Commentary

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Oxpentifylline, tumour necrosis factor-α and Crohn’s disease

One of the conceptual difficulties in targeted, specific immunotherapy for the treatment of chronic inflammatory bowel disease (IBD) lies in the fact that, in diseased mucosa, virtually every known inflammatory mediator is raised. Given the potent biological activity of these mediators and the fact that many of them have overlapping functions, it would seem naive to assume that inhibiting a single molecule or receptor would have beneficial effects. However, as reviewed in this issue by van Deventer (see page 443), treatment of patients with antibody directed against tumour necrosis factor-α (TNF-α) seems to be a useful new treatment for steroid refractory Crohn’s disease. The mechanism of action is unknown. The antibody binds to both soluble and membrane bound TNF-α and so at least part of its activity probably results from direct neutralisation. The cA2 anti-TNF-α antibody used is a chimeric protein with a human IgG1 heavy chain and there is the possibility that it can bind to membrane TNF-α, activate complement and lyse the TNF-α secreting cell. The cell type(s) which secrete TNF-α in Crohn’s disease are not known in any detail, although some are probably macrophages. None the less, these experiments are highly encouraging for “proof of concept” and suggest that TNF-α may be a key mediator in gut inflammation. Now that the TNF-α convertase (the metalloenzyme which cleaves the membrane form of TNF-α to release the soluble molecule) has been cloned, it should be possible to design small molecular weight inhibitors to prevent TNF-α release from the cell membrane.

Oxpentifylline (pentoxifylline; PTX) is a phosphodiesterase inhibitor which has been shown in many studies to inhibit TNF-α transcription and protein production in vivo and in vitro by increasing intracellular cyclic AMP concentrations. An obvious question, therefore, is does PTX have any effects on the release of TNF-α in Crohn’s disease? Reimund and colleagues in this issue (see page 475) confirm the work of many others and show that PTX inhibits spontaneous and inducible TNF-α production by blood mononuclear cells in a dose dependent fashion, but not secretion of interleukin-8 (IL-8), IL-6 or IL-1β. Inhibition was modest at low concentrations of PTX (20–40% at 1–10 µg/ml) but at 100 µg/ml was quite striking (80%). The IC50 was rather high, at 25 µg/ml. When PTX was added to cultured endoscopic biopsy specimens from patients with active IBD, different results were obtained which are difficult to interpret. First, PTX inhibited both IL-1β and TNF-α production. Second, no dose response was evident. At all PTX concentrations (1–100 µg/ml), TNF-α production was inhibited modestly (30–50%) and although the authors claim an IC50 of 25 µg/ml, the data do not support this. The lack of dose response is especially worrying and it is regrettable that the authors did not attempt to use concentrations below 1 µg/ml.

Based on these results, should one use PTX in IBD? I would say that Reimund et al’s data are not convincing. To substantiate this, an open label study from Bauditz and colleagues, also reported in this issue (see page 470), shows that a four week course of PTX given orally has no beneficial effect in steroid dependent, chronic active Crohn’s disease. There was no improvement in the Crohn’s disease activity index, in laboratory parameters, nor endoscopic healing. The dose used, 400 mg four times a day, is compatible with previous studies which have showed efficacy in vivo in other diseases. The only parameter to change was the quality of sleep which improved as a result of fewer night sweats and less myalgia. In some patients blood monocytes were tested in vitro for their ability to secrete TNF-α before and after treatment with PTX. There was a tendency for reduced secretion after treatment, but this did not achieve statistical significance. In an important positive control, healthy volunteers received PTX for two days. Secretion of TNF-α by blood mononuclear cells after lipopolysaccharide stimulation was notably reduced after treatment. It would have been extremely interesting to determine whether mucosal TNF-α transcripts or protein concentrations were reduced after PTX treatment because if they were, the presence of continuing inflammation would suggest that TNF-α is not required for disease. However, as this was not done, we have no idea whether enough PTX reached the inflamed gut to be pharmacologically active.

Several conclusions can be drawn from these papers, the main one being that in vivo veritas remains as true as ever. The approach by Reimund et al of adding PTX to colonic biopsy specimens in vitro is probably not the best way to tackle this problem as, in my experience, tissue survival is very poor, although this did not seem to be the case in their study. It is also not known whether the TNF-α found in the supernatants was actually synthesised by cells in the biopsy sample or whether it merely seeped out of the interstitial fluid or was released by dead or dying cells. The disappointing effects of PTX in vivo, however, should not detract from the real hope that anti-TNF-α therapy will prove to be an important new advance in the treatment of Crohn’s disease, and that real progress will be made when we understand the mechanism of action.

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