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Impairment of trefoil factor family 3 function in inflammatory bowel disease

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Trefoil factor family 3 (TFF3), or intestinal trefoil factor, is one of the trefoil factor peptides that is exclusively expressed by goblet cells of the small and large bowel. Several experiments had suggested a key role of trefoil factor peptides in protecting the gastrointestinal mucosa from injury and promoting recovery. Mice overexpressing TFF3 displayed increased resistance to intestinal damage and ulceration. The question can thus be asked: does TFF3 have a healing role in inflammatory bowel disease (IBD), where destructive inflammation is the final common pathway?

In IBD, pathological processes are associated with aberrant expression of many proinflammatory cytokines, including tumor necrosis factor α (TNF-α). TNF-α triggers degradation of IκB, the inhibitor of nuclear factor κB (NFκB), thereby allowing translocation of NFκB into the nucleus. Recruitment of this transcription factor results in transcriptional activation of multiple components of the inflammatory response and leads to further NFκB activation. Antibodies against TNF-α and inhibitors of its production are widely used in the treatment of IBD. For example, sulphasalazine, one of the most effective agents for IBD, inhibits TNF-α-induced NFκB activation via inhibition of IκB phosphorylation.

The expression of TFF3 in IBD was recently studied by a group of researchers from the Institute of Human Genetics in Tübingen, Germany.[1] The study was able to demonstrate the downregulation of TFF3 gene by transcriptional repression after TNF-α stimulation. TNF-α induction in colon cancer line HT29 mediated activation of NFκB and was shown to evoke up to 10-fold reductions in TFF3 expression. The researchers also used a rat model of 2,4,5-trinitrobenzene sulphonic acid (TNBS) induced colitis, which simulated features similar to those found in human ulcerative colitis. Following TNBS administration, lesions of variable severity were found in these animals and activated NFκB was expressed in macrophages, stromal cells and some epithelial cells in the middle and upper third of the crypts, accompanied by weak TFF3 expression in goblet cells by immunohistochemistry. NFκB expression paralleled a marked reduction in TFF3 expression. The recovery of the normal intestinal epithelium was accompanied by a significant reduction in NFκB expression and restoration of normal TFF3 expression in goblet cells.

The strong reduction of TFF3 peptide expression in this rat model of colitis was associated with inflammation and NFκB recruitment. Reduction in TFF3 action may partially explain the impairment of wound healing in IBD. This study suggested that therapeutic activation of TFF genes may generate opportunities for treatment of gastrointestinal disease.

Arief Suriawinata, MD

References

1 Loncar MB, Al-azzeh ED, Sommer PS, *et al*. Tumor Necrosis Factor α and Nuclear Factor Kappa B Inhibit Transcription of Human TFF3 Encoding a Gastrointestinal Healing Peptide. Gut 2003;52: 1297–1303.

The role of *BRAF* mutation in colorectal carcinogenesis

It is well known that dysregulated activation of *RAS* in the RAS-RAF-MEK-ERK (mitogen activated protein kinase-MAPK) signal transduction pathway plays a critical role in colorectal carcinogenesis. A *RAS* mutation, *KRAS* in particular, is present in 30–50% of colorectal carcinoma, and is a gatekeeper gene that dictates, in part, tumor progression through the hyperplasia–adenoma–carcinoma sequence. Recent studies suggest that *BRAF*, an immediate downstream effector of *KRAS,* can serve as an alternative to *KRAS* in activating this pathway. There is a relatively high frequency of *BRAF* mutation in a subset of colorectal carcinomas in which no *KRAS* mutations are detectable. Furthermore, *RAS* mutation and the most common *BRAF* mutation (V599E) show a mutually exclusive relationship, suggesting that *BRAF* (V599E) mutation is a critical, nonrandom oncogenic event. The colorectal carcinomas associated with either *KRAS* or *BRAF* mutation are phenotypically similar, yet are biologically diverse. Does this alternative carcinogenic factor, *BRAF* mutation, have the same impact on carcinogenesis as *KRAS*? Can the biological or clinical heterogeneity of colorectal carcinomas be attributed to different precursor lesions resulting from mutation of either *BRAF* or *KRAS*?

Chan *et al* addressed these issues by demonstrating that *BRAF* (V599E) mutation was associated with a precursor lesion, serrated adenoma, which

was morphologically distinct from adenomas or dysplasia associated with *KRAS* mutation. They found that *BRAF* (V599E) mutation was present in serrated adenomas at a surprisingly high frequency (~100%), and in a significant percentage of hyperplastic and dysplastic lesions with serrated features. In addition, they also found that *BRAF* (V599E) and *KRAS* mutations were mutually exclusive in all colorectal lesions.[1] These findings suggest that acquiring *BRAF* mutation drives carcinogenesis in the hyperplasia-to-serrated adenoma-to-carcinoma pathway, whereas *KRAS* mutation promotes progression in the hyperplasia-to-adenoma (tubular or villous)-to-carcinoma sequence.

Besides morphological differences, *BRAF* and *KRAS* mutation may also induce other genetic or epigenetic effects resulting in different biological outcomes. A study by **Rajagopalan *et al***[2] has shown that *BRAF* mutation is associated with mismatch repair (MMR) deficiency. Colorectal carcinomas with MMR tend to occur in the right side of the colon, to be poorly differentiated, to have a better survival and a reduced likelihood of metastasis, and to show different response to chemotherapy. If *BRAF* mutation is truly associated with MMR, this group of patients with *BRAF* mutation would, therefore, require closer clinical scrutiny.

Despite the unique effects of *BRAF* and *KRAS* on colorectal carcinogenesis, their exact role in determining the tumor's biological heterogeneity is difficult to assess. This issue can only be reliably addressed when the entire course of progression from hyperplasia to adenomas to carcinoma is followed and the emergence of *BRAF* or *KRAS* mutation is examined in each step. This type of study, however, is ethically and technically unfeasible. Retrospective study, such as this one by **Chan *et al***, in which patients with carcinomas and coexistent precursor lesions were analyzed for *BRAF* and *KRAS* mutation, may provide an invaluable insight into the molecular mechanisms of colorectal carcinogenesis.

Ruliang Xu, MD and Gabriel Levi, MD

References

1 Chan TL, Zhao W, Leung SY, *et al*. *BRAF* and *KRAS* mutations in colorectal hyperplastic polyps and serrated adenomas. Cancer Res 2003; 63:4878–4881.
2 Rajagopalan H, Bardelli A, Lengauer C, *et al*. Tumorigenesis: *RAF/RAS* oncogenes and mismatch-repair status. Nature 2002; 418:934.