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Title: Comprehensive Spatial and Single Cell Mapping of Castleman Disease Reveals Pathogenic Stromal Cells and Cytokine Pathways

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Summary: Castleman disease (CD) is characterized by marked by anomalous lymph node morphology. The pathogenesis of the two major subtypes of CD: unicentric CD (UCD) and idiopathic multicentric CD (iMCD), is not known. To determine the cellular and molecular basis of CD, we analyzed the spatial proteome, transcriptome, immune repertoire, and pathogenic mutations in UCD, iMCD, HHV8-associated MCD and reactive lymph nodes. CD was characterized by increased macrophages, plasmacytoid dendritic cells, endothelial cells, plasma cells and lymph node stromal cells that formed unique spatial neighborhoods with close interactions among lymphoid and non-lymphoid cells. Concentric interdigitation of follicular dendritic cell (FDC) cytoplasmic meshworks in between mantle zone B cells was the basis of ‘onion skin’ diagnostic feature of CD. VEGF, IL-6, MAPK, and extracellular matrix pathways were elevated in stromal cells of CD. CXCL13+ FDCs, PDGFRA+ interfollicular reticular cells, and ACTA2-positive perivascular reticular cells were identified as the predominant source of increased VEGF expression and IL-6 signaling in CD. VEGF secretion by FDCs was the basis of ‘penetrating vasculature’ feature of CD. Stromal cells of CD activated JAK-STAT, TGFβ, and MAPK pathways via ligand-receptor interactions involving collagen, integrins, complement components, and VEGF receptors. T, B and plasma cells were polyclonal but showed class-switched and somatically hypermutated IgG1+ plasma cells consistent with stromal cell-driven germinal center process. In conclusion, we established that stromal cell activation and function underlies the key clinical and pathologic features of all subtypes of CD and reveal new targets for treatment.