cell lines also express IL-10 mRNA and protein after activation.^{9,10}

The pathophysiology of chronic inflammation of mucosal or synovial surfaces is not yet known and there are restricted therapeutic options for these conditions. Although investigated in depth, the analysis of pro-inflammatory mediators has not revealed a single process exclusively responsible for the chronic inflammation. The discovery of contra-inflammatory cytokines, which may be involved in the physiological down regulation of acute inflammatory responses, has rekindled interest in the characterisation of disturbances in contra-inflammatory immunoregulation. Preliminary data indicate that inflammatory

bowel disease (IBD) may be characterised by inadequate production of IL-10 by lamina propria T cells.¹¹ In parallel, strong efforts are currently underway to develop IL-10 as an anti-inflammatory drug in chronic IBD, rheumatoid arthritis, psoriasis, and AIDS.

The paper by Braunstein *et al*, in this issue (see page 215), examines the capacity of normal lamina propria T lymphocytes (LPL-T), in comparison with T lymphocytes obtained from peripheral blood (PBL-T), to secrete IL-10. The authors obtained LPL-T from "normal" intestine which was obtained at the resection margins in patients with colonic adenocarcinoma. This may have compromised their results as lymphocytes adjacent to colorectal tumours also show signs of immunological activation.¹²

Braunstein *et al* show that in the presence of autologous monocytes, IL-10 secretion could be induced by stimulation via CD2 or the T cell receptor CD3 complex. LPL-T secreted much greater amounts of IL-10 than PBL-T. Further analysis revealed that IL-10 is mainly secreted by CD45RO positive CD4 (T helper) cells. CD45RO negative PBL-T cells proliferated but did not release IL-10. More than 90% of normal LPL-T cells display the CD45RO phenotype indicative of memory T cells.^{13,14} In contrast, PBL-T cells are composed of about equal percentages of naive (CD45RA+, CD45RO-) and memory (CD45RA-, CD45RO+) T cells.^{13,14} Naive and memory T cells have distinctly different responses to stimulation via CD2. Whereas naive T cells require monocytes for a proliferative response, memory T cells do not.¹⁵

CD2 stimulation of LPL-T cells resulted in greater release of IL-10 compared with purified PBL-T selected for the memory phenotype. Therefore, the different composition of memory and naive T cells could not account for the differences between PBL-T and LPL-T. A recent study by Targan *et al* indicated that LPL may be adapted specifically to facilitate CD2 stimulated cytokine secretion.¹⁶ Braunstein *et al* showed that co-stimulation of CD2 and the tyrosine phosphatase CD45, which is functionally involved in CD2 signalling, could induce IL-10 secretion in PBL-T at levels similar to CD2 monostimulated LPL-T. However, co-stimulation of CD2 and CD45 in LPL-T cells resulted in reduced IL-10 secretion.

The data presented by Braunstein *et al* reveal important differences between lamina propria and peripheral blood T cells. The findings may be important for understanding the maintenance of a non-inflammatory state in the normal intestinal mucosa. Contra-inflammatory pathways are of particular importance in the control of inflammation in this tissue and for the maintenance of a non-inflammatory, immune activated state which is necessary for the immunological barrier function of mucosal surfaces.¹⁷ Further understanding of the physiological actions of IL-10, which also regulates epithelial cell apoptosis via

regulation of nuclear factor- κ B activation (Kühbacher T, Lohmann RD, Schreiber S, unpublished data) will reveal important insights into the relation between chronic inflammation and malignant transformation.

In IBD, an increased percentage of naive T cells can be detected within the lamina propria. These may be recruited from the circulation.¹⁹ Braunstein *et al.*'s data suggest that these cells will show an impaired ability to secrete IL-10 even after CD2 stimulation.

Therefore, the data suggest a mechanism by which a regulatory deficit at the level of contra-inflammatory T cell immunoregulation might occur in IBD and support the notion that administration of IL-10 will improve chronic mucosal inflammation.¹⁹

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- 1 de Waal Malefyt R, Yssel H, Roncarolo M-G, Spits H, de Vries JE. Interleukin 10. *Curr Opin Immunol* 1992; **4**: 314–22.
- 2 Schreiber S, Heinig T, Thiele HG, Raedler A. Immunoregulatory role of interleukin 10 in patients with inflammatory bowel disease. *Gastroenterology* 1995; **108**: 1434–44.
- 3 Fiorentino DF, Bond MW, Mosmann TR. Two types of mouse T helper cells. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *J Exp Med* 1989; **170**: 2081–5.
- 4 Fiorentino DF, Zlotnik A, Vieira P, Mosmann TR, Howard M, Moore KW, *et al.* IL-10 acts on the antigen presenting cell to inhibit cytokine production by Th1 cells. *J Immunol* 1991; **146**: 3444–51.
- 5 Ding L, Shevach EM. IL-10 inhibits mitogen-induced T cell proliferation by selectively inhibiting macrophage costimulatory function. *J Immunol* 1992; **148**: 3133–9.
- 6 Fukushima K, West GA, Klein JS, Levine AD, Fiocchi C. Opposite modulatory activity of IL-10 and IL-4 on lamina propria mononuclear cells (LpMC) is stimulus-dependent [abstract]. *Gastroenterology* 1993; **104**: A702.
- 7 Kühn R, Löhler J, Rennick D, Rajewsky K, Müller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993; **75**: 263–74.
- 8 de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10 (IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J Exp Med* 1991; **174**: 1209–20.
- 9 Yssel H, de Waal Malefyt R, Roncarolo M-G, Abrams JS, Lahesmaa R, Spits H, *et al.* IL-10 is produced by subsets of human CD4+ T cell clones and peripheral blood T cells. *J Immunol* 1992; **149**: 2378–84.
- 10 Vieira P, de Waal-Malefyt R, Dang M, Johnson KE, Kastelein R, Fiorentino DF, *et al.* Isolation and expression of human cytokine synthesis inhibitory factor (CSIF/IL-10) c-DNA clones: homology to Epstein-Barr virus open reading frame BCRF1. *Proc Natl Acad Sci USA* 1991; **88**: 1172–7.
- 11 Fukushima K, West GA, Dobrea GM, Sasaki I, Matsuno S, Fiocchi C. Differential IL-10 production between ulcerative colitis (UC) and Crohn's disease (CD): enhanced levels in UC are macrophage but not T cell derived [abstract]. *Gastroenterology* 1995; **108**: A820.
- 12 Ostenstad B, Lea T, Schlichting E, Harboe M. Human colorectal tumour infiltrating lymphocytes express activation markers and the CD45RO molecule, showing a primed population of lymphocytes in the tumour area. *Gut* 1994; **35**: 382–7.
- 13 De Maria R, Fais S, Silvestri M, Frati L, Pallone F, Santoni A, *et al.* Continuous in vivo activation and transient hyporesponsiveness to TcR/CD3 triggering of human gut lamina propria lymphocytes. *Eur J Immunol* 1993; **23**: 3204–8.
- 14 Akbar AN, Terry L, Timms A, Beverly PCL, Janossy G. Loss of CD45R and gain of UCHL1 reactivity is a feature of primed T cells. *J Immunol* 1988; **140**: 2171–8.
- 15 Kasahara Y, Miyawaki T, Kato K, Kanegane H, Yachie H, Yokoi T, *et al.* Role of interleukin 6 for differential responsiveness of naive and memory CD4+ T cells in CD2-mediated activation. *J Exp Med* 1990; **172**: 1419–24.
- 16 Targan SR, Deem RL, Liu M, Wang S, Nel A. Definition of a lamina propria T cell responsive state. Enhanced cytokine responsiveness of T cells stimulated through the CD2 pathway. *J Immunol* 1995; **154**: 664–75.
- 17 Schreiber S, MacDermott RP, Raedler A, Pinnau R, Bertovich M, Nash GS. Increased activation of isolated intestinal lamina propria mononuclear cells in inflammatory bowel disease. *Gastroenterology* 1991; **101**: 1020–30.
- 18 Burgio VL, Fais S, Boirivant M, Perrone A, Pallone F. Peripheral monocyte and naive T-cell recruitment and activation in Crohn's disease. *Gastroenterology* 1995; **109**: 1029–38.
- 19 Schreiber S, Heinig T, Thiele HG, Raedler A. Immunoregulatory role of interleukin 10 in inflammatory bowel disease. *Gastroenterology* 1985; **108**: 1434–44.