Insights into immune pathogenesis and response to therapy of Crohn's disease patients by imaging mass cytometry

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Background & aims: Advanced therapies such as TNF-antibodies (e.g. adalimumab, [ADA]) or the IL-12/23 antibody ustekinumab (UST) often fail to induce durable remission in Crohn's disease (CD). Previous studies suggest that exhausted $CD8^+$ T-cells are associated with milder disease, whereas frequencies of IL-17A–producing $CD8^+$ T-cells are increased during active inflammation[1-3].

Methods:
Ileal biopsies from 86 CD patients were included. 54 received therapies with ADA or UST (n=27, each), while 32 patients did not receive advanced therapy. A 42-plex imaging mass cytometry (IMC) panel was used to delineate spatial relationships and macro-anatomical niches of tissue-resident, potentially exhausted ($PD\text{-}1^+$), and $IL\text{-}17A^+$ $CD8^+$ T-cell subsets, and to characterize their interactions with myeloid and stromal compartments.

Results:
$PD\text{-}1^+$ $CD8^+$ T-cells showed no clear association with disease activity but were strongly enriched within lymphoid follicles. Tissue-resident $CD8^+$ T-cells, mainly located in the epithelium, were enriched in remission as well as in chronic disease. $IL\text{-}17A^+$ $CD8^+$ T-cells correlated positively with disease progression and formed their own niche. $TREM1^+$ myeloid cells exhibited significant spatial proximity to all three mentioned $CD8^+$ T-cell subsets, implicating them in orchestration of $CD8^+$ T-cell phenotypes, while $PDPN^+$ fibroblasts emerged as key stromal contributors to active inflammation.

Conclusions:
Spatially resolved profiling reveals a shift in $CD8^+$ T-cell phenotypes along the disease course of CD — from tissue-resident to IL-17A–producing effector states— potentially coordinated by $TREM1^+$ myeloid cells and $PDPN^+$ fibroblasts. These microenvironmental interactions highlight candidate prognostic biomarkers and therapeutic targets in CD.

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