Perspectives

TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib

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COVID-19 (previously termed as 2019-nCoV), a novel coronavirus disease with high mortality, emerges as a pandemic disease. As of Mar. 8, 2020, COVID-19 has spread to 102 countries and caused 3584 deaths out of 105,586 confirmed cases [WHO, Coronavirus disease 2019 (COVID-19) Situation Report — 48]. There is no existing treatment specific for COVID-19. Current treatments are largely symptomatic. Development of effective prevention and treatment is an urgent need, especially for the life-threatening severe cases.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Many COVID-19 patients develop acute respiratory distress syndrome (ARDS), which leads to pulmonary edema and lung failure, and have liver, heart, and kidney damages.1,2 These symptoms are associated with a cytokine storm, manifesting elevated serum levels of IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFNγ, TNFα, IP10, MCP1, MIP1A and MIP1B. Compared with non-ICU patients, ICU patients have even higher levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα. Amongst these, several cytokines are involved in TH17 type responses. IL-1β and TNFα (TH17 and TH1 cells highly express TNFα), both promote TH17 responses and vascular permeability and leakage. TH17 cells themselves produce IL-17, GM-CSF (GM-CSF is mainly associated with TH1 cells in human), IL-21 and IL-22 (currently, there are no data on IL-21 and IL-22). IL-17 has broad pro-inflammatory effects on induction of cytokines G-CSF (responsible for
granulopoiesis and recruitment of neutrophils), IL-1β, IL-6, TNFα (the latter 3 cause systemic inflammatory symptoms, including fever); chemokines KC, MIP2A, IL-8, IP10, MIP3A (attracting and recruiting more immune infiltrates); and matrix metalloproteinases (participating in tissue damage and remodeling). IL-17 (and GM-CSF) are associated with autoimmune and inflammatory diseases. IL-21 is required for TH17 cell maintenance and germinal center responses in autoimmune and inflammatory diseases. IL-21 is required and remodeling. IL-17 (and GM-CSF) are associated with matrix metalloproteinases (participating in tissue damage and likely promotes pulmonary viral infection including SARS-CoV-2, which results in tissue damage and likely promotes pulmonary edema; targeting the TH17 pathway may benefit the patients with TH17 dominant immune profiles.

Since it will take several years to develop specific drugs to treat COVID-19, repurposing currently marketed drugs would provide valuable opportunities. There are several antibody-based TH17 blockades (anti-IL-17, anti-IL-17R and anti-IL-23p40) available; however, the antibody-based treatment is expensive and has only a narrow spectrum of effects. Several RORγt (and RORα) inhibitors currently on clinic trials would be promising TH17 blockers in a near future. Here, we propose an alternative method to inhibit TH17 responses.

STAT3, a transcription factor, mediates IL-6 and IL-23 signals for TH17 cell initial differentiation and effector function. Both IL-6 and IL-23 activate STAT3 through JAK2 (IL-6 also uses JAK1),

whereas IL-21 activates STAT3 (and STAT1 and STAT5) through JAK1 and JAK3. We postulate that JAK2 inhibitors can be used to restrict the proinflammatory function of existing TH17 cells. In addition to JAK2 inhibitors, several FDA approved STAT3 inhibitors are also promising but may affect IL-21 signals in B cells. Type I interferons are important in anti-viral immunity, but type I interferons employ JAK1 and TYK2 to activate STAT1 and STAT2. Therefore, specific JAK2 inhibitors would not disrupt the signals of type I interferons.

We tested Fedratinib (SAR302503, TG101348), a JAK2 inhibitor approved by FDA for myeloproliferative neoplasms, on TH17 cell cytokine production. Fedratinib is specific for JAK2 but does not affect JAK1, JAK3 and TYK2. We found that Fedratinib treatment decreased the expression of IL-17 by murine TH17 cells, and this suppressive effect was even more profound when IL-23 was added (Fig. 1). In addition, Fedratinib also inhibited the expression of IL-22 by TH17 cells (Fig. 1). Besides, Fedratinib only has marginal effects on IL-21 expression (Fig. 1), suggesting that Fedratinib does not compromise IL-21 mediated B cell function. In addition, GM-CSF also uses JAK2 to transduce signals; therefore, JAK2 inhibitor would also suppress GM-CSF function. In a murine model of multiple sclerosis, a TH17 and TH1-driven autoimmune brain disease, subcutaneous administration of JAK2 inhibitor tyrphostin B42, during the disease induction, greatly decreased the disease severity. In summary, JAK2 inhibitor Fedratinib can suppress the production of several TH17 signature cytokines (and likely also the effects of IL-6 on other types of cells), therefore promising to prevent the deteriorating outcomes of TH17 associated cytokine storm in COVID-19 and other severe viral infections. The JAK2 inhibitor can also be used in combination of anti-viral drugs and supportive treatments. Because JAK2 inhibition is reversible, transient treatment with this inhibitor before the disease transition from serious to critical or during the critical phase would not affect TH17 responses essential for innate immune responses and immunity against extracellular pathogens.

**Declaration of Competing Interest**

All authors have no conflicts of interest to declare.

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**Abbreviations**

COVID-19 coronavirus disease-2019

TH — T helper cell
SARS severe acute respiratory syndrome  
CoV coronavirus  
MERS Middle East Respiratory Syndrome  
FDA U.S. Food and Drug Administration  
JAK Janus kinase  
ARDS acute respiratory distress syndrome  
IL interleukin  
IL-17R interleukin 17 receptor  
G-CSF granulocyte colony-stimulating factor  
GM-CSF Granulocyte-Macrophage Colony Stimulating Factor  
IFN interferon  
TNF tumor necrosis factor  
IP10 Interferon gamma-induced protein 10  
MCP1 Monocyte Chemoattractant Protein-1  
MIP1 macrophage inflammatory protein 1  
ICU intensive care unit  
CCR CC chemokine receptor  
ROR RAR-related orphan receptor  
STAT signal transducer and activator of transcription protein  

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