4 Intestinal myofibroblast-specific Tpl2-Cox-2-PGE2 pathway links innate sensing to epithelial homeostasis.

Roulis M, Nikolaou C, Kotsaki E, Kaffe E, Karagianni N, Koliaraki V, Salpea K, Ragoussis J, Aidinis V, Martini E, Becker C, Herschman HR, Vetrano S, Danese S, Kollias G

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Recommendations:

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INTERESTING HYPOTHESIS | NEW FINDING | NOVEL DRUG TARGET

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A wealth of genes have been associated with susceptibility to inflammatory bowel disease (IBD), but plausible links to pathogenic mechanisms have been identified for only a handful. This limits the extent to which insights from genome-wide association studies (GWAS) studies can be exploited therapeutically. In the current article, Roulis and colleagues show that the IBD-associated kinase tumor progression locus-2 (Tpl2) is expressed in intestinal myofibroblasts and, following intestinal injury, is required for innate immune sensing and subsequent activation of the COX2 pathway that restores epithelial integrity. Intriguingly, the increased susceptibility to colitic damage of mice lacking Tpl2 in myofibroblasts can be rescued by exogenous administration of a stable analogue of prostaglandin E2. Thus, the findings reported may indicate a simple approach to restoring mucosal integrity in IBD.

Disclosures
None declared

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INTERESTING HYPOTHESIS | NEW FINDING

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This paper reinforces the concept of an interaction between epithelial and mesenchymal cells at the physiological level; moreover, it demonstrates that intestinal crypt myofibroblasts are crucial for the response of epithelial cells to inflammatory and damaging stimuli. It shows that mice with complete or myofibroblast-limited deficiency of tumor progression locus-2 kinase (Tpl2) exhibit an increased epithelial cell response to experimental colitis-induced lesions, despite a similar degree of inflammation compared to non-deficient controls. Tpl2 produced by crypt myofibroblasts acts through the stimulation of arachidonic acid metabolism as well as through cyclooxygenase-2/prostaglandin E2 activation. Moreover, Tpl2 appears decreased in myofibroblasts isolated from patients with Crohn's disease compared to those isolated from control patients, suggesting that it may play a role in the development of the disease.

Disclosures
None declared

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Abstract:

ABSTRACT

Tumor progression locus-2 (Tpl2) kinase is a major inflammatory mediator in immune cell types recently found to be genetically associated with inflammatory bowel diseases (IBDs). Here we show that Tpl2 may exert a dominant homeostatic rather than inflammatory function in the intestine mediated specifically by subepithelial intestinal myofibroblasts (IMFs). Mice with complete or IMF-specific Tpl2 ablation are highly susceptible to epithelial injury-induced colitis showing impaired compensatory proliferation in crypts and extensive ulcerations... more »
without significant changes in inflammatory responses. Following epithelial injury, IMFs sense innate or inflammatory signals and activate, via Tpl2, the cyclooxygenase-2 (Cox-2)-prostaglandin E2 (PGE2) pathway, which we show here to be essential for the epithelial homeostatic response. Exogenous PGE2 administration rescues mice with complete or IMF-specific Tpl2 ablation from defects in crypt function and susceptibility to colitis. We also show that Tpl2 expression is decreased in IMFs isolated from the inflamed ileum of IBD patients indicating that Tpl2 function in IMFs may be highly relevant to human disease. The IMF-mediated mechanism we propose also involves the IBD-associated genes IL1R1, MAPK1, and the PGE2 receptor-encoding PTGER4. Our results establish a previously unidentified myofibroblast-specific innate pathway that regulates intestinal homeostasis and may underlie IBD susceptibility in humans.

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