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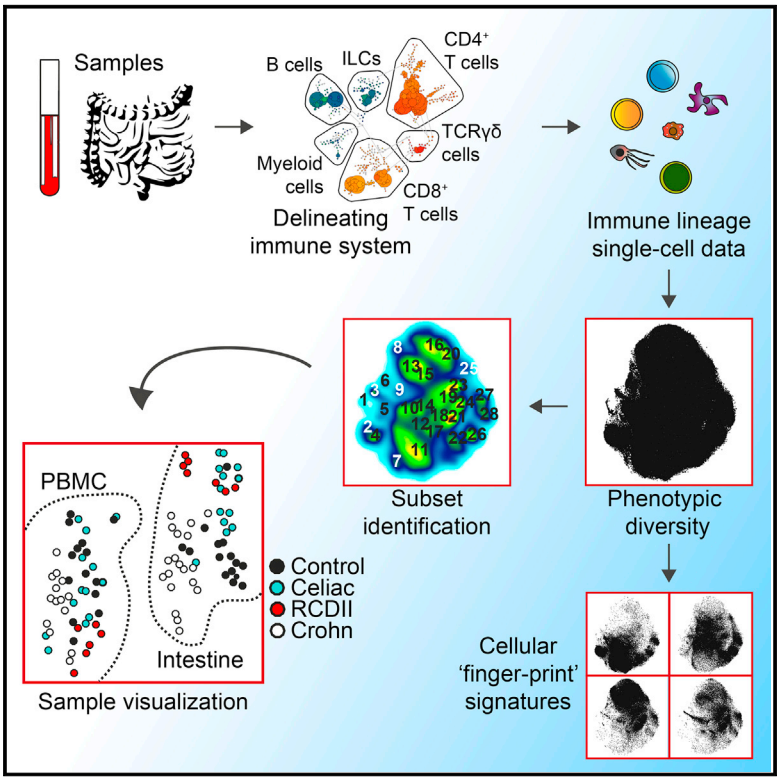
Mass Cytometry of the Human Mucosal Immune System Identifies Tissue- and Disease-Associated Immune Subsets

Graphical Abstract



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In Brief

The role of immune subsets in intestinal pathology has been studied, but a system-wide analysis is lacking. Koning and colleagues use mass cytometry to dissect the human mucosal immune system in health and disease. They identify immune subsets with tissue- and disease-specificity with implications for diagnostic procedures and individualized therapeutics.

Highlights

- Performed high-dimensional analysis of human mucosal immune system by mass cytometry
- Data-driven approaches revealed previously unrecognized immune cell heterogeneity
- Identified mucosal lymphoid malignancies and their cellular precursors
- Data visualizations identified tissue- and disease-associated immune subsets

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Mass Cytometry of the Human Mucosal Immune System Identifies Tissue- and Disease-Associated Immune Subsets

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SUMMARY

Inflammatory intestinal diseases are characterized by abnormal immune responses and affect distinct locations of the gastrointestinal tract. Although the role of several immune subsets in driving intestinal pathology has been studied, a system-wide approach that simultaneously interrogates all major lineages on a single-cell basis is lacking. We used high-dimensional mass cytometry to generate a system-wide view of the human mucosal immune system in health and disease. We distinguished 142 immune subsets and through computational applications found distinct immune subsets in peripheral blood mononuclear cells and intestinal biopsies that distinguished patients from controls. In addition, mucosal lymphoid malignancies were readily detected as well as precursors from which these likely derived. These findings indicate that an integrated high-dimensional analysis of the entire immune system can identify immune subsets associated with the pathogenesis of complex intestinal disorders. This might have implications for diagnostic procedures, immune-monitoring, and treatment of intestinal diseases and mucosal malignancies.

INTRODUCTION

The intestinal immune system protects us from bacterial, viral, and parasitic infections. Disruption of intestinal homeostasis, however, can lead to a variety of autoinflammatory intestinal diseases, including celiac disease (CeD) and Crohn's disease (CD), which together have a prevalence of 1,500 per 100,000 adults in the Western world (Kappelman et al., 2013; Rubio-Tapia et al., 2012). Both diseases are multifactorial and encompass a broad spectrum of clinical phenotypes and ages of onset. CeD is a disease of the small intestine caused by pro-inflammatory $CD4^+$ T cell responses specific for dietary gluten and concomitant destruction of the epithelium due to activation of intraepithelial $CD8^+$ T cells. The introduction of a strict gluten-free diet constitutes a highly effective treatment for CeD but nevertheless 2%–5% of patients develop refractory CeD type II (RCDII) with persistent inflammation. RCDII is characterized by a monoclonal outgrowth of aberrant intra-epithelial lymphocytes (IELs) from which an aggressive enteropathy-associated T cell lymphoma (EATL) evolves in 40% of patients (Al-Toma et al., 2007). In contrast, CD affects the terminal ileum and/or colon and results from aberrant immune responses against the microbiota (Pascual et al., 2014). CD is usually treated with the use of lifelong pharmacotherapy (Randall et al., 2015), including biologicals (e.g., anti-TNF) to reduce chronic inflammation and to accomplish sustained remission. Despite achieving states of remission, perianal fistulas occur in 25% of CD patients and this is accompanied by multiple relapses and a poor prognosis due to insufficient healing (Molendijk et al., 2014; Schwartz et al., 2002).

Although the role of several immune subsets in driving intestinal pathology has been studied in CeD (Jabri and Sollid, 2009), RCDII (Verbeek et al., 2008), and CD (Geremia et al., 2014), a system-wide approach that simultaneously interrogates immune subsets across all major lineages on a single-cell basis is currently lacking. High-dimensional mass cytometry (cytometry by time-of-flight; CyTOF) now offers the possibility to analyze many cellular markers simultaneously, providing an opportunity to analyze the mucosal immune system with unprecedented resolution (Bandura et al., 2009). Novel computational tools have been developed to handle the high-dimensional single-cell datasets that originate from mass cytometry (Amir et al., 2013; Bendall et al., 2011; Shekhar et al., 2014). In the current study, we applied mass cytometry to analyze the composition of the immune compartment present in intestinal biopsies and paired peripheral blood mononuclear cell (PBMC) samples of patients with inflammatory intestinal diseases and controls. We identified 142 distinct immune cell subsets and through computational