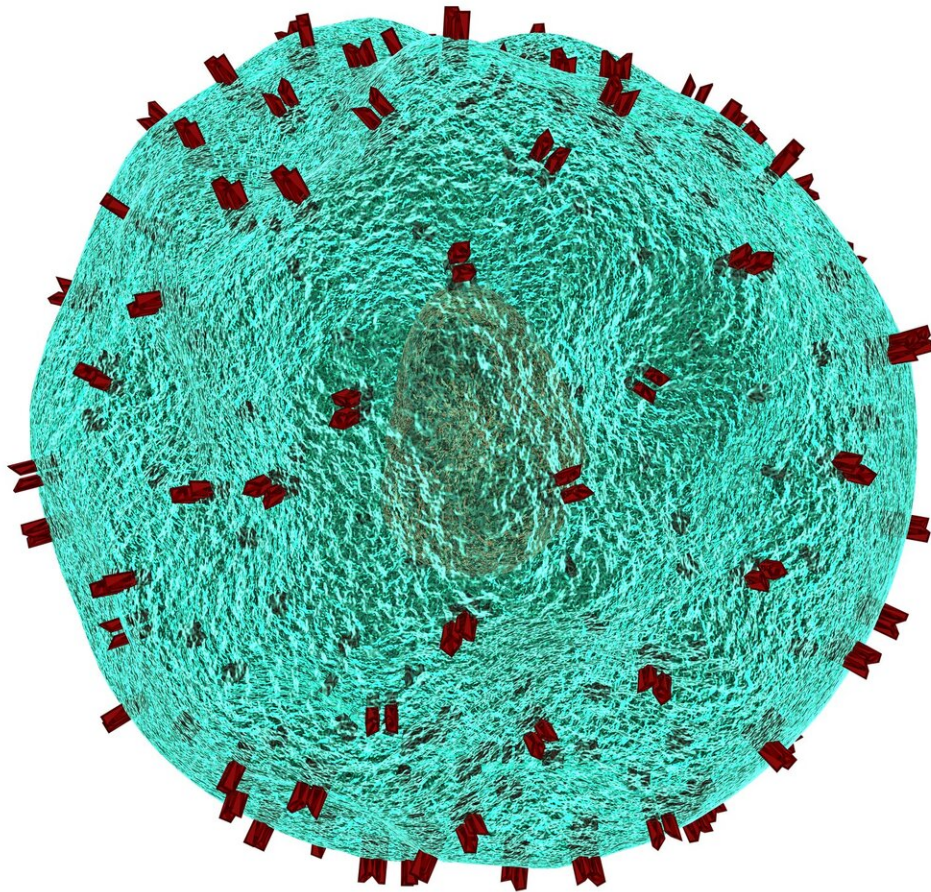


# Identification of two pathways for SARS-CoV-2 entry into cells

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SARS-CoV-2 is the virus that has caused the COVID-19 pandemic. Ideally, to prevent its spread, treatments should target the early stages of infection before the virus penetrates cells. A joint investigation by INRAE and Heidelberg University, Germany, has revealed the mechanisms by which the virus enters host cells. The results, published in *EMBO Journal* on 23rd June, show that SARS-CoV-2 uses two entry pathways: a fast route in cells expressing a specific protease (TMPRSS2) on their surface and a slow route in cells devoid of this protease. These findings offer new perspectives for the development of antiviral strategies that would target both cell entry pathways adopted by SARS-CoV-2.

Since early 2020, SARS-CoV-2, the [virus](#) responsible for COVID-19, has infected more than 179 million people worldwide and caused at least 3.8 million deaths. Apart from vaccination, the most [effective strategy](#) to limit the spread of the disease would involve drug treatments that target the early stages of infection and prevent the virus from penetrating cells. To this end, it is essential to understand how the virus achieves this entry. Inspired by studies of MERS-CoV, another coronavirus identified in 2012 and which caused Middle East Respiratory Syndrome, the research team focused on the cell entry [pathway\(s\)](#) used by SARS-CoV-2 to infect different cell types.

## **Fast and slow pathways**

The scientists infected cell models mimicking different types of tissues—such as lung, colon, or kidney—and infected them with the SARS-CoV-2 virus. In the course of their work, it became clear that certain cells were infected very rapidly (within 10 minutes) and others

more slowly, about 50 minutes after binding of the virus to the cell surface. The team was able to demonstrate that the fast entry route correlates with the presence of a protease—TMPRSS2—at the surface of infected cells. In this scenario, SARS-CoV-2 exclusively used the TMPRSS2 pathway to penetrate cells. TMPRSS2 was notably found in the lungs and intestine, two organs where high levels of the virus are detected. When the TMPRSS2 protease was absent, the virus followed another route through the endolysosomal pathway that was slower, most probably because of the many complex cell mechanisms involved. Indeed, to follow this pathway, the virus notably requires a low pH (or an acid environment) to enable functioning of the endolysosomal proteases necessary for its activation. Other mechanisms are also involved, such as intracellular endolysosomal trafficking, and might represent interesting alternative targets for drug development or repurposing.

These findings show that the virus has developed the ability to utilize several cell entry mechanisms to infect as many cell types as possible, which may explain its high proliferative potential in the body and its rapid spread throughout the population. They also shed new light on the inefficiency of some treatments that target only one of the two entry routes. This study lays the foundations for the development of new antiviral strategies against SARS-CoV-2 infection involving more effective treatments that simultaneously target both viral entry pathways into [cells](#).

**More information:** Jana Koch et al, TMPRSS2 expression dictates the entry route used by SARS-CoV-2 to infect host cells, *The EMBO Journal* (2021). [DOI: 10.15252/emboj.2021107821](https://doi.org/10.15252/emboj.2021107821)

Provided by INRAE

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