BIM–BH3-MIMETIC THERAPY FOR RA

Studies in animal models have suggested that inducing controlled, localized apoptosis of synoviocytes could be an effective strategy for ameliorating joint inflammation and damage in patients with rheumatoid arthritis (RA). However, identification of agents capable of achieving this aim safely has proved challenging. In a study published in *Arthritis & Rheumatism*, Scatizzi and colleagues report promising findings for just such an apoptosis-promoting agent.

The Bcl-2 family of proteins contains both antiapoptotic and proapoptotic members, which possess at least one of four functionally important Bcl-2 homology domains (BH1–4). Bim (also known as Bcl-2-like protein 11), a proapoptotic Bcl-2-family protein that contains only the BH3 domain, has been studied previously as a potential therapeutic target in cancer. In the current study, its role in RA was investigated using a range of *in vitro* and *in vivo* techniques.

Bim expression was decreased in macrophages from synovial tissue samples from RA patients. It also seemed to have a role in limiting macrophage activation, as demonstrated by the finding that macrophages isolated from *Bim*$^{-/-}$ mice expressed increased levels of inflammatory markers and interleukin-1β following stimulation with lipopolysaccharide.

The therapeutic potential of an engineered BH3-mimetic peptide (TAT–BH3) was tested in the K/BxN serum-transfer mouse model of experimental arthritis. Mice that received intraperitoneal injections of TAT–BH3 showed ameliorated arthritis development and increased apoptosis of myeloid cells in arthritic joints compared with control mice.

The authors conclude that Bim–BH3-mimetic agents might have therapeutic value in RA and other autoimmune diseases that are characterized by a failure to remove autoreactive cells.

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Original article Scatizzi, J. C. *et al.* Bim–Bcl-2 homology 3 mimetic therapy is effective at suppressing inflammatory arthritis through the activation of myeloid cell apoptosis. *Arthritis Rheum.* **62**, 441–451 (2010)