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CROHN'S DISEASE

TCF1 regulates Paneth cell α-defensins

A new study by Beisner *et al.* suggests that the transcription factor TCF1 (also known as TCF7) is involved in ileal Crohn's disease pathogenesis. TCF1 was shown to transactivate the expression of *DEFA5* and *DEFA6*, genes that encode two Paneth cell α-defensins.

TCF1 is part of the Wnt signalling pathway, which regulates Paneth cell biology. Amongst other roles, Paneth cells help to maintain intestinal barrier function by secreting antimicrobial peptides such as α-defensins. Importantly, phenotypic dysfunction of Paneth cells is a feature of Crohn's disease.

As the *DEFA5* and *DEFA6* promoters contain TCF1 binding sites, the investigators overexpressed TCF1 *in vitro*. A subsequent increase in the promoter activity of both defensins was observed. Moreover, mutating the TCF1 binding site at -130 nucleotides upstream of the transcriptional start site led to decreased *DEFA5* and *DEFA6* promoter activity. Electophoretic mobility shift assays (which detect direct protein–DNA interactions) confirmed that TCF1 binds to the *DEFA5* promoter to regulate its expression. Mutating the binding sites abrogated the TCF1–*DEFA5* interaction.

Analysis of ileal biopsy tissue from 14 patients with ileal Crohn's disease showed a dramatic reduction in the expression of *TCF1*, the active isoform of *TCF1* (which binds β-catenin) and *DEFA5* compared with healthy controls. In addition, immunohistochemistry revealed that TCF1 colocalizes with markers of Paneth cells. The authors propose that decreased TCF1 expression might contribute to Paneth cell dysfunction and development of ileal Crohn's disease.

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Original article Beisner, J. *et al.* TCF-1 mediated Wnt signalling regulates Paneth cell innate immune defense effectors HD-5 and -6: implications for Crohn's disease. *Am. J. Physiol. Gastrointest. Liver Physiol.* doi:10.1152/ajpgi.00347.2013