COVID-19

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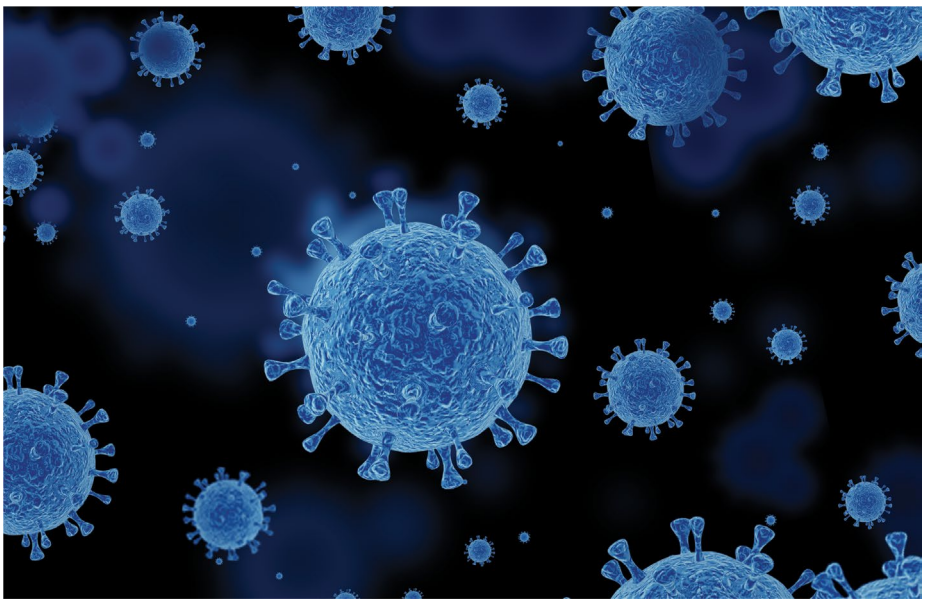
SARS-CoV-2-induced loss of CHK1 causes DNA damage

SARS-CoV-2 infection promotes cellular phenotypes that are associated with aging, such as senescence and proinflammatory cytokine release. However, the molecular pathways that link SARS-CoV-2 with these phenotypes are not fully understood. Now, a study by Ubaldo Gioia, Sara Tavella and colleagues shows that SARS-CoV-2 infection leads to a loss of CHK1, which causes a shortage in dNTP and impairs DNA replication, thus initiating a DNA damage response (DDR), inflammation and senescence.

"The idea of a mechanism clicked in my head when I attended an RNA conference in the earliest days of the pandemic, before any lockdown", says corresponding author Fabrizio d'Adda di Fagagna. "Narry Kim from Seoul National University showed her preliminary results from nanopore RNA sequencing of infected cells. Staggeringly, two out of three sequenced RNAs were of viral origin! Such an amount of RNA synthesis immediately meant to me that the cell was getting into trouble: where would the cell find three times the amount of rNTP than normally needed?"

The researchers began by infecting human cells with SARS-CoV-2. They observed that SARS-CoV-2 infection causes DNA damage and an altered DDR associated with a proinflammatory phenotype and senescence; it was also associated with a downregulation of effector kinase CHK1. As loss of CHK1 is sufficient to cause replication stress and DNA damage accumulation, the team measured dNTP levels and cell cycle progression. They observed that SARS-CoV-2 infection decreases dNTP concentrations and impairs S-phase progression. Deoxynucleotide supplementation in the culture medium of infected cells reduces DDR activation, DNA damage accumulation and proinflammatory cytokine expression.



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"Our study shows that SARS-CoV-2 infections causes the degradation of CHK1, thus reducing ribonucleoside-diphosphate reductase subunit M2 (RRM2) expression and ribonucleotide reductase (RNR) activity and thereby shifting the balance of cellular nucleotide metabolism in favor of rNTP and in disfavor of dNTP. This generates DNA damage", explains d'Adda di Fagagna. "In addition, DNA damage repair is impaired: surprisingly, 53BP1 foci cannot assemble. This is because they depend on the function of damage-induced long noncoding RNA (dilncRNA) generated at sites of DNA damage. We discovered that viral N protein binds to dilncRNA and blocks 53BP1 condensation."

The researchers also measured the DDR markers 53BP1, CHK1 and RRM2 in lungs from mice infected with SARS-CoV-2 and in lung and nasal mucosa sections from patients who died of COVID-19. These results are consistent with their in vitro data.

"Key to this study was the collaboration with experts in the field, like Alessandro Marcello's group, to perform all real viral infections (no pseudoviruses)", continues d'Adda di Fagagna. "Also essential was access to infected tissues form mice and patients, and a great pathologist, Claudio Tripodo, who assessed DDR in these tissues."

In future studies, the authors note it will be interesting to establish whether the mechanisms they uncovered contribute to long-COVID pathology.

Overall, this study sheds light on the mechanisms that underlie the cellular effects of SARS-CoV-2 infection, particularly DNA damage, inflammation and senescence.

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