Macrophage activation syndrome and COVID 19: Immune - Epigenetic programming in play

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Summary

Idiopathic association of the ongoing COVID-19 pandemic with many diseases appears to be multifactorial. SARS-CoV-2 enters into host cells via ACE-II receptor and triggers the secretion of copious amount of IL-6; promote pulmonary fibrosis and Th2 / 17 programming of lungs, leading to severe lung pathology in COVID-19 patients. This virus interact and tweak all kind of cells like epithelium, macrophages, dendritic cells, and T cells and exploit them in a way that support its replication for progression of disease. Out of several pathophysiological manifestations, Macrophage activation syndrome is responsible for acute respiratory distress syndrome (ARDS) and subsequent death of COVID-19 patients.¹ This is mainly accompanied by the increased infiltration of $Fc\gamma R1^+$ macrophages and other immune cells like neutrophils that contribute to Th2/Th17 programming of lung cells in COVID-19 patients. However, in view of durability and plasticity, macrophages are responsible for high-grade inflammatory response and mortality in patients.

State of Art

Once derailed, hyper active alveolar macrophages secrete high levels of IFN- γ , IP-10 (IP-10), IL-6, IL-17, TNF- α along with TGF- β and IL-10 / 23 in severe cases of COVID-19. This prudently demonstrates MAS and the Th2/Th17 programming in the infected lungs.² This is accompanied by the activation of inflammasome pathways which are crucial drivers of Th17 response. We believe that prolonged activation of CD14+ monocytes and phagocytosis of dead neutrophils by these cells contributes to NETosis in lung. This promotes Th2 bias in the lungs, decrease maturation of DC and monocytes, lymphocyte/neutrophils ratio and increases the risk of COVID-19 patients for death. In this context, *in situ* reprogramming of Th2/Th17 programmed macrophages towards M1 phenotype macrophages is believed to afford protective immunity in COVID-19 cases¹.

Professional immune cells like committed macrophage rely upon Toll like Receptors and associated pathways which are the guardian for Th1/2/17 effector responses in during any infection including SARS-CoV-2.³ Among various TLRs on macrophages, TLR-4, 5, 3, 7, and 9 actively sense spike proteins (N, S or G) or mRNA of NSP-10, S2, and E proteins of SARS-CoV-2 and promote M1 polarization of macrophages⁴. Apart from ACE-2, the spike protein of SARS-CoV-2 uses TLR-2, 4 and 5 signaling pathways also via MyD88 and triggers Th1 effector response through NF- κ B and ERK signaling cascade.⁵ Given this, tweaking TLR signaling cascades by using agonists can restore or promote Th1 response in derailed macrophages in COVID-19 patients. Mimicking TLR-5 signaling can augment Th1 programming of macrophages and afford anti viral potential in these cells. Furthermore conjunction therapy with antivirals and TLR-7 agonists may benefit patients³ but whether this would reprogram macrophage also is open question and deserves attention. Combination of Tocilizumab and TLR-4 antagonists is believed to help in Th1 polarization of macrophage and in turn patients with severe disease displaying ARDS. Conjunction treatment of patients with Remdesivir with TLR-7 agonist is expected to overcome immune escape mechanism of viruses.

While promoting Th1 programming of infected macrophage is advantageous for host in controlling viral burden by the macrophages, balancing out cytokine storm, on other hand, in spite of being pre requisite yet a bottleneck for reducing fibrosis in patients. Several antagonists like M5049, hydroxychloroquine sulfate, FTY-

720/ceramide-1 phosphate can competitively inhibit/alter the binding of spike proteins with TLRs and S-1P signaling respectively and believed to mitigate/arrest MAS and subsequently lung fibrosis.⁶ In this context, the administration of hydroxychloroquine in COVID-19 patients has shown to interfere with TLR signaling and mitigate inflammatory syndrome in patients. This is mainly due to interference of hydroxychloroquine in binding of DNA/RNA with endosomal TLRs with their ligands⁷.

Inflammatory programming of macrophage relies of several intracellular pathways like nk-kb / STAT / and p38MAPK which are associated with TLR. Of these p38MAPK pathway is one of the host factors implicated in lung and heart injury in COVID-19 patients.^{8,9} P38MPAK is decisive for sterile inflammatory responses, desmoplastic reactions, and T cell exhaustion, epigenetic programming of host contributing to the severity of COVID-19 cases. Other than this, p38 MAPK controls macrophage's plasticity via promoting ER stress, unfolded protein responses, and glucose intolerance associated with energy imbalance in the infected host. SARS-CoV-2 directly up regulates p38 activity directly for promoting its replication in epithelium and macrophages.¹⁰ The p38MAPK promotes Th2 bias, fibroblast activation significant for the SARS-CoV-2 induced aberrant inflammation in the lung. Therefore we strongly believe targeting p38MAPK could be of direct interest for not only tempering plasticity of infected macrophages, lowering pathogenic inflammatory pathways as well as T- cell exhaustion which is also seen in severely infected cases.

Most intriguingly p38MAPK are known to activate several intrinsic factors known as differentially expressed mi/lncRNAs for promoting Meta / sterile inflammation. These are tissue specific cues and influence both immunogenic / refractory pathways in host. lncRNA landscape is proposed as a prognostic factor responsible for the severity of COVID-19 cases.¹⁵ Among pool of miRNAs; miR-15b-5p, miR-15a-5p, miR-548c-5p, miR-548d-3p, miR-409-3p, miR-30b-5p and miR-505 have been validated as potent targets for controlling SARS-CoV-2 infection.¹⁶ These miRNAs regulate the expression of ACE-2 in various organs, including the kidney, heart, blood vessels, and lungs which are important for COVID-19 pathophysiology.¹⁷

Current evidence suggests that set of lncRNA like *WAKMAR2*, *EGOT*, *EPB41L4A-AS1*, and *ENSG00000271646*, *MALAT1*, and *NEAT1* contribute in skewing the immune response against SARS-CoV-2 infection.^{11,12} For instance *NEAT1*

overexpression stabilizes the mature caspase-1 to promote interleukin-1 β production and modulate inflammasome activation¹³ which is associated with Th2/ 17 programming of immune cells. *MALAT1* promotes Th1 effector responses and apoptosis in airway epithelial cells conditioned DCs and cardiac cells^{2,14} via miR-125b and p38MAPK / NF- κ B pathways.³ This loop is potentially involved in the maturation of monocyte / DC and their T cell programming ability which is essential for adaptive immunity of host.

Perspective

Thus, we believe that adjusting TLR / p38MAPK pathways in conjunction with epigenetic factors like lncRNA-miRNA would be a prudent approach not only for augmenting immunity of COVID-19 infected cases but also for enhancing their sensitivity for currently employed drugs. Taken together, such strategy would be helpful in curbing SARS-CoV-2 virus for managing COVID-19 disease.

Conflict of Interest:

Authors declare no conflict of interest.

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