infusion of MSCs into inflamed UC tissue or CD fistulas induces up-regulation of immunomodulatory molecules in MSCs that are unique for the patient's cytokine milieu and that play a role in the immunomodulatory properties of the cells. Differences in cytokine expression between patients may explain the different clinical efficacies that are observed following MSC therapy.

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Differences in NOTCH signalling between stricturing and penetrating behaviour in Crohn's disease

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Background: Fibrosis and fistula development constitute the main complications associated to Crohn's disease. Notch signalling has been implicated in lung, kidney, liver, and cardiac fibrosis and in various disease conditions such as scleroderma. We aim to analyse here the pattern of NOTCH ligands, receptors, and effectors expression in surgical resections from stenotic and fistulizing CD patients and to determine the potential role of these ligands in favouring fistula and fibrosis.

Methods: CD patients (n = 41) were categorised according to Montreal classification (age at diagnosis, location, and behaviour). mRNA was isolated from resections of patients presenting a stricturing (B2, n = 26) or a penetrating (B3, n = 15) behaviour or from unaffected mucosa of patients with colorectal cancer (control, n = 15). The expression of Notch ligands, receptors, and effectors (HES1 and MATH1) was determined by RT-PCR or WB. Correlations between data were analysed using Pearson's correlation coefficient (*$p < 0.05$).

Results: A higher mRNA expression of NOTCH3 and NOTCH4 receptors was detected in CD patients compared with controls; in addition, the expression of these markers was higher in the fistulizing than in the stenotic behaviour (Table 1). The fistulizing group presented a generalised overexpression of NOTCH ligands (JAG2, DLL3, and DLL4) compared with controls and among them, only DLL3 expression was up-regulated in the stenotic group (Table 1). Similar levels of HES1 and MATH1 mRNA expression were detected between different groups while protein levels of HES1 were higher in the fistulising group than in control or stenotic groups (3.4 ± 0.1 A.U*#, 2.8 ± 0.2 A.U and 2.0 ± 0.1 A.U, respectively). The expression of DLL3 significantly correlated with FSP1 (r = 0.77, p = 0.04*), DESMIN (r = 0.80, p = 0.03*), and SNAIL1 (r = 0.59, $p < 0.04$*), only in intestinal tissue from the fistulizing CD group.

Conclusions: Activation of the Notch signalling pathway is detected in Crohn's disease patients presenting a penetrating (B3) behaviour compared with those with a structuring (B2) phenotype and it may be involved in fistula development over fibrosis.

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APL expression is down-regulated in an animal model of chronic colitis

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Background: Apelin (APL), originally isolated from alimentary tract, has been defined as the endogenous ligand for APJ, which is a known G protein-coupled receptor. It has been reported that APL is up-regulated in the colonic tissues of murine model of dextran sodium sulphate (DSS)-induced acute colitis, and it is suggested to be associated with the pathogenesis of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, in humans. However, the mechanism and function of APL in the context of IBD are still not well understood. Here, we analysed APL expression in the murine model of chronic colitis.

Methods: Each cell type in the colonic tissue, including epithelial cells and lamina propria lymphocytes, were first isolated from wild-type C57BL6 mice (WT) to assess APL expression. Next, naïve T cells isolated from WT were adoptively transferred into Rag-deficient mice ($Rag^{-/-}$) to induce chronic colitis, followed by isolation of splenic and colonic $CD4^+$ T cells from these T-cell-reconstituted $Rag^{-/-}$ to compare with those of WT. In addition, WT naïve T cells were differentiated into either Th1, Th2, or Th17 *in vitro* to analyse APL expression. Finally, the $Rag^{-/-}$ receiving naïve T cells were administered synthetic APL peptide to assess the severity of colitis.

Results: Semi-quantitative PCR (qPCR) revealed that $CD4^+$ T cells express relatively higher level of APL compared with other cell types including the epithelia in colonic tissue from WT. However, APL expression in the colonic tissues from the $Rag^{-/-}$ induced chronic colitis was unexpectedly down-regulated compared with those without colitis, which is not consistent with the previous report using acute DSS colitis model. Subsequently, qPCR revealed significantly decreased APL expression in the splenic and colonic T cells from $Rag^{-/-}$-induced colitis compared with that of WT. APL expressions in all of the differentiated T cells *in vitro*, such as Th1, Th2, and Th17, were also significantly down-regulated compared with that of non-differentiated control. Given these results, synthetic APL peptide was injected into the $Rag^{-/-}$ that underwent T-cell reconstitution to antagonise the APL down-regulation. This resulted in reduced severity of colitis compared with that of vehicle-injected control.

ΔCT	NOTCH1	NOTCH2	NOTCH3	NOTCH4	JAG2	DLL1	DLL3	DLL4	HES1
Non-IBD	14.2 ± 0.4	9.9 ± 0.2	17.4 ± 0.2	13.4 ± 0.3	16.02 ± 0.2	23.2 ± 0.3	20.4 ± 0.7	18.9 ± 0.2	9.5 ± 0.3
B2	14.5 ± 0.2	9.9 ± 0.2	16.0 ± 0.3*	11.5 ± 0.3*	15.0 ± 0.3	23.1 ± 0.5	15.7 ± 0.7**	19.5 ± 0.4	9.8 ± 0.3
B3	13.6 ± 0.2	9.2 ± 0.4	14.8 ± 0.3**#	9.6 ± 0.9**#	14.1 ± 0.2**	23.0 ± 0.4	16.4 ± 0.9*	17.6 ± 0.3*#	9.2 ± 0.3

Relative mRNA expression of NOTCH ligands and receptors vs. the housekeeping gene β-ACTIN in intestinal mucosa. Significant differences vs. the respective Non-IBD patients are shown by *$p < 0.05$ or **$p < 0.05$ and vs. B2 CD patients by #$p < 0.05$.