Blood proteins related to immunoregulation or cellular junctions reveal distinct biological profiles associated with the risk of short-term versus mid/long-term relapse in Crohn's disease patients stopping infliximab

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Background: In Crohn's disease (CD), biologics can induce mucosal healing and stable remission. After reaching this target, treatment de-escalation could be considered but the risk of relapse needs to be estimated. Current biomarkers used to predict relapse (C-reactive protein: CRP, faecal calprotectin) offer a limited prognostic capacity. Furthermore, they only monitor inflammation while we recently highlighted various and distinct pathological processes associated with the risk of short-term (<6 months) and mid/long-term (>6 months) relapse in

CD patients stopping infliximab. Herein, the aim of our study was to further characterise this distinction.

Methods: Serum abundance of 92 proteins were measured by proximity extension assay (immune response panel, Olink) at baseline of the STORI cohort (infliximab diScon-Tinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors, n=102). Association of markers with the risk of relapse was determined by univariable Cox model in stratified (relapse <6 months or >6 months) and non-stratified datasets. Study of protein characteristics and enrichment analyses were performed to find biological patterns differentiating short-term from mid/long-term relapsers. To evaluate the predictive capacity of markers, we combined them systematically by pairs ('AND' or 'OR' logical operators) and used log-rank statistics with false discovery rate (FDR) correction (Benjamini-Hochberg).

Results: The risk of mid/long-term relapse was associated with a decreased circulating level of anti-inflammatory effectors while the risk of short-term relapse was associated with an increased circulating level of pro-inflammatory effectors (Fig. 1A, 1B).

The risk associated with the downstream signalling of cytokine and pattern recognition receptors showed an opposite pattern in the short-term versus mid/long-term relapsers (Fig. 1D, 1E).

The risk of short-term relapse was characterised by a perturbed circulating level of proteins inducing tolerance and immunity in antigen presenting cells (Fig. 2A, 2B).

The risk of mid/long-term relapse was characterised by an increased circulating level of proteins promoting lymphocyte tolerance (Fig. 2D, 2E) and a decreased circulating level of cellular junction proteins (Fig. 3).

We found 1223 (short-term relapse dataset), 233 (mid/long-term relapse dataset) and 101 (non-stratified dataset) novel marker combinations with FDR<0.05 and higher Z-scores than CRP and faecal calprotectin. The best combinations are showed in Fig. 4.

Conclusion: In CD patients stopping infliximab, blood proteins linked to immunoregulation or cellular junctions support the distinct profiles of short-term and mid/long-term relapsers. These proteins showed a capacity to predict the relapse.

Figure 1

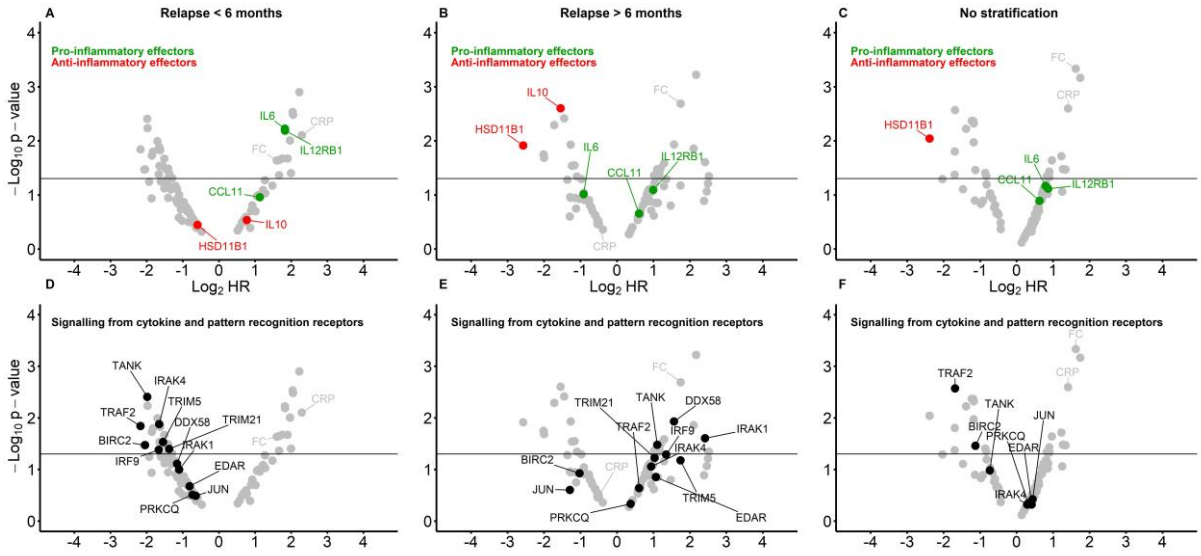

Figure 2

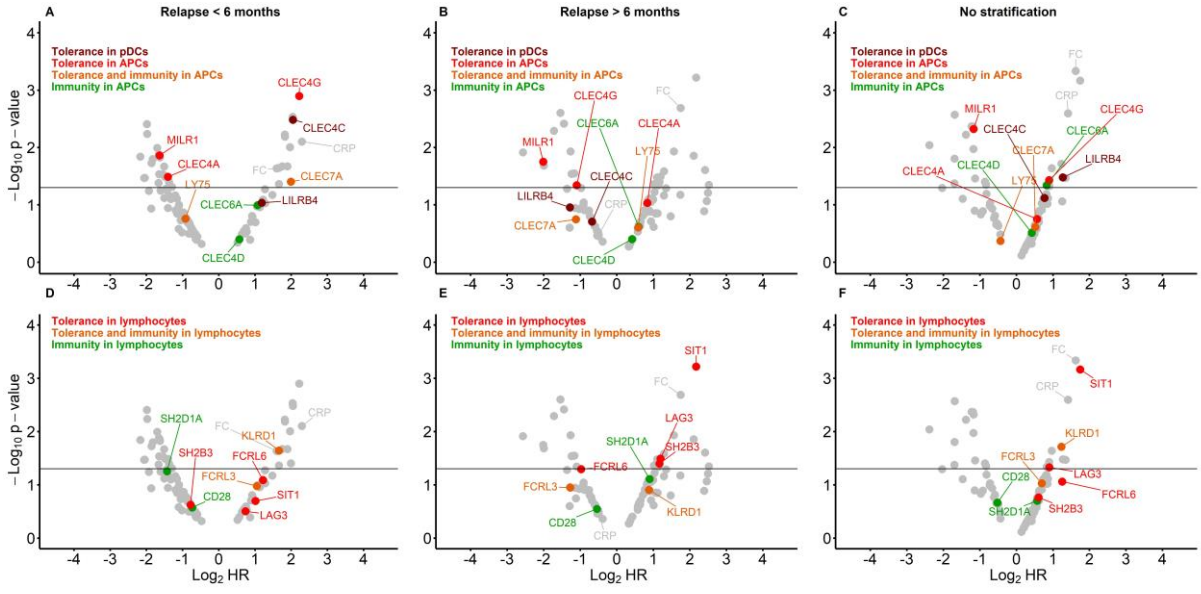

Figure 3

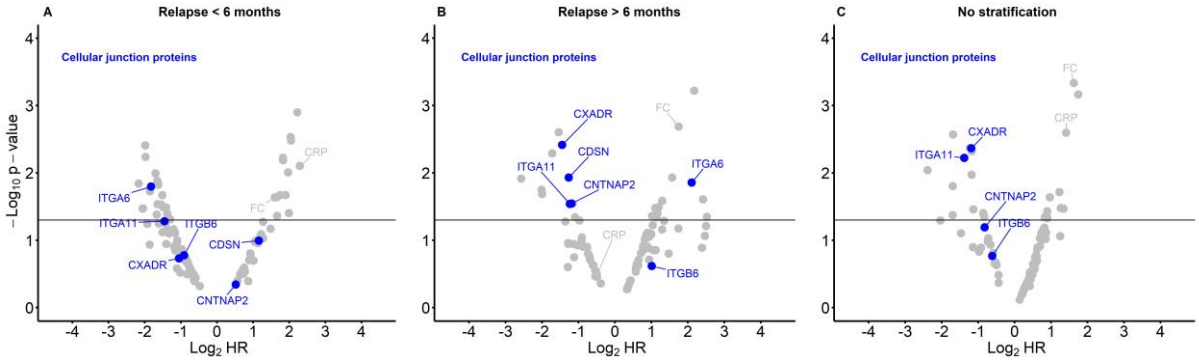

Figure 4