CPQ Medicine (2020) 10:3
Editorial

COVID-19 War, (Non-)Pyrogenic Actions and Reactions

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Received: 17 August 2020

Published: 07 September 2020

Keywords: *COVID-19 Biomarkers; Pyrogen; Inflammation*

Worldwide, all nations are distressing from the COVID-19 pandemic outbreak with unexpected death rate about one million, which the exact mechanism how systemic blood is responding not elucidated completely [1-4].

According to Wang *et al*. 2020 data indicated that all patients without or with fever showed significant differences between 'clinical characteristics' symptoms. Their data shockingly revealed that none of the other symptoms alone showed significant differences between COVID-19 patients without- or with fever i.e. neither comorbidities like cardiovascular diseases nor CT positive rates, however. There is still some missing links, One might wonder what it is. Reconsideration of the characteristics of severe fevered patients revealed that a significant population of COVID-19 were aged patients. Because of the significantly increased probability of severe events in fevered COVID-19 patients, Wang *et al* 2020 further checked subgroups and found 5 main differences and association with aging- related diseases namely 1. severe fevered patients were older a median age 57 vs. 42 years; 2. had a higher fraction of primary comorbidity diseases i.e. hypertension; and cardiovascular disease; severe respiratory symptoms; and 3. ground-glass change in chest CT appearance; 4. a decreased lymphocyte count and proportion; but 5. higher levels of CRP median [2].

Though, from last year's propagation by "Media" either non- or Scientifics articles that were fully aimed at the COVID-19 Biomarkers, we observed different claims about I. Early clinical symptoms like at very first stages fever, coughing; and II. at late stages expression of COVID-19 in lungs indication ARDS, Pneumonia

and at last but not least III. Clinical end-stage COVID-19 infection progression by complex phenomenon cytokines storm and increased death rate, however [2-8]. Moreover, Wang *et al* 2020 data highlighted more in detail about different respiratory supports and oxygen therapies, which did not affect COVID-19 patients without and with fever, significantly (P>0.05). Amazingly, smoking and alcohol had also no effects on such COVID-19' patients without and with fever. One might wonder what would be the COVID-19's mutants mechanism of action, when aging-related comorbidities (ARCs) increased risk of activation of death receptors, however, increased "the significance of combined ARCs and pyrogenic phenomenal processes (PPPs).

The PPPs are substances (usually of biological origin) that cause fever with or without or with COVID-19 infection. The best-studied pyrogen is bacterial lipopolysaccharide (LPS, also known as endotoxin), found in the membrane of gram-negative bacteria [4]. Up to 2019, Medici trained to recognize how one (un)known microorganism works as an antigen in the human body. Suddenly, a superbug viral antigen appeared, which so-called 'COVID-19' that did not follow Patho-Physiology rules. Confusions and misinformation and lack of appropriate data resulted in a chaotic cascade of responses, which we are living now with no clear future, and an appropriate retaliation plan. Suddenly all taught Sciences were worthless. The speed of information(-management) is so high that Medici could not reflect logically. One might wonder what happened to (non-) pyrogenic issues last year? What happened to fever and heat as a biomarker? So many thermometers were manufactured and sold, worldwide.

Gromkowski SH *et al*. 1989 [5] studied the effect of the PPPs on the regulation of inflammatory processes in an *in-vitro* system. Since TNF, a central mediator in inflammation is both 'a pyrogen' and "a cytokine capable of inducing the death of certain cell", they examined the relationship between the PPPs' shock and TNF-mediated immune killing. Heat shock transiently decreased the sensitivity of the fibro-sarcoma cells via TNF-mediated lysis, however. Incubating inflammatory T lymphocytes in elevated temperature transiently abolished/inhibited their lytic potential and their ability to secrete TNF. Gromkowski *et al* 1989 data showed that the pyrogen activity of TNF could control cytolytic processes during inflammation, either by inducing protective protein(s) synthesis in target cells or by arresting TNF secretion by effector T lymphocytes [6].

Besides, Prostaglandin E2 (PGE2) has been shown to increase the transcription of pro-IL-1β. Though, PGE2 via the cAMP/protein kinase; a pathway is potently inducing IL-1β transcription, as well as boosting the ability of LPS inhibiting the production of TNF-α, while speculatively these processes might be regulated by the UPR machinery and calcium overload, inter- and intracellularly [1], which could being "leaked" by aging-related diseases, chronically.

Furthermore, because the PGE2 mediates the PPPs of IL-1β, these effects might be especially relevant for the role of monocytes in the induction of fever in COVID-19 patients [6-9]. In addition, fever might, therefore, occur in the absence of a septic shock response because of the inhibiting effect of PGE2 on TNF-α production, which might help to solve the problem, to restrict access of COVID-19, hypothetically.

Because of COVID-19 rapid emergence, there is a lack of evidence-based data regarding its viral behavior and host response following infection and inflammation [1,3]. Of course, chemokines, prostaglandins, and

cytokines storms, which are produced by different kinds of cellular and humoral cells, phagocytes, inflammasome might is a chaotic (non-)immune cells' response to a broad range of (un-)known infections [3,7,8] One might logically hypothesize that whether COVID-19 singular can produce/ induce so considerable first-, second-, third messengers expression and affect signal transduction in a confused processing manner, leading to random shut down, merely.

Through several signaling pathways, TNF-α controls vasodilation, infiltration, and adhesion of leukocytes at the site of inflammation, complement, and coagulation cascade activation, respiratory burst in polymorphonuclear leukocytes and it is also a pyrogenic cytokine. On one hand, the TNF-α up-regulation has also been observed in coronavirus' infections other than COVID-19 and seems to play a key role in lung injury, too [8]. On the other hand, IL-1β is expressed in a tightly regulated way by myeloid cells and released by the inflammasome, without interfering with Neutrophils and lymphocytes, however. Recall, the TNF-α promotes neutrophil recruitment and Th17 differentiation. If monoclonal antibodies blocking IL-1β pathway which has been proposed to treat COVID- 19, the IL-6 might play a crucial role in COVID-19, particularly in the related acute respiratory distress syndrome and during cytokine storm prevalence [1,8].

The major risk factors to fatal outcome in COVID-19 patients is proven to be elderliness and pre-existing metabolic and cardiovascular diseases, share in common the characteristic of being chronic degenerative diseases of inflammatory associated with malfunctioning heat shock response (MHSR) which all were not significant factor without an association with fever. Heck TG *et al*. 2020 suggested innovative molecular components of the MHSR, the principal metabolic pathway leading to the physiological resolution of inflammation, is an anti-inflammatory biochemical pathway that involves molecular chaperones of the heat shock protein family during homeostasis- threatening stressful situations (e.g., thermal, oxidative and metabolic stresses). The entry of COVID-19 in target cells, on the other hand, exacerbates the already-jeopardized MHSR in certain subjects, unsystematically. In addition, the cellular response against any kind of viruses involves interferon-mediated inflammatory responses including significant involvement of pyrogenic processes. Although, some subjects develop non-pyrogenic reactions. Taken together, contracted subjects might with the MHSR not resolve virus-induced inflammatory burst, remaining susceptible to exacerbated forms of inflammation. Previously we introduced Mortal Calcium Overload- UPR-side effects, which might play a key role in fatal "cytokine storm" and random shut down of organs [1]. How the mutated variants of the COVID-19 can cause ARCs' non-pyrogenic clinical symptoms still is a very important indicator to wonder in the near future.

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