Biomarker predicts who will have severe COVID-19

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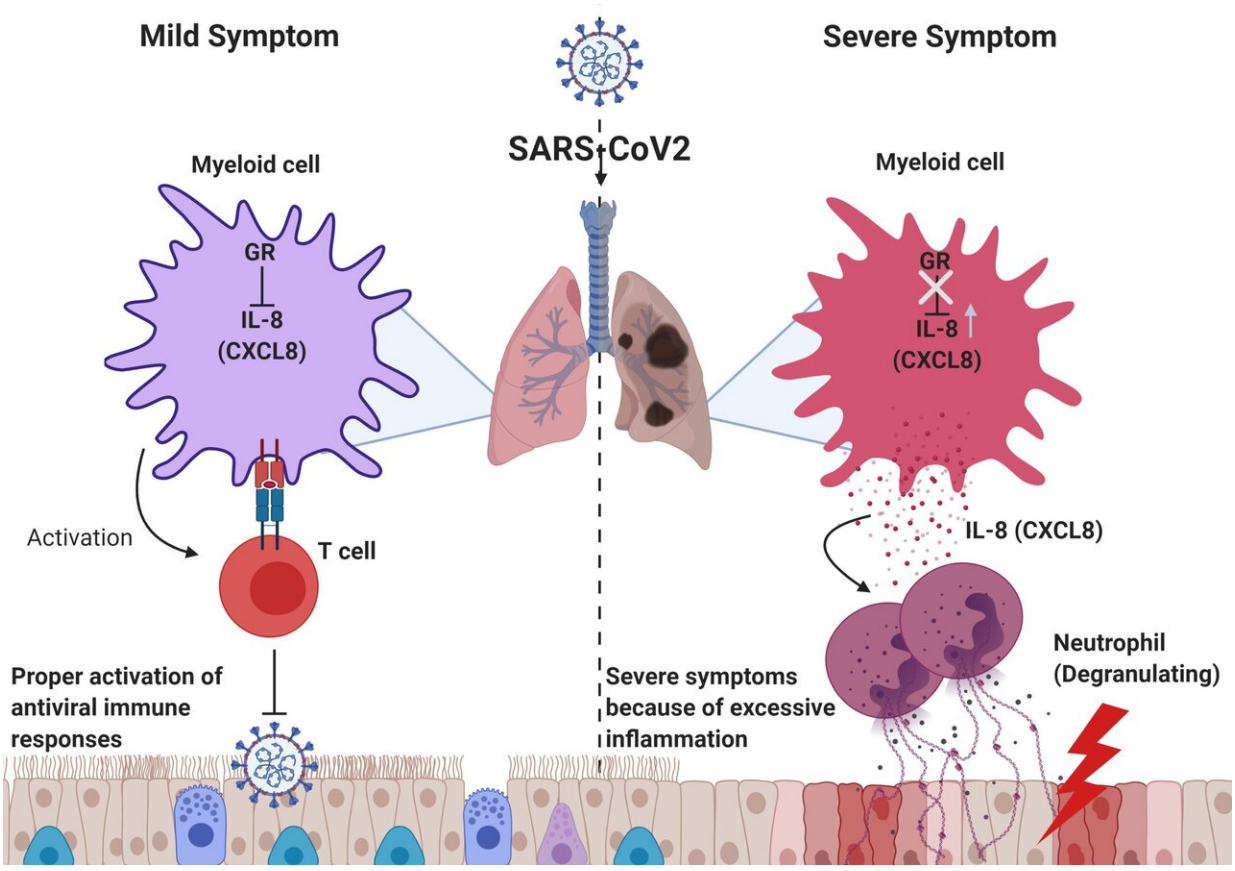

Figure. Low glucocorticoid receptor (GR) expression led to excessive inflammation and lung damage by neutrophils through enhancing the expression of CXCL8 and other cytokines. Credit: The Korea Advanced Institute of Science and Technology (KAIST)

KAIST researchers have identified key markers that could help pinpoint patients who are bound to get a severe reaction to COVID-19 infection. This would help doctors provide the right treatments at the right time, potentially saving lives. The findings were published in the journal Frontiers in Immunology on August 28.

People's immune systems react differently to infection with SARS-CoV-2, the virus that causes COVID-19, ranging from mild to severe, life-threatening responses.

To understand the differences in responses, Professor Heung Kyu Lee and Ph.D. candidate Jang Hyun Park from the Graduate School of Medical Science and Engineering at KAIST analyzed ribonucleic acid (RNA) sequencing data extracted from individual airway cells of healthy controls and of mildly and severely ill patients with COVID-19. The data was available in a public database previously published by a group of Chinese researchers.

"Our analyses identified an association between immune cells called neutrophils and special cell receptors that bind to the steroid hormone glucocorticoid," Professor Lee explained. "This finding could be used as a biomarker for predicting disease severity in patients and thus selecting a targeted therapy that can help treat them at an appropriate time," he added.

Severe illness in COVID-19 is associated with an exaggerated immune response that leads to excessive airway-damaging inflammation. This condition, known as acute respiratory distress syndrome (ARDS), accounts for 70% of deaths in fatal COVID-19 infections.

Scientists already know that this excessive inflammation involves heightened neutrophil recruitment to the airways, but the detailed mechanisms of this reaction are still unclear.

Lee and Park's analyses found that a group of immune cells called myeloid cells produced excess amounts of neutrophil-recruiting chemicals in severely ill patients, including a cytokine called tumor necrosis factor (TNF) and a chemokine called CXCL8.

Further RNA analyses of neutrophils in severely ill patients showed they were less able to recruit very important T cells needed for attacking the virus. At the same time, the neutrophils produced too many extracellular molecules that normally trap pathogens, but damage airway cells when produced in excess.

The researchers additionally found that the airway cells in severely ill patients were not expressing enough glucocorticoid receptors. This was correlated with increased CXCL8 expression and neutrophil recruitment.

Glucocorticoids, like the well-known drug dexamethasone, are anti-inflammatory agents that could play a role in treating COVID-19. However, using them in early or mild forms of the infection could suppress the necessary immune reactions to combat the virus. But if airway damage has already happened in more severe cases, glucocorticoid treatment would be ineffective.

Knowing who to give this treatment to and when is really important. COVID-19 patients showing reduced glucocorticoid receptor expression, increased CXCL8 expression, and excess neutrophil recruitment to the airways could benefit from treatment with glucocorticoids to prevent airway damage. Further research is needed, however, to confirm the relationship between glucocorticoids and neutrophil inflammation at the protein level.

"Our study could serve as a springboard towards more accurate and reliable COVID-19 treatments," Professor Lee said.

More information: Jang Hyun Park et al. Re-analysis of Single Cell Transcriptome Reveals That the NR3C1-CXCL8-Neutrophil Axis Determines the Severity of COVID-19, *Frontiers in Immunology* (2020). DOI: 10.3389/fimmu.2020.02145