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Perspective

Immunometabolism and potential targets in severe COVID-19 peripheral immune responses

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In a recent single cell transcriptomic investigation of the peripheral immune responses of the patients with severe COVID-19 [1], no substantial expression of pro-inflammatory cytokines has been identified in the peripheral monocytes and lymphocytes, while these peripheral immune cells exhibit phenotypes of heterogeneously expressed interferon-stimulated genes in certain COVID-19 patients. These genes may contribute to the inhibitory response to the viral entry, translation, replication and egress. Questions remain regarding why the peripheral cytokine production is constrained, what additional roles these peripheral immune cells may play in COVID-19 pathophysiology, and which potential targets can be explored for facilitating COVID-19 therapeutics.

Useful clues to this question may be probed from the differentially-expressed (DE) genes in the severe COVID-19 patients revealed by the investigation of the peripheral immune responses in severe COVID-19 [1]. Noticeably, several immunometabolism genes and regulators are heterogeneously upregulated in the peripheral immune cells of 1-4 of the 7 COVID-19 patients (Table S1). Immunometabolism shapes immune cell responses [2] and material releases [3]. The possible effects of these immunometabolism genes to COVID-19 need to be investigated. In particular, the pentose phosphate pathway (PPP) contributes to inflammatory macrophage responses, and PPP suppression diminishes LPS-induced cytokine secretion [4]. In dendritic cells, PPP mediated glycolysis drives lipogenesis and facilitates cytokine production [5]. PPP in B-cells is repressed possibly as a safeguard against malignant transformation [6]. There are two key PPP enzymes G6PD and PGD. Only PGD is upregulated in the CD14+ monocytes of 3 patients and in the dendritic cells and B-cells of 1 patient, while G6PD is not among the reported DE genes and upstream regulators [1]. Therefore, inadequately expressed PPP enzymes may partly contribute to the insignificant peripheral cytokine production in these COVID-19 patients.

In macrophages, CES1 hydrolyzes cholesteryl ester to promote lipid drop formation and the efflux of cholesterol and lipid drops [3,7], which influences the plasma lipid and lipoprotein homeostasis [3] and in certain circumstances facilitates the release of the intracellular viral particles by

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the formation of lipoprotein vehicles [7]. Significantly, CES1 is upregulated in the CD14+ monocytes of 4 of 7 COVID-19 patients [1]. Hence, further investigation is warranted for determining whether the upregulated CES1 facilitates coronavirus release from the peripheral macrophages of the COVID-19 patients.

Immunometabolism may also play some roles in B-cell dysregulation in severe COVID-19. In response to infections, B-cells differentiate into antibody-producing plasma cells, during which the relevant metabolic processes are highly regulated. B cells rely on sustained glycolytic flux to proliferate and produce antibody. Despite the broad increase in metabolism of activated B cells, glycolysis and the specific conversion of pyruvate to lactate appears essential for proliferation and antibody secretion [8]. In particular, B-cell DNA class switch and somatic hypermutation requires the activation-induced cytidine deaminase (AID), while AID-induced TOP1 downregulation is critical for the somatic hypermutation and the subsequent differentiation into antibody-producing cells [9]. Moreover, B-cell differentiation depends on G1 cell-cycle arrest, which involves the inhibition of cyclin D3/CDK6-mediated pRb phosphorylation [10]. In addition, it has been showed that cyclin D3-CDK6 phosphorylates and inhibits the catalytic activity of two key enzymes (PFK1, PKM2) in the glycolytic pathway which redirects the glycolytic intermediates into PPP [11], thereby promoting its activity and inflammation. TOP1 and CDK6 are upregulated in the B-cells of 1 COVID-19 patient respectively. Thus, one may question whether the upregulated TOP1 and CDK6 hinder the proper differentiation of the peripheral B-cells in individual COVID-19 patients.

Given the key roles of the immunometabolism genes PGD and CES1 and the regulators TOP1 and CDK6 in COVID-19 pathophysiology, patient-stratified targeting of these enzymes by drug repurposing or new agents may complement the primary COVID-19 therapeutics by hindering the release of cytokines and coronaviruses, and by maintaining the proper B-cell differentiations in the peripheral immune responses. We searched drugs or drug leads that inhibit these enzymes (Table S1) from the Drugbank and TTD databases and from the literatures using keyword combination of enzyme name (or synonymes) and “inhibitor”. There is a PGD inhibitor Physcion for potential anticancer and anti-infection therapeutics. CES1 is an off-target of two cholinesterase inhibitors Paraoxon and Chlorpyrifosoxon, with potent inhibitory activity against CES1. These agents may be useful drug leads or drug repurposing candidates (Table S1).

As shown in Table S1, there are a number of approved and clinical trial drugs as potential drug repurposing candidates for the treatement of COVID-19. There are 2 approved drugs (Ribociclib, LY2835219), and 3 clinical trial drugs (PD-332991, G1T38, Trilaciclib) against the target CDK6 for the treatment of cancers. TOP1 is targeted by 1 approved drug (Topotecan) and 11 clinical trial drugs (Camptothecin, Exatecan, Beta-Lapachone, Diflomotecan, Lipotecan, ABI-011, DRF-1042, Genz-644282, Intoplicine, GZ402674, Namitecan) for cancers.

Traditional Chinese medicines (TCMs) have also been repurposed for COVID-19 treatment by the recommendation of the National Health Commission of China (NHCC). The clinical efficacy of one NHCC-recommended TCM, Lianhuaqingwen capsules, has been revealed by a multicenter, prospective, randomized controlled trial of 284 COVID-19 patients [12]. To determine if the four enzymes are targeted by some of the NHCC-recommended TCMs, we evaluated 11 NHCC-recommended TCMs, focusing on the experimentally-determined potent ($\leq$1 μM) inhibitory activities against these four enzymes, by using the method for investigating the common targets between the NHCC-recommended TCMs and those of the recent COVID-19 target discovery studies [13]. There are ~1–2 dozen targets of potent activities (potent targets) for each NHCC-recommended TCM (Table S2). Significantly, the 4 enzymes are among the targets of 10 of the NHCC-recommended TCMs.

There are 5 TCMs (Huoxiang Zhengqi capsules, Lianhua Qingwen capsules, Jinhuaqinggan granules, Shufengjiedu capsules, Fangfengtongsheng pills) for treatment of particular phenotypes in the medical observation period. And the other 5 TCMs (Xuebijing injection, Huashibaidu formula, Xuanfeibaidu formula, Qingfeipaidu decoction, Suhexiang pills) are recommended in the clinical treatment phase. Specifically, there are 3 TCMs (Huashibaidu formula, Qingfeipaidu decoction, Xuebijing injection) for the treatment of severe cases, the first two of which either co-target PGD and CDK6 or simultaneously target CDK6 and TOP1, Xuebijing injection target CES1. Suhexiang pills which target TOP1 are for critical cases. There is a TCM (Xuanfeibaidu formula) for the treatment of two phenotypes of mild and general cases which target PGD and CDK6 (Table S1). These results suggest the repurposing potential of these TCMs against the key pathophysiological factors in the COVID-19 peripheral immune responses.

Experimental evidences indicated the important roles of immunometabolism in the peripheral immune responses in the COVID-19 patients. In particular, metabolic reprogramming of immune cells is essential for both inflammatory as well as anti-inflammatory responses [14], T-cell metabolic remodeling is intrinsically linked to T-cell development, activation, and function [15], immunometabolic processes in immune cells facilitate viral particle releases [7]. Targeting immunometabolism has been explored as an anti-inflammatory strategy [14] complementing other established anti-inflammatory therapeutics [16]. A number of drugs and traditional medicines may be repurposed for targeting immunometabolism for facilitating the treatment of COVID-19.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2021.07.001.

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