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Review Article

Candidate biomarkers for idiopathic multicentric Castleman disease

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The clinical manifestations of idiopathic multicentric Castleman disease (iMCD) are thought to be caused by an excess of inflammatory cytokines; however, the mechanism is yet to be known. In addition to IL-6, inflammatory cytokines, such as IL-1β and TNF-α, are noted to be elevated in iMCD, which are common in autoinflammatory diseases. The first-line treatment for iMCD is an IL-6 inhibitor. Furthermore, increases in inflammatory cytokines such as serum IL-10 and IL-23, chemokines such as CXCL13 and CXCL-10 (especially in iMCD-TAFRO), and VEGF-A have been observed, and their relationship to pathogenesis has attracted the attention of researchers. The PI3K/Akt/mTOR pathway, JAK/STAT3 pathway, and type I IFN as drivers have recently been identified as important signals and are expected to be therapeutic targets in cases where IL-6 inhibitors are ineffective.

Keywords: iMCD, IL-6, JAK-STAT pathway, PI3K/Akt/mTOR pathway, Type I IFN

INTRODUCTION

Castleman disease (CD) is a lymphoproliferative disorder that was first described by Benjamin Castleman in 1956.[1] CD manifests itself into two clinical forms: the localized form, unicentric Castleman disease (UCD), and the multicentric form, multicentric Castleman disease (MCD).[2] Lymphadenopathy in UCD patients is localized and, in many cases, asymptomatic, and clinical examination reveals no abnormalities. MCD, on the other hand, is a systemic disease characterized by symptoms such as fever, night sweats, weight loss, and malaise, as well as multiple lymphadenopathies. The C-reactive protein (CRP) levels are elevated, albumin levels are low, and hemoglobin levels are low, indicating chronic inflammation in many cases.

MCD can be caused by human herpes virus type 8 (HHV8-related MCD),[2] but the majority of cases in Japan are of unknown origin and are classified as idiopathic MCD (iMCD). Some patients with iMCD present with features of TAFRO syndrome. TAFRO syndrome is a clinically defined concept. It was reported as an acute or subacute systemic inflammatory disease characterized by thrombocytopenia, anasarca (generalized edema, pleural effusion and/or ascites), fever (generalized inflammation), reticulin fibrosis (fibrosis of bone marrow, megakaryocytosis of bone marrow), and organomegaly (hepatosplenomegaly, lymph node enlargement) by Takai *et al*. in 2010.[3] Patients with TAFRO syndrome often do not have enlarged lymph nodes or, if they do, they are mild and do not present with hypergammaglobulinemia. However, there are patients who present with the clinical features of TAFRO syndrome but whose lymph node histopathology is CD-like, and these are classified as iMCD-TAFRO. Other types of iMCD are categorized as iMCD-NOS (iMCD-not otherwise specified). Comparing the clinical features of TAFRO syndrome not diagnosed as iMCD-TAFRO and those cases with lymphadenopathy and diagnosed as iMCD-TAFRO, TAFRO syndrome not diagnosed as iMCD-TAFRO type may be more severe and have a higher mortality rate and less efficacy with IL-6 inhibitors. Also, in iMCD-TAFRO, the histopathology is a mixture of both hypervascular and plasma cell type. Thus, compared to iMCD-NOS, the pathogenesis of iMCD-TAFRO is more complex, suggesting that different pathologies may coexist. Currently, there are no specific biomarkers for iMCD or TAFRO syndrome, as well as no biomarkers to differentiate between iMCD-NOS and iMCD-TAFRO.

ROLE OF IL-6 IN iMCD

The etiology of iMCD remains unknown, but the clinical

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manifestations observed in iMCD are primarily due to hypercytokinemia, including interleukin-6 (IL-6).[4,5]

Figure 1 shows the IL-6 signaling pathway. IL-6 exerts its biological activity through two types of molecules, IL-6R and gp130. When IL-6 binds to membrane-bound IL-6R (mIL-6R), a homodimer of gp130 is induced, forming a high-affinity receptor complex composed of IL-6, IL-6R, and gp130.[6] This receptor signaling system is called classic signaling. Soluble IL-6R (sIL-6R), which lacks the cytoplasmic portion of mIL-6R and is produced by enzymatic cleavage or selective splicing of mIL-6R, also has the ability to bind IL-6, and this IL-6/sIL-6 complex can also form a complex with gp130.[7] This receptor signaling system is called IL-6 trans-signaling. The formation of either the IL-6 classic or trans-signaling ligand-receptor complexes leads to the activation of multiple intracellular signaling pathways including the JAK/STAT pathway, the Ras-MAPK pathway, the p38 and JNK MAPK pathways, the PI3K/Akt/mTOR pathway, and the MEK-ERK5 pathway.[8] IL-6 is a multifunctional inflammatory cytokine that plays a variety of roles in immune cells, hematopoietic stem cells, osteoclasts, mesangial cells, hepatocytes, and epidermal keratinocytes. Although increased IL-6 levels have been found in the germinal centers of lymph nodes from patients with iMCD,[4,9] indicating that IL-6 plays an important role in the disease's pathogenesis, the mechanisms underlying IL-6 overproduction in patients with iMCD have not been fully elucidated. Immunohistochemical analysis of lymph nodes from iMCD patients revealed that the germinal center of hyperplastic lymph nodes is the site of IL-6 production in iMCD, with germinal center B cells and follicular dendritic cells being the primary sources of IL-6.[4]

INFLAMMATORY CYTOKINES OTHER THAN IL-6 IN iMCD

In iMCD, hyper-IL-6emia has been observed, and IL-6 inhibitors, such as tocilizumab (TCZ) and siltuximab, are the mainstay of treatment and are recommended by the guidelines.[10] In Japan, regardless of the disease activity, TCZ is widely used, with 42% of mild cases, 40% of moderate cases, and 57% of severe cases treated with TCZ in patients with iMCD.[11] However, some patients with iMCD do not respond to IL-6 inhibitors, implying that inflammatory cytokines other than IL-6 play an important role in the pathogenesis of iMCD. Some MCD patients with low serum IL-6 levels before treatment induction do not respond to anti-IL-6 therapy, as per reports.[12] IL-1β and tumor necrosis factor (TNF)-α are pro-inflammatory cytokines that stimulate IL-6 production via NF-κB signaling, and elevated levels of these cytokines have been reported in iMCD patients,[13,14] which implies that inhibiting IL-1β and TNF-α may be a therapeutic strategy for MCD. There is a case report that treatment with an IL-1 receptor antagonist was effective in patients with iMCD refractory to anti-IL-6 therapy.[15]

In a study comparing the cytokine profiles of patients with iMCD-NOS, iMCD-TAFRO, and healthy subjects,[16] iMCD-TAFRO patients were noted to have significantly higher serum interferon gamma-inducible protein 10kDa (IP-10) and lower platelet-derived growth factor (PDGF)-AA levels at the time of flare compared to the other two groups. Furthermore, patients with both iMCD-TAFRO and iMCD-NOS had higher levels of serum IL-10, IL-23, and vascular endothelial growth factor-A (VEGF-A). A strong correlation was observed between serum IP-10 and the presence of

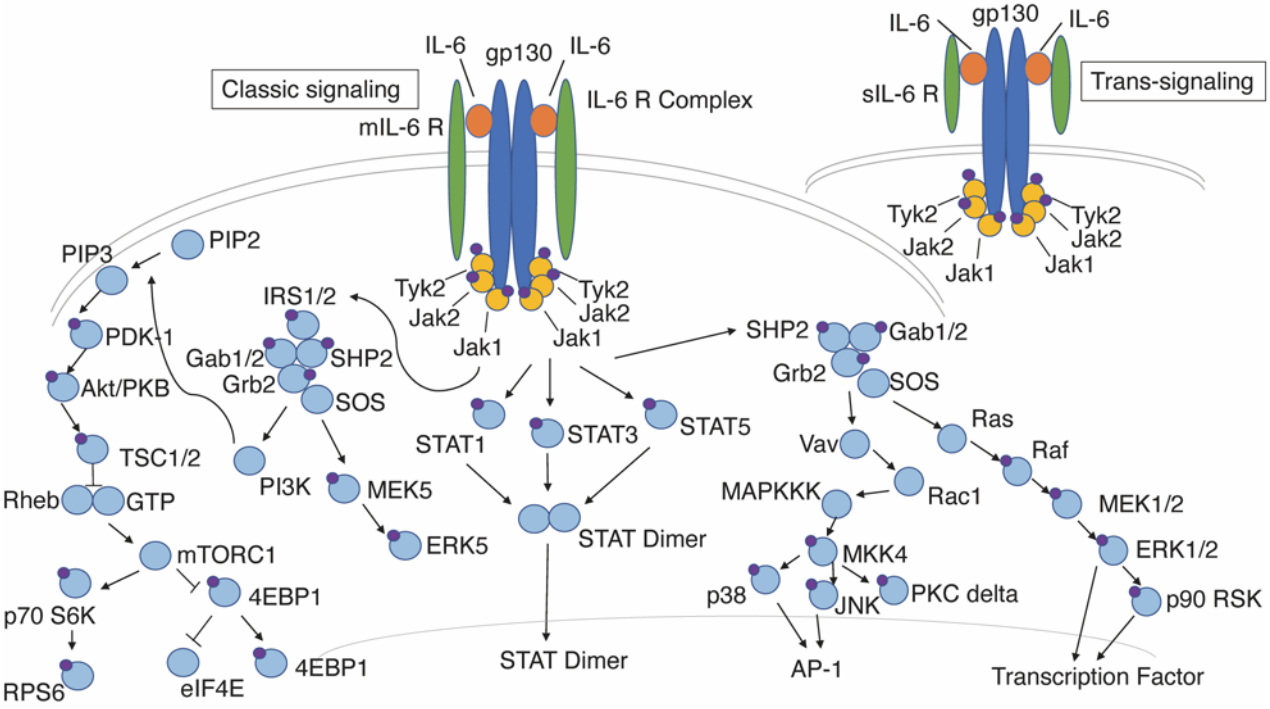

Fig. 1. IL-6 signaling pathways.

iMCD-TAFRO, implying that IP-10 may be involved in the pathogenesis of iMCD-TAFRO.

In another study,[17] which quantified 1129 proteins in 13 plasma samples from 6 iMCD patients during the flare and remission phases to identify potential mediators of iMCD pathogenesis, they found acute phase reactants SAA, Haptoglobin, CRP, non-pancreatic secretory phospholipase A2 (NPS-PLA2), and complement 3b (C3b), and cytokines or chemokines including tissue inhibitor of metalloproteases-1 (TIMP-1), chemokine C-X-C motifchemokine ligand 13 (CXCL13), C-C motif ligand (CCL) 23 (CCL23), CCL21, and CCL14 as upregulated proteins in flare. Among them, NPS-PLA2, was the only one that was significantly increased (P = 0.017). The gene-set enrichment analyses revealed that chemokines and complement were the only significantly enriched pathways. Chemokines were found to be the most abundant, implying that iMCD is caused by a chemokine storm. Chemokine CXCL13, which is required for B-cell homing to the germinal center, was found to be the most abundant cytokine in all patients (log2 fold-change = 3.22). Immunohistochemical staining revealed that in a stromal meshwork pattern, CXCL13 expression was also significantly higher in the lymph node germinal centers of iMCD compared to controls. In addition, the IL-10 and IL-23 were upregulated in iMCD-TAFRO, but only marginally in iMCD-NOS, the results differed from the report by Iwaki *et al*.[16] In iMCD patients, VEGF-A expression was elevated. VEGF-A, which promotes cell survival, angiogenesis, and vascular permeability, has previously been reported to be elevated in iMCD,[18] and patients frequently exhibit VEGF-related symptoms.

For some biomarkers, an association with clinical symptoms is suggested. For example, IL-6 is associated with fever, fatigue, and elevated CRP, VEGF-A may be associated with fluid retention due to increased vascular permeability, and chemokines, such as CXCL13, may be associated with lymphadenopathy. It is assumed that the profiles of elevated cytokines and chemokines are partly different between iMCD-NOS and iMCD-TAFRO. Further research is needed on the association of different disease types with biomarkers and clinical manifestations.

NEW INSIGHTS INTO THE PATHOGENESIS OF iMCD

Association of iMCD with autoinflammatory diseases

Previous reports have described iMCD cases with germline mutations in inherited autoinflammatory disease-related genes such as familial Mediterranean fever (*MEFV*).[19-22] Furthermore, one previously reported case suggests that homozygous *CECR1* mutations contribute to adenosine deaminase dysfunction, resulting in a Castleman disease (CD)-like phenotype in children that can be treated successfully with IL-6 inhibitors.[23,24] Autoinflammatory mechanisms have been implicated in the pathogenesis of iMCD, and 14 Japanese patients with iMCD were evaluated.[25] The genetic analysis of 31 autoinflammatory disease-related genes was performed using targeted next-generation sequencing; variants in the *MEFV* gene were found in 10 of the 14 iMCD patients. The patients were then divided into two groups, one with *MEFV* variants (except E148Q variant) and the other without *MEFV* variants, and their clinical characteristics were compared: patients with *MEFV* variants except E148Q were significantly more likely to have a fever and had significantly lower hemoglobin levels than patients without *MEFV* variants. Among the iMCD cases with *MEFV* gene variants was one with a novel heterozygous Ile729Met mutation in exon 10.[21] Molecular dynamics simulation analysis confirmed that this novel mutation has changed the local interactions of the human pyrin B30.2 domain and has the potential to activate the inflammasome by increasing experimental inflammatory cytokines. These findings suggest that pyrin dysfunction caused by *MEFV* gene germline mutations may induce IL-6 production via inflammasome signaling and contribute to the development of iMCD.

Insights into the PI3K/Akt/mTOR pathway

The findings that sirolimus, which is a mammalian target of rapamycin (mTOR) inhibitor, was effective in refractory iMCD[26] suggests that the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway is activated in the pathogenesis of iMCD. Inhibiting this pathway inhibits not only the proliferation of T cells and B cells in iMCD but also the expression of VEGF, which is expected to be particularly effective in some patients with IL-6 inhibitor-refractory iMCD. Recent studies have found that in patients with IL-6 inhibitor-refractory iMCD, in addition to CD8-positive T-cell activation by flow cytometry and elevated VEGF-A by serum cytokine panel, proteomics analysis revealed an increased PI3K/Akt/mTOR pathway.[17,27] Sirolimus treatment was able to reduce CD8-positive T-cell activation and the VEGF-A levels significantly, and clinical remission was achieved in all cases.[27] In patients with IL-6 inhibitor-refractory iMCD-NOS, we have also isolated CD4-positive T cells from the peripheral blood and performed RNA sequencing before and after sirolimus treatment.[28] This revealed that sirolimus treatment significantly reduced regulation of the mTOR-related pathways, including mTOR signaling, Huntington disease signaling, and elF4 and p70S6K signaling. This suggests the presence of an IL-6-independent pathway through mTOR activation, not only in iMCD-TAFRO but also in iMCD-NOS patients who are resistant to IL-6 inhibitors. In such cases, an mTOR inhibitor, such as sirolimus, is expected to be effective.

JAK/STAT pathway as a potential new therapeutic target

Even though IL-6 inhibition is ineffective in some patients, analysis of IL-6 inhibitor siltuximab responders and nonresponders revealed that IL-6-JAK-STAT3 signaling was also significantly enriched in siltuximab nonresponders.[29] Furthermore, peripheral blood mononuclear cells from iMCD patients in remission show hypersensitivity to IL-6 stimulation in vitro, which can be reversed by JAK1/2 inhibition.[30]

These findings suggest that dysregulation of the IL-6-JAK-STAT3 signaling pathway may play an important role in iMCD. Tissue-based IHC analysis revealed that pSTAT3 expression in the interfollicular spaces of the lymph nodes in iMCD was significantly higher than normal and that there was no difference in IL-6 and pSTAT3 expression between siltuximab responders and nonresponders.[29] The enrichment of IL-6-JAK-STAT3 signaling in iMCD serum proteome, the suppression of hypersensitivity to cytokine stimulation by JAK1/2 inhibition, the increased pSTAT3 expression in iMCD, and no difference in IL-6 and pSTAT3 expression between responder and nonresponder suggest that the JAK-STAT3 pathway may be involved in iMCD pathogenesis, including siltuximab nonresponder, under the control of activating ligands other than IL-6 or via abnormalities downstream of IL-6. Targeting other aspects of the IL-6-JAK-STAT3 pathway may be useful for siltuximab nonresponders, with drugs such as ruxolitinib, which is a JAK1/2 inhibitor.

Role of type I IFN as a driver

A report described a targeted approach to identify candidate cellular drivers and mechanisms of iMCD-TAFRO through cellular and transcriptomic studies.[31] Using flow cytometry, they examined changes in cellular subsets during iMCD-TAFRO flare compared with remission and healthy subjects. $CD8^+$ T cells represented a greater fraction of all $CD3^+$ T cells in iMCD-TAFRO patients compared with healthy subjects. For $CD4^+$ T cells in iMCD-TAFRO patients, they observed a trend toward a reduced relative frequency of $CXCR5^+CD4^+$ T cells during flare compared with healthy subjects. Within this population of $CXCR5^+CD4^+$ T cells, they identified a trend toward an increased frequency of circulating T follicular helper cells (cTfh) coexpressing PD-1 and the activation marker TIGIT in flare versus remission. These data demonstrate the presence of both $CD4^+$ and $CD8^+$ T cell activation during iMCD-TAFRO flare. For NK cells, a significant increase in the relative frequency of CD56bright NK cells compared with $CD16^+$ NK cells were seen within the NK cell compartment during iMCD-TAFRO flare compared with healthy subjects. They also observed a trend toward an increased ratio of classical ($CD14^+CD16^-$) to nonclassical ($CD14^-CD16^+$) monocytes in iMCD-TAFRO flare and remission when compared with healthy subjects. There was also a trend toward an increased absolute number of classical monocytes in flare compared with remission.

Next, single-cell RNA sequencing (scRNA-seq) of three paired samples of iMCD-TAFRO was performed to define potential underlying mechanisms driving T cell activation and innate cell expansion in iMCD-TAFRO flare. They compared the ratio of differences in gene expression between the flare and remission data sets to determine whether any of the Molecular Signatures Database (MSigDB) 50 hallmark gene sets were enriched within clusters of classical and nonclassical monocytes, NK cells, and $CD4^+$ and CD8+ T cells by Gene Set Enrichment Analysis. They identified the HALLMARK_INTERFERON_ALPHA_RESPONSE gene set as the only gene set significantly enriched ($P < 0.05$, FDR $q < 0.05$) across classical monocytes, nonclassical monocytes, NK cells, and CD8+ T cells. Quantification of the natural log-fold change gene expression between flare and remission identified the consistent upregulation of genes from the HALLMARK_INTERFERON_ALPHA_RESPONSE gene set across all 3 patients and all cell populations investigated. These data suggest the presence of an enhanced IFN-I gene signature within multiple immune cell populations during iMCD-TAFRO flare. They also discovered an association between IFN-I response gene expression and the mTOR gene signature in classical monocytes. Furthermore, in vitro IFN-I stimulation of monocytes and T cells from iMCD-TAFRO patient remission samples induced increased mTOR activation compared with healthy donors, which can be suppressed via mTORC1 or JAK1/2 inhibition. These findings lend support to the theory that IFN-I signaling contributes to the pathogenesis of iMCD-TAFRO via increased JAK-dependent mTOR activation. Inhibiting IFN-I may be beneficial for iMCD-TAFRO treatment. Future clinical trials with drugs that inhibit IFN-I, such as anifrolumab, are expected.

CONCLUSION

Figure 2 depicts the proteins that have reportedly increased in iMCD patients, as well as their potential activation pathways. Because iMCD is a heterogeneous disease, the pathogenesis of iMCD-TAFRO and iMCD-NOS may differ. The histopathology of iMCD-TAFRO often takes the hypervascular type, whereas the plasma cell type is typical for iMCD-NOS. This difference in histopathology between the two is expected to be reflected in the biomarkers. For example, the mTOR pathway and serum IP-10 are considered biomarkers reflecting the hypervascular type, and IL-6 as a biomarker reflecting the plasma cell type, but detailed analysis has not been performed, and further studies on the relationship between histopathology and biomarker abnormalities are warranted. The prognosis of iMCD-TAFRO is similar to that of TAFRO syndrome. Overproduction of IL-6 and non-IL-6 factors has been determined to be central to the pathogenesis of iMCD and TAFRO syndrome, and IL-6 inhibitors are effective for the NOS type but less effective for the TAFRO type. The NOS type is primarily driven by the IL-6 pathway, whereas the TAFRO type is primarily driven by non-IL-6 pathways as well as the IL-6 pathway. More research is needed to determine the disease spectrum of iMCD-NOS/iMCD-TAFRO/TAFRO syndrome.

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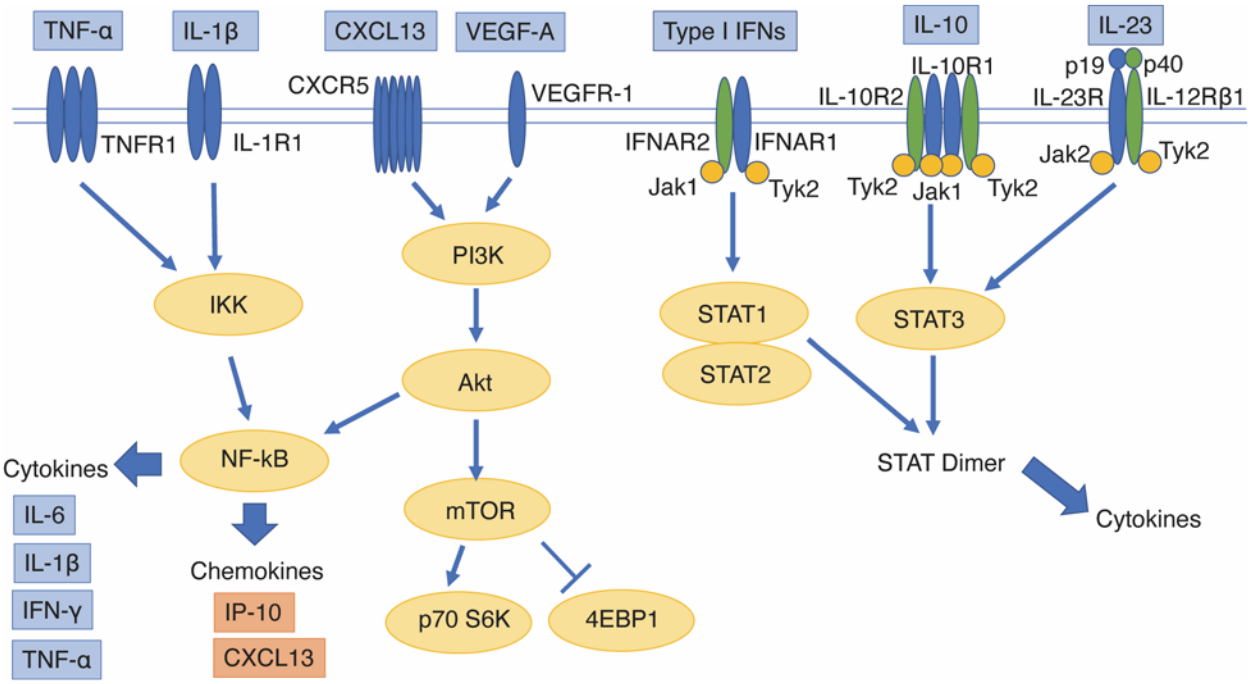

Fig. 2. Proteins that have been reported to be elevated in iMCD patients (other than IL-6) and their potential activation pathways.

related diseases".

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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