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Nearly 70 years later: the continued unraveling of Castleman Disease.

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Much progress has been made in our understanding of Castleman Disease over the past 60-70 years since it was first described in 1954.¹ Castleman Disease is a heterogeneous group of lymph node disorders with shared pathologic findings. The histopathology of CD spans a spectrum with on the one end lymph nodes showing regressed or atretic follicles with prominent follicular dendritic cell networks, expanded mantle zones consisting of small B-lymphocytes and prominent interfollicular hyalinized vessels referred to as the hyaline vascular type. On the other end is the plasmacytic pathology characterized by increased numbers of hyperplastic follicles, marked interfollicular plasmacytosis with also increased vascularity.

Clinically, a unicentric forms (UCD) affecting one lymph node station and a multicentric form involving multiple lymph node areas (MCD), have now been recognized. Patients with MCD often have inflammatory symptomatology driven by hyper cytokinemia. There is a predilection for hyaline vascular pathology in UCD and plasmacytic findings in MCD, but there is considerable overlap. Cytokines and chemokines such as IL6 and VEGF play an important role in driving the phenotype of the idiopathic form of MCD (iMCD), but the cellular origins of these factors have not been identified. UCD is treated with surgery and iMCD with antibodies that target IL6 with 33-50% responding.^{2,3} These response rates also underscore the notion that a better understanding of iMCD is sorely needed to improve the therapeutic options for all.

UCD and iMCD have remained poorly understood disorders in terms of molecular pathogenesis, cellular etiology and signaling pathways. In this issue, Horna et al. report the first lymph node transcriptome analysis of UCD and iMCD supplemented by immunohistochemistry for CXCL13 and C4d, a marker of the classical complement pathway.⁴ Similar to the histopathology, the transcriptomes of UCD and iMCD have both common and distinct features. There was for instance over representation of genes involved in collagenous fibrosis in UCD and increased expression of proteasome genes reflective of the increased plasmacytosis often seen in iMCD. iMCD lymph nodes showed upregulation of genes in the m-TOR complex consistent with recent findings that m-TOR is activated in multiple cell types in the inter-follicular space in iMCD and the presence of a serum m-TOR proteomic signature.⁵

An unexpected shared feature of UCD and iMCD was the upregulation of the complement effector *C3* and components of the classical component pathway (UCD: *C1S* and *C1R*; iMCD *C4* and *C4B*) suggesting that complement activation play a role in the B cell activation/plasma cell differentiation as well the inflammatory response seen in Castleman Disease. Immunohistochemistry showed that C4d was often, but not exclusively, located within or near follicular dendritic cells (FDCs) in regressed germinal centers as well as in mantle zones.

The chemokine CXCL13 was also increased in expression in both UCD and iMCD, and CXCL13 was mostly localized to FDCs. CXCL13 is one of the most upregulated chemo/cytokines in iMCD by proteomic studies.⁶ CXCL13 plays a role in the attraction and differentiation of B-lymphocytes, and help to orchestrate the germinal center architectural organization and B-cell response. It seems likely that excess CXCL13 produced by FDCs play a critical role in abnormal B-cell follicle formation observed in Castleman Disease.

A further common feature of UCD and iMCD histopathology was the increased vascularity. Many patients with iMCD have elevated serum VEGF. Interestingly, the expression of the *FLI* gene, which encodes for the vascular endothelial growth factor receptor 1 (VEGFR-1) was upregulated in both UCD and iMCD. Transcripts for the pro-angiogenic factor placental growth factor (PGF), which is a ligand for VEGFR-1, were also increased in both forms of CD. Not previously described in Castleman Disease was the upregulation of the apelin receptor (UCD and MCD) as well as apelin (UCD), which also serve to promote angiogenesis.

A recent paper by Wing et al. examined the expression of immune related genes in UCD and MCD lymph nodes.⁷ In common with the findings reported by Horna et al, there was overexpression of *CXCL13* in both UCD and MCD. There was again increased representation of genes involved in the complement cascade, angiogenesis and VEGF signaling. Unique to UCD were increased expression of genes for extracellular matrix modification suggesting stromal remodeling and specific to MCD were plasma cell related genes, genes involved in cytokine signaling and inflammation (IL-1, IL13 and IL-4) as well as enrichment for IL6 pathways genes.

Common themes emerge from both data sets, which include the importance of angiogenesis in CD, which is consistent with the vascular histopathology. The involvement of the complement pathway in Castleman Disease raises the question whether this could be a therapeutic target especially in iMCD patients suffering from thrombotic micro-angiopathy and renal failure. Clearly, FDCs play an important role in the pathogenesis of both UCD and MCD. A recent Japanese study in a mouse model of iMCD showed that anti-CXCL13 antibody was able to mitigate the inflammatory syndrome underscoring the notion that CXCL13 may be a novel therapeutic target (Kikushige presented at the International Symposium on Castleman Disease, 2021)..

The cellular origin of IL6 production has been contested with some suggesting that it is produced outside the lymph node compartment consistent with the findings by Horna et al, whilst others have implicated lymph node B-lymphocytes, macrophages and follicular dendritic cells. The data from Wing et al. suggest that IL6 was present in CD31-positive endothelial cells, while VEGF was found in FDCs and interfollicular M2 macrophages.

Overall, the present findings suggest potential alternative pathways, which can be targeted in anti-IL6 therapy non-responders using anti-complement agents, anti-CXC13 monoclonals and molecules that bind VEGF and placental growth factor. Other research has identified m-TOR and the JAK-STAT pathway as potential therapeutic targets. A clinical trial with the m-TOR inhibitor sirolimus is in progress (NCT03933904).^{8,9} It is encouraging to see that the veil over the enigma of Castleman Disease is slowly lifted and that a more thorough understanding of this disease will likely result in better therapies in the near future.

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