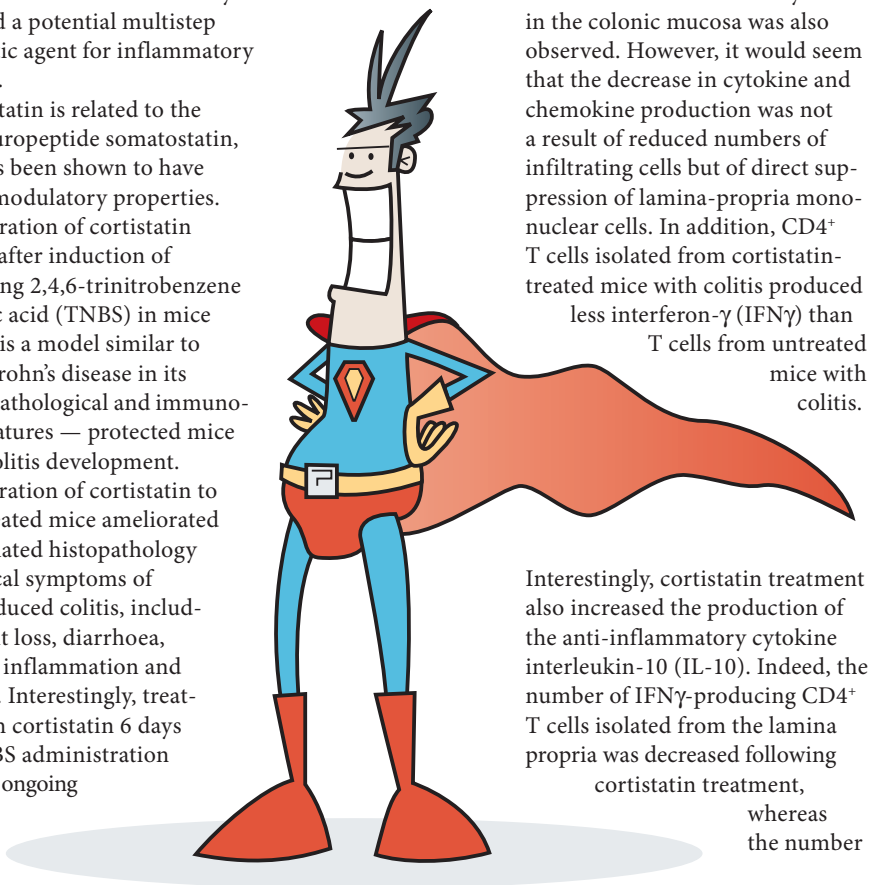
IMMUNOTHERAPY

Cortistatin to the rescue

The quest to find specific, effective and safe therapeutic agents for inflammatory disorders such as Crohn's disease and septic shock is an ongoing struggle. Now, two new studies by Gonzalez-Rey *et al.* describe a recently discovered endogenous factor, cortistatin, as an effective anti-inflammatory factor and a potential multistep therapeutic agent for inflammatory disorders.

Cortistatin is related to the cyclic neuropeptide somatostatin, which has been shown to have immunomodulatory properties. Administration of cortistatin 12 hours after induction of colitis using 2,4,6-trinitrobenzene sulphonic acid (TNBS) in mice — which is a model similar to human Crohn's disease in its clinical, pathological and immunological features — protected mice against colitis development. Administration of cortistatin to TNBS-treated mice ameliorated the associated histopathology and clinical symptoms of TNBS-induced colitis, including weight loss, diarrhoea, intestinal inflammation and mortality. Interestingly, treatment with cortistatin 6 days after TNBS administration abrogated ongoing disease and was also effective at reducing disease recurrence.



Analysis of the inflammatory mediators in the colon showed a substantial reduction in the production of various pro-inflammatory cytokines and chemokines in mice treated with cortistatin. Decreased infiltration of inflammatory cells in the colonic mucosa was also observed. However, it would seem that the decrease in cytokine and chemokine production was not a result of reduced numbers of infiltrating cells but of direct suppression of lamina-propria mononuclear cells. In addition, $CD4^+$ T cells isolated from cortistatin-treated mice with colitis produced less interferon-γ (IFNγ) than T cells from untreated mice with colitis.

Interestingly, cortistatin treatment also increased the production of the anti-inflammatory cytokine interleukin-10 (IL-10). Indeed, the number of IFNγ-producing $CD4^+$ T cells isolated from the lamina propria was decreased following cortistatin treatment, whereas the number of IL-10-producing cells was increased. This observation indicates that cortistatin induces the generation and/or activation of IL-10-producing T cells that might contribute to the observed protection against colitis development.

In a separate study, this group also showed a protective role for cortistatin in a model of septic shock. Administration of cortistatin protected mice against endotoxin-induced lethality and associated histopathology. These effects seem to be mediated through the suppression of pro-inflammatory cytokine, chemokine and acute-phase protein production. Cortistatin treatment was also associated with increased IL-10 production in this model.

These data indicate that cortistatin is a potent anti-inflammatory agent that suppresses the production of pro-inflammatory mediators while increasing IL-10 production in two different disease models. Therefore, the authors suggest that cortistatin might represent a potential therapeutic agent for Crohn's disease and septic shock.

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ORIGINAL RESEARCH PAPERS
Gonzalez-Rey, E. *et al.* Cortistatin, an antiinflammatory peptide with therapeutic action in inflammatory bowel disease. *Proc. Natl Acad. Sci. USA* **103**, 4228–4233 (2006) | Gonzalez-Rey, E. *et al.* Cortistatin, a new antiinflammatory peptide with therapeutic effect on lethal endotoxemia. *J. Exp. Med.* **203**, 563–571 (2006)

FURTHER READING Greenwood, J., Steinman, L. & Zamvil. S. S. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nature Rev. Immunol.* **6**, 358–370 (2006)