THE FUTURE OF THERAPY FOR RA

Prodrug targeting PI3K shows therapeutic potential

The complexity of rheumatoid arthritis (RA) results from the involvement of several immune cell types, common to which are signaling networks involving kinases. Phosphatidylinositol 3-kinases (PI3Ks) are particularly important in the inflammatory response, and the PI3K inhibitor wortmannin has well-established anti-inflammatory properties. Stangenberg and colleagues have successfully demonstrated the therapeutic potential of a new, slow-release form of wortmannin to inhibit PI3K in a mouse model of inflammatory arthritis.

"A problem with wortmannin," explains Umar Mahmood, who led the study, "is its short active blood half-life, combined with its narrow therapeutic index." The researchers therefore used a novel self-activating viridin (SAV) prodrug that slowly releases wortmannin. "The subsequent continuous generation of active wortmannin at a sustained level in the target tissue enables the strong anti-PI3K effects of wortmannin to be conferred using a clinically translatable dosing approach," continues Mahmood.

Stangenberg *et al.* showed a dose-dependent reduction in ankle swelling when SAV was administered concurrent with arthritis induction (the prevention model) by injection of K/BxN mouse serum. Histologic analysis revealed no accompanying cartilage erosion and minimal inflammation. The researchers used an imaging-based approach to demonstrate a reduction in the levels of protease activity (an early indicator of inflammation in arthritis). When given after arthritis induction (the treatment model), SAV again reduced joint swelling and protease activity. Joint swelling was also reduced greatly by SAV in the transgenic K/BxN model, which shows a more severe and destructive form of arthritis than seen with the serum-transfer system.

SAV moderately reduced the extent of K/BxN serum-induced increases in endothelial permeability and, using a series of labeling experiments, the investigators showed that the prodrug reduced the extent of neutrophil attachment to endothelial cells and endothelial cell activation by tumor necrosis factor. SAV also inhibited neutrophil functions, such as the generation of reactive oxygen species and degranulation.

From a clinical perspective, the team hopes to assess any potential synergies between SAVs and other anti-inflammatory approaches, as well as improving the pharmacokinetics of SAV itself.

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Original article Stangenberg, L. *et al.* Abrogation of antibody-induced arthritis in mice by a self-activating viridin prodrug and association with impaired neutrophil and endothelial cell function. *Arthritis Rheum.* **60**, 2314–2324 (2009).