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Letter to the editor

Is procalcitonin a part of human immunological response to SARS-CoV-2 infection or “just” a marker of bacterial coinfection?

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ABSTRACT

Elevated PCT level in COVID-19 was associated with higher risk of severe disease and higher risk of overall mortality. An increased PCT level of PCT in COVID-19 patients especially in severe cases would be assumed as bacterial coinfection. Could PCT level increase in SARS-CoV-2 infection without bacterial coinfection? Several SARS-CoV-2 proteins activate STAT3-dependent transcriptional pathways particularly in monocytes, that could lead to increased PCT production. STAT3 α isoform could cause increased ACE2 expression, resulting more SARS-CoV-2 infected cells and further production of PCT.

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Dear Editor,—As the coronavirus disease 2019 (COVID-19) pandemic ensues, studies have shown association between procalcitonin (PCT) with severity and prognosis of COVID-19 patients [1,2]. Studies have also shown association between bacterial coinfection with severity and prognosis of COVID-19 patients [2,3]. To the best of our knowledge, there has been no study on direct association between PCT and bacterial coinfection in COVID-19 patients. Many studies showed PCT that can accurately differentiate culture-negative and culture-positive sepsis from non-infectious diseases, thus making it a biomarker in diagnosis of bacterial sepsis [4]. An increased level of PCT in COVID-19 patients especially in severe cases would be assumed as bacterial coinfection. Could PCT level increase in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection without bacterial coinfection? Could it be that PCT is part of human immunological response to SARS-CoV-2, especially in severe cases of COVID-19? Here we describe the potential immunological mechanisms in which SARS-CoV-2 can increase the PCT level in the absence of bacterial coinfection.

Previous studies found that in severe acute respiratory syndrome (SARS) PCT level did not increase, contrary to bacterial and fungal pneumonia where the PCT level increased. SARS and COVID-19 are caused by coronavirus that share similar structure, so it is speculated that both coronavirus would render similar human immune system response and PCT level would not increase in COVID-19 unless there is bacterial coinfection [1]. A study showed that bacterial coinfection in COVID-19 was associated with increased mortality [2]. Bacterial coinfection increases the degree of systemic inflammation, thus increasing the severity of the disease and worsen the prognosis [5]. It was suggested that in COVID-19 patients PCT levels appeared to depend on disease severity, and that bacterial coinfection might be present in many patients, especially with severe and critical disease [1,6].

PCT is a polypeptide precursor of the hormone calcitonin, which is mainly produced by the C-cells of the thyroid gland and other cells such as monocytes. PCT production increases in the presence of cytokines caused by bacterial infection and lipopolysaccharides (LPS). It does not increase in sterile inflammation or viral infection [4]. The

elevated PCT is sustained by the increased levels of interleukin (IL)–1 β , tumor necrosis factor (TNF)- α and IL-6 in bacterial infection. In viral infection interferon (IFN)- γ level is increased, which inhibited PCT production [6]. PCT production in monocytes is regulated by microRNA (miR)–125b via signal transducer and activator of transcription 3 (STAT3) [7]. After LPS stimulation on monocytes, miR-125b level decreased, STAT3 and phosphorylated STAT3 level increased, promoting the expression of PCT [8].

There are new findings on the SARS-CoV-2 proteins and their role in the pathogenesis of COVID-19 based on studies on SARS-CoV-1. Several SARS-CoV-1 and SARS-CoV-2 proteins have similar antagonist activity against IFNs and the downstream Janus kinase (JAK)-STAT signaling pathways based on a comparative genetic structural study [9]. SARS-CoV-2 proteins inhibit the function of STAT1 and IFNs, and cause a compensatory activation of STAT3 in human cells infected by SARS-CoV-2 [10]. SARS-CoV-2 proteins that have an increased anti-IFN-I activity are open reading frame (ORF) 3b variant (56 aa), ORF6, and non structural protein 1 (NSP1) [10,11]. As the SARS-CoV-2 inhibits STAT1 phosphorylation, IFN-stimulated gene transcription in monocyte-derived dendritic cells and macrophages increases [12]. After ORF6 or NSP1 impair STAT1 function, the compensatory STAT1-independent pathways commences, making way to STAT3-dependent transcriptional pathways (Fig. 1(A)). STAT3 also have been shown to inhibits the STAT1-mediated IFN-1 response. This alternative STAT3 transcriptional pathways are responsible to most pathology found in severe COVID-19 patients such as increased coagulopathy/thrombosis, proinflammatory state, and T cell lymphopenia [10]. As mentioned above, in most viral infection the level of IFNs are increased, which caused inhibition of PCT production [6]. On the contrary, SARS-CoV-2 proteins inhibit the function of IFNs and up-regulate STAT3 signaling in monocytes, that would result in the increased PCT production. The increase of STAT3 in COVID-19, would lead to increased PCT production (Fig. 1(B)).

There is evidence of impaired function of monocytes in COVID-19 that was caused by enhanced viral growth due to non-neutralizing

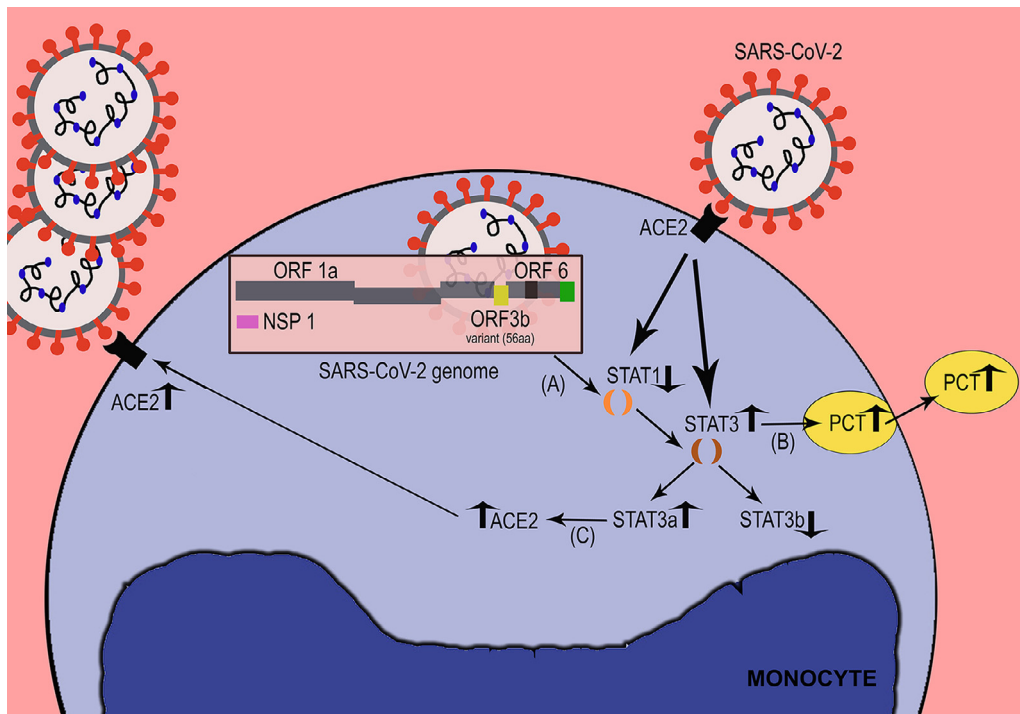


Fig. 1. Immunological mechanism of increased procalcitonin production in monocytes in COVID-19 infection. (A). COVID-19 proteins (ORF6 and NSP1) inhibit STAT1 phosphorylation and increased STAT3-dependent transcriptional pathways, resulting decreased STAT1 and increased STAT3. (B). Increased STAT3 signaling increased PCT production. (C) If the STAT3 α isoform of STAT3 increased, ACE2 mRNA and protein expression will also increased, leading to more entry of SARS-CoV-2 into other cells.

immunoglobulin M (IgM), IgG, complement, hypoxia, loss of antiviral function of macrophages due to lymphopenia, and hyperactivation of immature monocytes. Monocyte's impaired function and its dysregulated secretory production resulted in increased PCT production in COVID-19 [13].

A study on the role of STAT3 in regulating angiotensin converting enzyme 2 (ACE2) expression revealed that STAT3 has two isoform: STAT3 α which is the main isoform, and STAT3 β which encodes a truncated STAT3 protein. STAT3 α causes increased ACE2 mRNA and protein expression, and STAT3 β causes decreased ACE2 mRNA and protein levels [14]. There is still no evidence on which STAT3 isoform that is increased in COVID-19. If the STAT3 α is the isoform that is increased in COVID-19, the resulting ACE2 mRNA and protein expression increase would be beneficial for SARS-CoV-2 entry into cells (Fig. 1(C)). SARS-CoV-2 would infect more cells, the cycle repeats, and the viral loads will rise rapidly.

As a summary, we could say that STAT3-dependent transcriptional pathways in SARS-CoV-2 infection will increase STAT3 level, and also PCT production in monocytes. Increased STAT3 α will increase ACE2 production and provide SARS-CoV-2 entry to more cells including monocytes. As more monocytes are infected, STAT3 α level will increase further and this vicious cycle ensues. We hope this simplified version of could shed some light on how PCT as part of human immunological response, increases in COVID-19 even in the absence of bacterial coinfection. In depth investigations are in need to clarify this potential mechanism.

Conflict of interest

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