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CROHN'S DISEASE

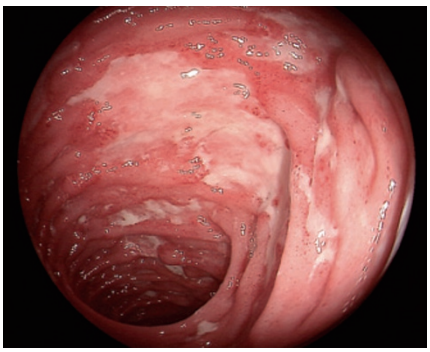
# Suppression of p21Rac1 signalling contributes to skip-lesion phenotype in Crohn's disease

"Differences in immune signalling might underlie the dichotomy observed in the intestine of patients with Crohn's disease, in which apparently healthy mucosa alternates with ulcerated intestinal lesions in so called skip-lesions," hypothesizes Maikel Peppelenbosch, author of a recent study published in *Science Translational Medicine*. Kinome profiles of uninflamed tissue from patients with IBD showed a striking suppression of p21Rac1-dependent signalling versus inflamed tissue from patients with IBD and healthy individuals as controls. Reduced signalling owing to the deregulation of proteins affecting p21Rac1 GTP hydrolysis and loading was associated with improved innate immune function.

Peppelenbosch explains that the moderate suppression of p21Rac1 could cause phagocytes to become more efficient, thereby boosting local innate immunity and resulting in localized areas without inflammation.

This theory was borne out when the investigators inhibited p21Rac1 GTP loading with NSC23766 in monocytes derived from areas of patient tissue affected by Crohn's disease. After treatment, monocytes demonstrated levels of phagocytosis on a par with cells from healthy controls. In addition, monocytes isolated from areas of inflammation, which have hyperactive p21Rac1 signalling, displayed reduced rates of phagocytosis.

A mainstay of IBD treatment, azathioprine is a known p21Rac1 inhibitor, but until now has only been linked with modifying adaptive immunity. Now, the authors of this study have found that 6-thioguanine (the bioactive metabolite of azathioprine) stimulates innate immune function by increasing phagocytosis and IL-8 production. The improvement in innate immune function could contribute to azathioprine-related maintenance of remission in patients with IBD.



Endoscopic image of an intestine with IBD, courtesy of M. Peppelenbosch.

The identification of defective p21Rac1 signalling in patients with IBD provides novel therapeutic avenues to explore. As such the authors plan on initiating a clinical trial using more-specific p21Rac1 inhibitors that could decrease the adverse effects observed with current IBD therapies.

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**Original article** Parikh, K. *et al.* Suppression of p21Rac signaling and increased innate immunity mediate remission in Crohn's disease. *Sci. Transl. Med.* **6**, 233ra53 (2014)