A translational approach to identifying and targeting TNF signaling in idiopathic multicentric Castleman disease

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Abstract

Idiopathic multicentric Castleman disease (iMCD) is a rare, idiopathic, immunological disease with an unknown etiology. It is characterized by multiple enlarged lymph nodes with unique histopathological features and systemic inflammatory resulting from cytokine release syndrome that can rapidly develop into multiorgan failure and death. Inhibition of the pro-inflammatory cytokine interleukin-6 (IL-6) with tocilizumab, the sTNFR1 Fab fragment therapy for MCD, is an effective treatment for approximately one-third of patients. A large number of patients do not respond to tocilizumab therapy and require additional potential treatments for patients. To characterize the immune dysregulation in iMCD, previous analysis of patient data and patient sera identified several cytokines differentially expressed between healthy controls and iMCD patients. Applying multiple machine learning approaches to identify TNF as an important cytokine for the disease, this study is the first to utilize flow cytometry to demonstrate that TNF was upregulated in CD4+ T cells from iMCD patients. We also utilized a novel machine learning strategy to predict TNF inhibition as a novel therapeutic target. This study provides new insights into the pathogenesis of iMCD and identifies TNF inhibition as a potential therapeutic strategy for iMCD.

Background

Idiopathic Multicentric Castleman Disease (iMCD)

Cytokine Storm

Lymphadenopathy

Histopathological Abnormalities

Healthy

iMCD

Non-responders

Responders

What other pathways contribute to cytokine storms in iMCD?

Figure 1: Characteristics of idiopathic multicentric Castleman disease (iMCD) and research question. Idiopathic multicentric Castleman disease characterized by rare, idiopathic, immunological diseases with unknown etiology. The disease is characterized by multiple enlarged lymph nodes with unique histopathological features and systemic inflammatory resulting from cytokine release syndrome that can rapidly develop into multiorgan failure and death. Inhibition of the pro-inflammatory cytokine interleukin-6 (IL-6) with tocilizumab, the sTNFR1 Fab fragment therapy for MCD, is an effective treatment for approximately one-third of patients. A large number of patients do not respond to tocilizumab therapy and require additional potential treatments for patients. To characterize the immune dysregulation in iMCD, previous analysis of patient data and patient sera identified several cytokines differentially expressed between healthy controls and iMCD patients. Applying multiple machine learning approaches to identify TNF as an important cytokine for the disease, this study is the first to utilize flow cytometry to demonstrate that TNF was upregulated in CD4+ T cells from iMCD patients. We also utilized a novel machine learning strategy to predict TNF inhibition as a novel therapeutic target. This study provides new insights into the pathogenesis of iMCD and identifies TNF inhibition as a potential therapeutic strategy for iMCD.

Conclusions

1) Experimental and unbiased machine learning approaches identify TNF as an important pathogenic mediator of iMCD and a novel therapeutic target.

2) The flow cytometry data observed among naive CD4+ T cells contribute to iMCD pathogenesis, in part by over-producing TNF.

References


