Promoting the post COVID-19 alveolar regeneration by targeting cellular signaling pathways through small molecule intervention.

[1, 2]Jahnavi Chintalapati and [2]Ravikiran S. Yedidi*

[1]Dr. Lankapalli Bullayya College, Visakhapatnam, AP, India; [2]The Center for Advanced-Applied Biological Sciences & Entrepreneurship (TCABS-E), Rajahmundry, AP, India.

(*Correspondence to RSY: tcabse.india@gmail.com)

The year 2019 was the beginning of the conqueror Severe acute respiratory syndrome virus (SARS-CoV-2) causing Coronavirus disease-2019 (COVID-19) which claimed more than four million lives and affected more than 230 million lives around the world and still counting, thus earning the status of a pandemic. The effect of the virus is not proportionate, consequently severity of COVID-19 varies between individuals. In general, infected people experience mild to moderate respiratory illness and recovery depends on the strength and balance of the immune system. However, in severe cases it results in alveolar damage due to the accumulation of fluid and mucus collected in air sacs as a result of inflammation and cytokine storm which eventually causes respiratory failure and further complications. It is life threatening in cases of old age and comorbidities. To resolve this, corresponding cell signalling pathways are targeted to promote alveolar regeneration for the recovery from the infection/inflammation mediated alveolar damage thus reducing the fatality.

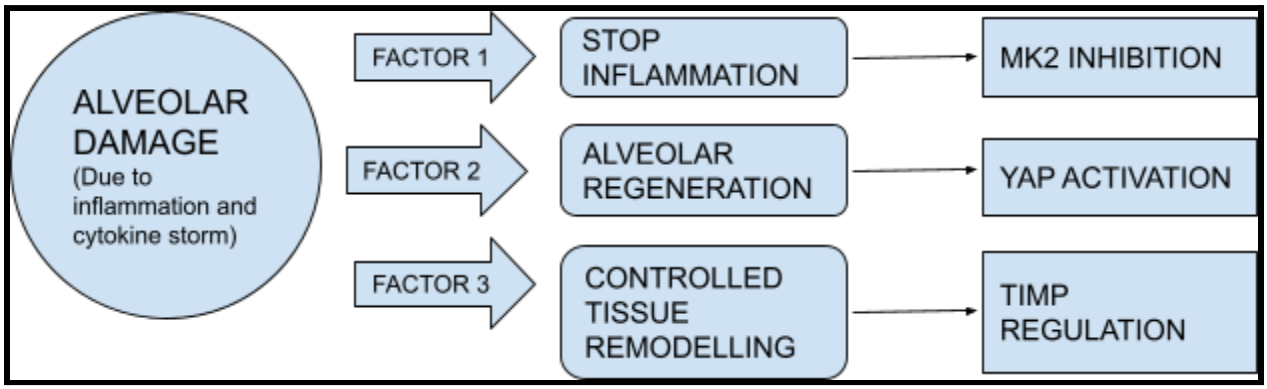

Figure 1. Overview of the proposed strategy for the modulation of cellular pathways towards alveolar regeneration.

When the SARS-CoV-2 viral particles enter the alveoli, they continue to replicate. On the contrary, immune cells identify the virus and produce cytokines as a part of inflammatory response from the body against the infection. These cytokines in turn attract more immune cells such as macrophages, neutrophils etc,. from the circulation to the site of infection resulting in additional production of cytokines forming a cycle of inflammation known as cytokine storm, which leads to damage of lung cells. Cytokine storm is the result of sudden surge in circulating levels of various proinflammatory cytokines which include IL-1, IL-6, TNF-α and interferon. The walls of alveoli begin to break down as they are filled up with fluids rushing from blood vessels thereby blocking gaseous exchange. Lung injury which is a consequence of this destructive effect can progress into acute lung injury or further severe form Acute Respiratory Distress Syndrome (ARDS)

which accounts for cytokine storm linking mortality in COVID-19 patients. Production of proinflammatory cytokines in overabund -ance prompts the aggravation of ARDS and moreover results in multi-organ failure (1). Henceforth, bringing down the cytokine storm is the major target.

In order to iron out the alveolar damage, ceasing the inflammation is prioritized. To boot, alveolar regeneration must be stimulated with controlled tissue remodelling. To achieve this, three factors will be designed with specific functions as depicted in Figure 1. First, to counter inflammation, the MK2 cell signalling pathway is targeted. MK2 is involved in inflammatory responses. Production of inflammatory cytokines is regulated by MK2 (2). Upregulation of MK2 leads to production of interleukins and other cytokines causing the immune overreaction. A protac inhibiting MK2 will be designed to nullify the alveolar damage as the inhibitor suppresses the inflammation by downregulation (3). Besides terminating the conundrum, it is equally important to assist our immune system to recover quickly from the infection.Therefore JNK and P38 MAPK signalling pathway is targeted to promote alveolar regeneration and controlled tissue remodelling simultaneously by the second and third factor respectively. The second factor, performs the function of activating YAP (Yes associated protein) a key component of the pathway. YAP is a regulator of transcription that activates transcription of genes for cell proliferation. In this scenario, YAP directs alveolar type 2 cells proliferation which are attributed for regeneration as they can rebuild alveolar epithelium after lung injury as well as function as resident alveolar stem cells which undergo proliferation and differentiation to form new alveoli (4). This speeds up the recovery process and also wipes out the chance for other complications which are otherwise fatal. The tissue regeneration process must be orderly concerning to avoid giving a chance for fibrosis to arise. Thus the final factor focuses on regulating TIMP (Tissue inhibitor of metalloproteinase) which is a natural inhibitor of MMP (matrix metalloproteinases). MMP plays a pivotal role in tissue remodelling.Through MMP activity regulation, indirectly TIMPs regulate extracellular matrix (ECM) remodelling along with cell signaling. Balance of MMPs and TIMPs is critical for homeostasis (5). Furthermore, TIMP promotes cell proliferation, independent of metalloproteinase inhibition (6). The factor is designed to ensure harmony in the lungs through perfect remodelling of the affected tissue exploiting the natural function of TIMP.

Altogether, it puts a check to the cytokine storm and fosters congruous regeneration of the alveoli inclusive of clearing and replacing the damaged alveoli. The delivery system of the factors to the targeted site is through synthetic biology due to the high specificity and customizable nature that it offers. This approach has broader utility as it is also applicable to other respiratory diseases critically affecting the lungs for example tuberculosis. Thus is a single shot solution to settle lung tissue damage through small molecule intervention.

Currently, we are in the process of evaluating the small molecules that are proposed in this strategy. The data obtained from the *in vitro* and *in vivo* studies will be published in the future issues of TCABSE-J.

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How to cite this article?
Chintalapati, J. and Yedidi, R.S. (2021). *TCABSE-J*, Vol. 1, Issue 1:1-3. Epub: Apr13th, 2021.

Acknowledgements: The authors thank T*yi*DE-Toronto, Canada for helping to write this manuscript.

Funding: The authors thank TCABS-E, Rajahmundry, India and T*yi*DE-Toronto, Canada for financial support.

Conflict of interest: The strategic communication presented here is an ongoing project currently at TCABS-E, Rajahmun--dry, India. The authors invite collaborations without any conflict of interest.