Published in final edited form as:

Inflamm Bowel Dis. 2013 March ; 19(3): E39–E40. doi:10.1002/ibd.22960.

New Perspectives of an Old Cytokine

Ali Raza, MD and Mohamed T. Shata, MD, PhD

Department of Internal Medicine, Division of Digestive Diseases, University of Cincinnati
Cincinnati, Ohio

To the Editor

Inflammatory bowel disease (IBD) is characterized by an unusual and complex immune response in the gastrointestinal (GI) tract. Intestinal inflammation is a result of imbalance between immunosuppressive and proinflammatory responses.

Discovery of new types of CD4⁺ T-helper cells provided new opportunities in the understanding of IBD immunopathogenesis. Interleukin (IL)-2 is one of the oldest known cytokines, which is secreted by various lymphocytes. It has been known to exert both proinflammatory and immunosuppressive actions at different doses.¹ At higher doses, it is proinflammatory and is used as a chemotherapeutic agent in malignancies. At low doses, it promotes the development and function of CD4⁺, CD25^{high}, forkhead box P3 (FOXP3⁺) T-regulatory (T-reg) cells by preferentially engaging with its receptor on these cells.² Deficiency or neutralization of IL-2 has been shown to cause immune damage in animal models.³ Recently, Saadoun et al⁴ demonstrated the safety of low-dose IL-2 administration and substantial improvement of hepatitis C virus (HCV)-induced auto-immune vasculitis. We believe the same concept can be reproduced in other autoimmune diseases like IBD. Recently, preliminary data from our laboratory showed some interesting results about IL-2 levels in patients with IBD.⁵ In our ongoing cohort, we measured IL-2 in the plasma and in the supernatant of intraepithelial lymphocytes (IEL) isolated from colonic biopsy after in vitro stimulation with anti-CD3 in 10 IBD patients and 13 healthy controls. No significant difference ($P = 0.9766$) in the plasma levels of IL-2 in healthy controls compared to the IBD patients was observed (mean $\pm$ standard deviation [SD]; 1.03 ± 1.10 and 1.14 ± 1.11 pg/ml, respectively). However, the IL-2 levels in the supernatant of the anti-CD3-stimulated IEL were significantly higher ($P = 0.006$) in controls compared to IBD patients (mean $\pm$ SD; 1572.6 ± 3456.6 and 76.82 ± 158.09 pg/mL, respectively). The lower mucosal levels of IL-2 in IBD patients could be responsible for increased immune damage due to impaired T-reg functions. Low-dose IL-2 immunotherapy has been shown to have few side effects by Saadoun et al and its usage as a potential treatment modality for complex IBD patients may be worth a trial to prove its therapeutic benefits as shown by Saadoun et al.

Acknowledgments

Janssen Research and Development partially funded the ongoing research in our laboratory.

References

1. Bluestone JA. The yin and yang of interleukin-2-mediated immunotherapy. *N Engl J Med.* 2011; 365:2129–2131.
2. Malek TR, Castro I. Interleukin-2 receptor signaling: at the interface between tolerance and immunity. *Immunity.* 2010; 33:153–165.
3. Setoguchi R, Hori S, Takahashi T, et al. Homeostatic maintenance of natural FoxP3⁺CD25⁺CD4⁺ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. *J Exp Med.* 2005; 201:723–735. [PubMed: 15753206]

4. Saadoun D, Rosenzwajg M, Joly F, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med*. 2011; 365:2067–2077.
5. Raza, A.; Ahmed, K.; Navaneethan, U., et al. ACP Excellence in Medical Education. New Orleans: Apr 19–21. 2012 The IL-2 levels in supernatants of intra-epithelial mucosal lymphocytes stimulated in vitro with anti-CD3 were significantly higher in healthy adults compared to the patients with inflammatory bowel disease (IBD).