Combining two molecules blocks 95% of live viral infection in lung cells

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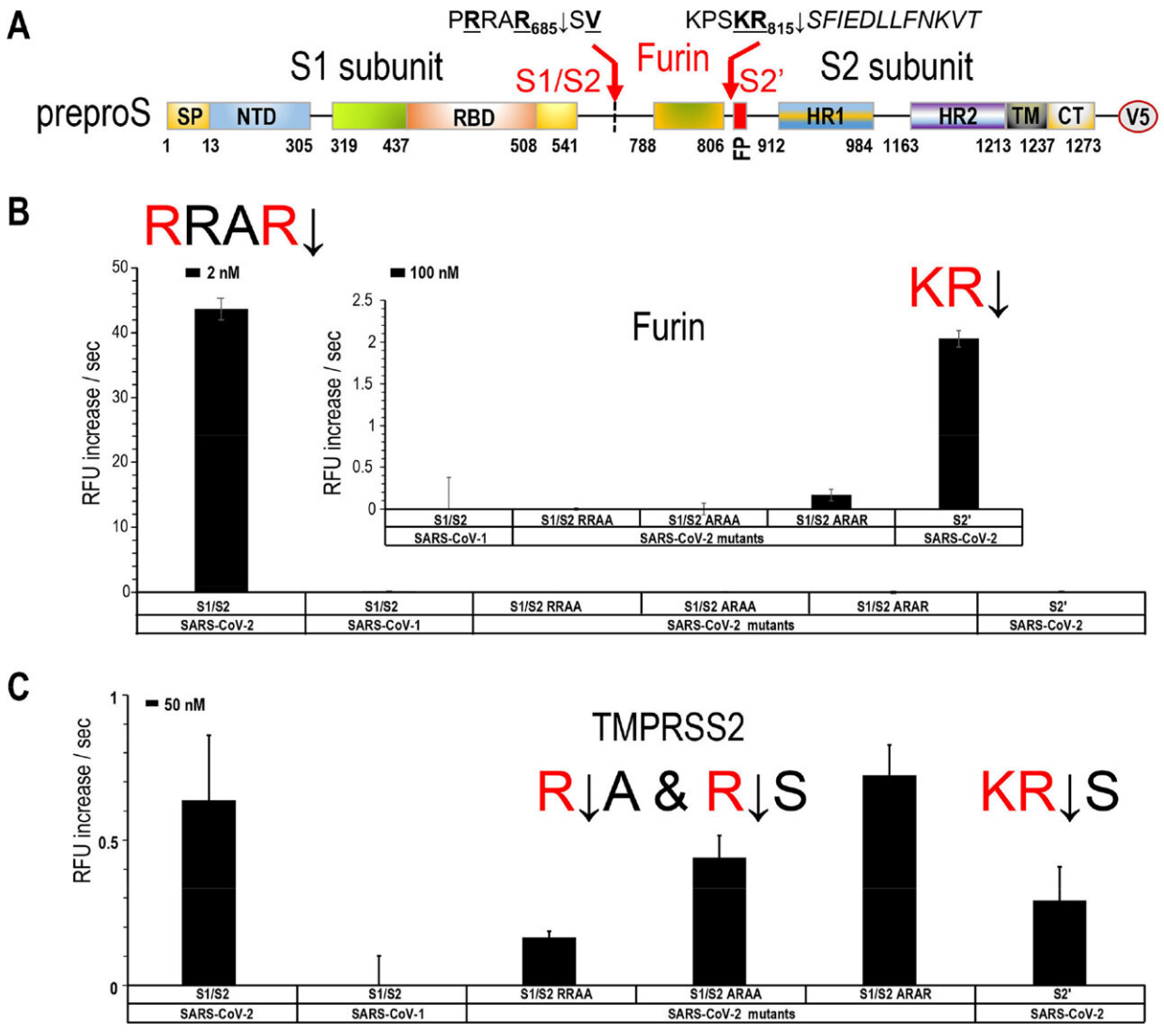

Processing of S peptides by furin and TMPRSS2. (A) Schematic representation of the primary structure of preproS, including its domains, the predicted furin-like S1/S2 site generating the S1 and S2 subunits, and the S2′ site preceding the

fusion peptide (FP). The signal peptide (SP), N-terminal domain (NTD), receptor binding domain (RBD) to ACE2, the two heptad repeats HR1 and HR2, the transmembrane domain (TM), the cytosolic tail (CT), and the C-terminal V5 tag are indicated. (B) In vitro furin activity against peptides mimicking the S1/S2 (and its mutants) and S2′ cleavage site sequences of the spike protein from SARS-CoV-2 and SARS-CoV-1, as described in Table 1. Each substrate was tested at final protease concentrations of 2 and 100 nM. (C) In vitro TMPRSS2 activity (at 50 nM) against peptides mimicking the indicated S1/S2 and S2′ cleavage site sequences as described in Table 1. Credit: *Journal of Virology* (2022). DOI: 10.1128/jvi.00128-22

COVID-19, in its multiple variants and its ability to thwart efforts to wipe it out, still has a lot of unknowns that make it impossible for scientists to declare victory over the disease, despite vaccines.

But now two Université de Montréal professors working at the Montreal Institute for Clinical Research (IRCM) have taken a big step towards understanding the coronavirus: they've identified and confirmed the power of two small molecules to block the infection of lung cells by SARS-CoV-2, the virus that causes COVID-19.

The finding by the teams of medical professor Nabil G. Seidah, the IRCM's director of biochemical neuroendocrinology research, and microbiology professor Éric A. Cohen, the IRCM's director of human retrovirology research, was published Monday in the *Journal of Virology*.

How it works and why

Viral entry into lung epithelial cells requires cleavage (↓) of the viral surface spike-glycoprotein of SARS-CoV-2 at two sites, S1/S2 (PRRAR↓) and S2' (KPSKR↓) to expose a fusiogenic sequence allowing

host membrane fusion with the infectious virus.

Seidah's team was already the first to predict that the 4-residue insertion (PRRA) in the spike sequence would result in a typical proprotein convertase furin-like cleavage at the S1/S2 sequence of PRRAR↓.

The new study validates this concept and shows unequivocally that furin cleaves at both sites, enhancing viral infection, the scientists say. They also show that another enzyme, TMPRSS2, cleaves the membrane-bound receptor ACE2 and releases it into the medium, promoting cellular entry of SARS-CoV-2.

The result: combining of potent small molecule inhibitors of furin (BOS compounds) and TMPRSS2 (Camostat) blocks the live viral infection of lung cells by more than 95 percent.

Another weapon to fight COVID-19

SARS-CoV-2, the etiological agent of COVID-19, has caused more than 6 million deaths worldwide, and that number is still rising. Seidah and Cohen say their powerful new antiviral approach will help reduce the spread of SARS-CoV-2.

That's especially important, they add, as other coronaviruses are widely expected to develop in the near future. Having new treatments in the antiviral arsenal, they say, will help society better prepare for future pandemics.

More information: Rachid Essalmani et al, Distinctive Roles of Furin and TMPRSS2 in SARS-CoV-2 Infectivity, *Journal of Virology* (2022). DOI: 10.1128/jvi.00128-22

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