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Identifying and Targeting TNF Signaling in Idiopathic Multicentric Castleman Disease

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To the Editor:

Idiopathic multicentric Castleman disease (iMCD) is a rare, life-threatening cytokine storm disorder of unknown etiology.[1] Patients experience generalized lymphadenopathy, systemic inflammation, and multi-organ failure due to excess interleukin-6 (IL-6) and other cytokines.[2] The most severe form of iMCD involves thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction, and organomegaly (iMCD-TAFRO). Prognosis is poor; 25–35% of patients die within five years.[3] IL-6 inhibition with siltuximab, which is the only FDA-approved therapy for iMCD, is effective in 40–50% of patients,[4] leaving anti-IL-6-refractory patients with few therapeutic options. Improved understanding of iMCD-TAFRO pathogenesis is urgently needed to identify new treatments.

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To identify novel, targetable pathways in iMCD-TAFRO, we analyzed patient biospecimens using proteomic, transcriptomic, *in vitro* modeling, and computational techniques. Serum proteomics comparing iMCD-TAFRO patients (n=26) to healthy controls (n=15) identified increased tumor necrosis factor (TNF) signaling in iMCD-TAFRO (Fig.1A; Fig. S1 in Supplementary Appendix). Single-cell RNA sequencing of peripheral blood mononuclear cells revealed that $CD4^+$ T cells, particularly naïve $CD4^+$ T cells, from iMCD-TAFRO patients had markedly increased expression of TNF (Fig.1B). *In vitro* studies confirmed these findings. Upon stimulation with PMA/I, over two-fold more naïve $CD4^+$ T cells from iMCD-TAFRO patients (43%) produced TNF compared to healthy controls (17%) (Fig.1C and Fig. S2). These results implicate TNF signaling in iMCD pathogenesis and suggest that it may be a therapeutic target. In parallel, we pioneered a novel machine learning (ML) approach to generate predictive scores for the likelihood of every FDA-approved drug to treat every disease. Adalimumab, a TNF inhibitor approved for multiple autoimmune disorders, was the top predicted treatment for iMCD following IL-6 inhibitors and interestingly, CD4 T-cell inhibition was identified in the potential mechanism (Fig. S3).[5]

We administered adalimumab to a highly treatment-refractory iMCD-TAFRO patient who was preparing for hospice care after experiencing multiple flares and relapsing on numerous treatments including Bruton's tyrosine kinase (BTK) inhibition most recently (Fig.1D–E). Remarkably, the addition of adalimumab induced a sustained remission lasting 22 months to date, representing his longest remission since diagnosis.

We employed multiple strategies to identify TNF signaling as a novel, targetable mechanism in iMCD-TAFRO. This study also highlights the potential of this novel translational approach—combining high-throughput 'omics data with *in vitro* studies and ML models—to rapidly identify and prioritize new treatment strategies for rare diseases. Further studies are warranted to evaluate TNF inhibition in larger cohorts of iMCD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References:

1. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020;383(23):2255–2273. DOI: 10.1056/NEJMra2026131. [PubMed: 33264547]

2. Fajgenbaum DC. Novel insights and therapeutic approaches in idiopathic multicentric Castleman disease. Blood 2018;132(22):2323–2330. DOI: 10.1182/blood-2018-05-848671. [PubMed: 30487129]

3. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. Am J Hematol 2012;87(11):997–1002. DOI: 10.1002/ajh.23291. [PubMed: 22791417]

4. Pierson SK, Lim MS, Srkalovic G, et al. Treatment consistent with idiopathic multicentric Castleman disease guidelines is associated with improved outcomes. Blood Adv 2023;7(21):6652–6664. DOI: 10.1182/bloodadvances.2023010745. [PubMed: 37656441]

5. Ma CY, Zhou ZH, Liu H, Koslicki D. KGML-xDTD: a knowledge graph-based machine learning framework for drug treatment prediction and mechanism description. Gigascience 2023;12 (In English). DOI: 10.1093/gigascience/giad057.

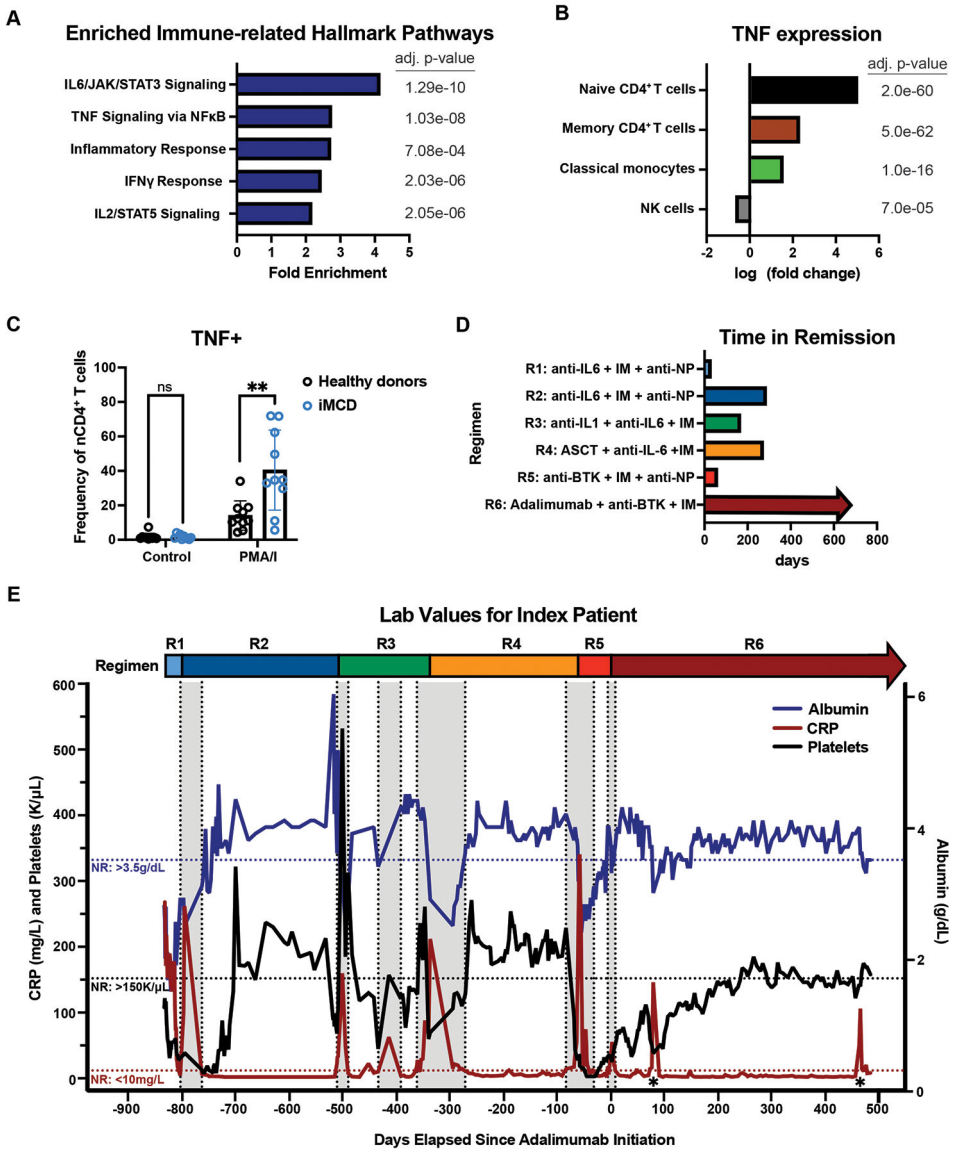

Figure 1. Identifying and targeting TNF signaling in iMCD-TAFRO.

Panel A shows enriched immune-related Hallmark pathways in iMCD-TAFRO (n=26) compared to healthy donors (n=15) from serum proteomics of 6,408 analytes. Panel B shows in peripheral blood mononuclear cell (PBMC) types with significantly different imputed TNF expression between iMCD patients in flare (n=3) and healthy controls (n=2) from single cell RNA sequencing (see Fig. S4 for cell type identification), including naïve $CD4^+$ T cells from iMCD-TAFRO patients with 31-fold (log_2=4.94) higher expression. In Panel C, PBMCs from iMCD-TAFRO patients (n=10) and healthy donors (HD) (n=10) were treated with phorbol 12-myristate 13-acetate/ionomycin (PMA/I) and TNF expression in naïve (n) $CD4^+$ T cells was measured by intracellular flow cytometry. **p<0.01. Panel D shows that after receiving 5 different regimens (R), including a combination of BTK inhibition, immunomodulators (IM), and anti-neoplastics (anti-NP) which failed when the patient relapsed for the fifth time, the addition of adalimumab treatment alongside continued BTK

inhibition and IM (R6) induced the longest remission to date. Table S1 includes complete treatment information. As shown in Panel E and Table S2, the patient's elevated C-reactive protein (CRP), hypoalbuminemia, thrombocytopenia, and organ dysfunction resolved within 60 days of treatment. Shaded gray bars indicate iMCD flares. Asterisks indicate documented infections.