

## LETTER TO THE EDITOR - REPLY

We thank Drs Van Kruiningen and Tonelli for their letter underlying the role of obstructed lymphatics in the pathogenesis of Crohn's disease (CD). Indeed, the forgotten role of lymphangitis in CD has been revisited.<sup>1</sup> Of note, it was consistently reported that at an early time, a fundamental alteration in CD occurs in the regional lymphatics of the intestine, highlighting the role of lymphatics in the genesis of disease.<sup>2</sup> Rahier et al<sup>3</sup> have confirmed that the lymphatic vessels' density was increased in CD patients compared with controls, with a progressive increase in lymphatic density seen from non-inflamed to inflamed areas and the phenomenon present in areas with no other marker of inflammation, suggesting an early event. However, a causal role for these alterations has not been consistently demonstrated in CD; the vast majority of predisposing genes highlighted in CD do not point toward a prominent role of lymphatics as a cause of the disease, and finally, marked and clinically significant fibrosis only occurs in a subset of CD patients and is associated to a specific immune-inflammatory process not necessarily associated with lymphatic abnormalities. This is why we did not address the impact of obstructed lymphatics in fibrosis and penetrating complications.

Moreover, our article mostly aimed at better describing the pathophysiology of intestinal damage lesions in CD to further allow the identification of new therapeutic targets to prevent and reverse tissue damage and especially fibrosis. We reported the direct antifibrotic action of several existing or newly developed molecules and cell therapies targeting transforming growth factor beta1 induced pathways, extracellular matrix deposition, and epithelial-to-mesenchymal transition. On the opposite, no clear target has emerged so far to prevent or correct lymphatic lesions described in CD, and there is no proof that it would impact transmural lesions and fibrosis development. Although research in this field is important and may help to better understand the pathogenesis of CD, over the short-term, we do not see it as a major way to find new treatments to treat transmural tissue damage and fibrosis in inflammatory bowel disease.

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## References

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2. Van Kruiningen HJ, et al. Gut 2008;57:1-4.
3. Rahier JF, et al. Aliment Pharmacol Ther 2011;34:533-543.

### CONFLICTS OF INTEREST

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