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Commentary

Adipocyte-Epithelial Interactions and Crohn's Disease - An Emerging Drug Target

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Crohn's disease is hallmarked by mesenteric abnormalities including thickening, shortening and extension of mesenteric fat over the intestinal surface ("fat wrapping" or "creeping fat") (Coffey et al., 2016; Peyrin-Biroulet et al., 2007; Sheehan et al., 1992; Crohn et al., 1932). Mesenteric and submucosal mesenchymal abnormalities overlap in histological appearance and both inflammatory fronts meet to generate transmural inflammation (Coffey and O'leary, 2016). Multiple cellular abnormalities underpin these histological changes, including increased collagen deposition (Li and Kuemmerle, 2014), fibroblast activation (Li and Kuemmerle, 2014), adipocyte hyperplasia (but not hypertrophy) and epithelial to mesenchymal transformation (Coffey et al., 2016; Peyrin-Biroulet et al., 2007). Cellular abnormalities occur in the connective tissue that (1) integrates mesentery and contiguous intestine and (2) is the adult remnant of mesenteric contributions to outer layers of the intestinal wall during organogenesis (Coffey et al., 2016; Coffey and O'Leary, 2016).

In Crohn's disease, mesenteric, mural and mucosal disease manifestations are topographically coupled as they increase in tandem (Coffey et al., 2016; Peyrin-Biroulet et al., 2007; Sheehan et al., 1992). Mucosal ulceration first develops at the mesenteric margin of the intestinal circumference (i.e. "axial polarity") (Crohn et al., 1932; Thompson, 1990). Here, where mesentery intersects intestine, mesenteric inputs are at their most concentrated. Takahashi et al. confirmed this coupling by immunostaining for perilipin (which identifies adipocyte droplets). Intestinal epithelial damage was marked where the intestine and mesentery were contiguous (Takahashi et al., 2017).

In investigating the cellular and molecular basis of this coupling, Takahashi et al. demonstrated a novel cellular axis involving intestinal epithelial cells (IECs) and adipocytes. Several properties of this axis were important. Firstly, they observed an increase in MMP-9 mRNA in IECs when co-cultured with adipocytes that had differentiated from murine embryonic fibroblasts. Importantly, no increase in MMP-9 mRNA expression was observed when IECs when these were co-cultured with murine embryonic fibroblasts. This differential responsivity is highly relevant and is further discussed below.

Takahashi et al. also observed a reduction in Villin-1 and glycoprotein 33 mRNA expression (both proteins exert anti-inflammatory effects) in IECs co-cultured with adipocytes. This profile of gene expression changes induced by co-culture with fibroblast-derived adipocytes point to the activity of an inter-cellular signalling pathway that could explain coupling of mesenteric, mucosal and mural manifestations seen in Crohn's disease.

The differential effect of adipcoyte and fibroblast co-culture with IECs is particularly important. Crohn's disease has multiple phenotypes characterised by different macroscopic features (inflammatory, stricturing and fistulating) (Gasche et al., 2000). The cellular and molecular basis of these differences are not well defined, but definition may be informed by the observations of Takahashi et al. In this context it is important to recall that the adipocytes generated by Takahashi et al. were firstly derived from murine embryonic fibroblasts. In addition, adipocyte (but not fibroblast) co-culture, led to an increase in epithelial MMP-9 mRNA expression.

Taking the above and other observations into account, an intuitive cellular hypothesis arises based on differential fibroblast differentiation, adipocyte generation and adipocyte/epithelial interactions. According to this hypothesis three scenarios are possible. In the first, adipocyte differentiation dominates. As a result, IEC/adipocyte cellular activity is substantial and triggers an overall inflammatory phenotype (increased MMP-9, IL-6 and TNF with reduced Villin-1 and glycoprotein 33 expression). In the second scenario, adipocyte differentiation is non-dominant. The adipocyte/epithelial axis is relatively less active and fibroblastic mesenchymal activities lead to an overall stricturing phenotype. In the third scenario, differentiation is balanced. As a result inflammation (driven by epithelial/adipocyte interactions) and fibrosis occur in tandem and lead to a fistulating phenotype. Hence, varying rates of fibroblast differentiation, coupled with differential potency of adipocyte/epithelial inputs could explain many of the phenotypic variations of Crohn's disease.

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The requirement for surgery, in any intestinal condition, is an excellent indicator of the success or failure of medical management. Overall, surgery rates appear largely unaltered in Crohn's disease, despite the global usage of monoclonal antibodies targeting either cytokines, integrins and other molecular mediators (Burke et al., 2013). This observation is partially explained by the findings of Takahashi et al. who showed that whilst a TNF neutralising antibody reduced mRNA levels in intestinal epithelial cells, adipocytes were unaffected. Given the relative importance of adipose mesenchyme in the mesentery and submucosa in Crohn's disease, alternate pharmacotherapeutic approaches may be required to reduce the requirement for surgical intervention. It is feasible that Takahashi et al. have identified one such approach, i.e. disrupting signalling between adipocytes and intestinal epithelia. They showed that MMP-9 mRNA production was increased in intestinal epithelium when cultured in adipocyte conditioned medium. The reverse did not hold in that MMP-9 mRNA expression did not increase in adipocytes cultured in epithelial conditioned medium. They also showed that targeting of NF-κB and STAT-3 disrupted the epithelial response to culture in adipocyte-conditioned medium. Hence, adipocyte-related induction of pro-inflammatory responses in intestinal epithelia may be pharmaco-therapeutically disrupted.

Emerging data indicate that inclusion of the mesentery during resection for ileocolic Crohn's disease, may lead to reduced rates of surgical recurrence (i.e. recurrence requiring surgical intervention)[1]. That being said, surgical intervention remains a radical intervention with risk, and the development of pharmaco-therapeutic means of targeting the adipose fraction of mesentery should be developed. The findings of the present study support future in vivo studies examining interactions between intestinal epithelial and mesenteric-derived mesenchymal cell populations (i.e. adipocyte and fibroblast fractions). They also support the development of non-invasive means of diagnosing and therapeutically altering mesenteric manifestations of Crohn's disease.

Conflict of interests

The authors declare no conflicts of interest.

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