

COVID-19 War, Highlights About Mechanism of Action

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Generally, patients and their family are frightening and suffering from the COVID-19 infectious with remarkable side effect-related attacks, which shockingly increased risk of death rate. In July 2020, still the exact mechanism how systemic blood and random shutdown of organs are occurring is not elucidated completely.

Now a day, 6 kinds of diseases cause a significant increase in mortality and morbidity rate either in- and/or out of Hospitals namely 1. Cancerogenous-, 2. Cardiovascular-, 3. allergy- 4. infection- 5. Biosimilars- 6. (novel-)side effect-related (un)known diseases i.e. sepsis.

Actually, one might wonder that why with so many developed scientific tools; Medici are suffering to predict the COVID-19 workings mechanism, globally. In one hand (overestimation), wonder whether people are attacked either by aliens or (biosimilar) superbugs made by certain laboratories that are causing horrible things. In another hand (underestimation), wonder how a normal virus could abruptly contaminate whole globe? and how COVID-19 infection-inflammation affects first-second-third messengers in a contracted host? All questions still remain for everybody a mysterious phenomenon.

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The COVID-19 is assumed that might be one the same kinds of viruses and antigens, which human history know thousand kinds of them, although always paid so many causalities, up to now.

Recall, generally occurring infections take place either acute or chronic, which is depending on 4 basic components and processes 1) Bioavailability of all (bio)chemicals, proteins, lipids, amino acids and different cellular building blocks 2) (ir-)responsiveness of immune response and 3) how strong host's immune system is; 4) (in-)activity of correlated genes and their products (proteins).

Additionally, infections could occur simultaneously with preexisting (pre- or post-) inflammatory response (- side effects) (correlated) disorders. For instance, when a subject already got flu and then contracted with the COVID-19 might develop neurodegenerative diseases [1]. Though, which preexisting disorder or disease was initiator? And which one was accelerators of death causes are not elucidated completely. Moreover, in some cases suddenly occurring distress syndromes are not exactly revealed, whether these clinical disorders are pre- or post-COVID-19 infections syndromes? Or they were ascending side effects of COVID-19 contamination.

Recently, different political Presidents try to manage Medicare/ Medicaid of COVID-19 with extraordinary accelerated guts-feeling-related solution, and how Basic and Clinical Scientists should think and act in a fast-tracked approach to tackle COVID-19 without need for knowing the whole mechanism of the COVID-19 mutants act. That was the last call to us (or any Medical Scientist) to take action and come forward with accelerated solutions without and/or with pilot studies, introduce and predict any kind of mathematical model system; and predict how the COVID-19 mutants could be tackled and being destroyed. Hence, in such manner could be speculate what the exact mechanism hypothetically is.

Based on evidences delivered up to now, one might guess that there are: I. Different mutants of COVID-19, which don't follow regular infection and killing mechanism; II. Each COVID-19 mutant could induce different mechanism of action; III. And contracted hosts randomly collaborate in an additive/ synergistic manner with COVID-19, and at least but not last IV. Contracted patients, who are recovered were not cured by one standard treatment. In the other hand, could be hypothesized that there are still some missing link(s) over the COVID-19 action mechanism, which needs more in details investigation; although there is no standard appropriate molecular, cellular, organs, and organismal model systems, which different Epidemiologist and Medici are working on it to predict preventive and therapeutic strategies.

Recently, one of the most attractive review over possible mechanism of COVID-19 action and reactions *in-vivo* is introduced by Pascarella G *et al.* in JIM 2020 that introduced how virus-induced inflammation pathways might work [2]. Their interesting aspects that in their review article were introduced are namely, considering perforin, Granzyme, and how phagocytes are releasing interleukins and chemokines i.e. IL-12, IL-15, and IL-18 to initiate chemotaxis. Nonetheless, how antigen presenting cells in hard tissues are functioning to present (neo)antigens. Subsequently, how natural killer cells (NKs), lymphocytes (ILC1), and T-helper cells being activated to migrate from soft into hard tissue and release their cytokines i.e. INF-gamma, TNF-alpha, IL-1, and IL-2, to yield cytokine storms, as a main response to SARS-COV-2 (COVID-19) inflammation and infection-related harms [3].

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We have previously highlighted about possible mechanism of the COVID-19 based on our (un)published evidence-based data, [4,5] and 3 submitted in progressions.

Now we are going to highlight more in details about COVID-19 mechanism of action, the variants that are infected and clinically contracted by patients in Iran. Our (practical) observations confirms partially Pascarella G *et al.* in JIM 2020 model system but we show here another extra phenomenal aspects, as well. For instance, how after COVID-19 enters systemic blood circulation and induces inter- and intracellular changes to white blood cells (WBCs), red blood cells (RBCs), Platelets (PLTs), studied in different model systems *in-vitro*, *ex-vivo*, *in-situ* (unpublished data Jul 2020). Our main results show that 1. Entrance of COVID-19 could be either indirect and/or directly, 2. Colonization and metastasis of COVID-19 might occurs via collaboration with intercellular unfolded protein response (UPR) machinery [6], 3. Subsequently cells got calcium overload and metabolic disorders [7], 4. Simultaneously different kinetic and dynamic interactions between the WBCs-RBCs-PLTs, and 5. Ultimately results in a random shut down of cells, and organs due to degranulation of different cells and tissues, eventually.

In addition, different study groups proposed that microbiomes play an important role in the pathogenesis of the COVID-19 and other viral infections. Modulation of the different organs' microbiota or their by-/ products as a mechanism for preventing COVID-19 metastasis and altering the pathogenesis of correlated side effects are different area of growing interest, however [8]. Endotoxins derived from Gram negative bacteria i.e. LPS and LOS must be considered as a key by-product metabolites from bacterial population of microbiota, which is responsible to initiate some vital steps of the UPR modulating network inducing cytokine storms.

At least but not last in 21th Century One might expect that after all novel and classic medical device research and developments, no One should be infected in-Hospitals at first place, and at second if however subject is infected, Medici could save contaminated subject's life, and finally an appropriate personalized Medicare/ Medicaid should fittingly take care of all. In 2030 experts will judge how Medici and non-Medici now have functioned.

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