Source : www.thehindu.com Date : 2023-05-21

NOVEL HOST-DIRECTED MOLECULES BLUNT SARS-COV-2, INFLUENZA VIRUS

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

May 20, 2023 08:45 pm | Updated 08:45 pm IST

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Indian researchers have, for the first time, been able to synthesise small molecules that can effectively halt the infection of cells by SARS-CoV-2 and influenza viruses by targeting the hosts. The approach adopted by the researchers is vastly different from the one that is usually used for making antivirals. In place of antivirals that directly target the virus in question, the team, co-led by researchers at IISER Mohali and IIT Ropar, attempted the host-directed therapy. Till date, no approved host-directed drugs are available for either SARS-CoV-2 or influenza virus.

In both cultured cells and animal studies, the small molecules that were synthesised by Dr. Prabal Banerjee's team at the Department of Chemistry, IIT Ropar showed over 95% efficacy in halting the infection of cells by SARS-CoV-2 and influenza viruses. The results were published in *PLOS Pathogens*.

While antivirals that target the virus become ineffective once the virus develops resistance, drugs that target the host cells to prevent the virus from infecting them, are expected to remain effective even when the virus evolves by accumulating mutations.

There is already evidence that the current FDA-approved drugs for treating SARS-CoV-2 and influenza virus infection are losing their efficacy due to the emergence of drug-resistant virus strains. In host-directed therapy, the challenge is that molecules can very often turn out to be toxic to the host cells, the reason why this approach has not been widely adopted.

The small molecules were not only effective (over 95%) against both SARS-CoV-2 and influenza viruses, they were not toxic to either cultured cells or mice even after prolonged exposure.

"We initially tested 28 compounds for their effectiveness in blocking influenza virus from infecting the lung cells. Of the 28 molecules screened, one molecule — 1,3-diphenylurea derivative (DPUD) — was able to block both SARS-CoV-2 and influenza virus infection by almost 100% in cells without being toxic to the cells," recalls Dr. Prabal Banerjee, who is one of the corresponding authors. "This prompted us to synthesise 22 additional DPUDs. Five of the total 23 DPUDs were found to be highly effective against both viruses, while one molecule tested against influenza virus and two tested against SARS-CoV-2 in mice were found to be highly effective without causing toxicity to the animals."

“The discovery of host-directed DPUD molecules was serendipity,” says Nirmal Kumar, a PhD student from IISER Mohali and first author of the paper. “When we began this work in early 2020, we were looking for potent anti-influenza agents through high-throughput screening of small molecules. We identified DPUDs that efficiently blocked influenza infection. After several experiments, we realised that the small molecules (DPUDs) were host-directed and found that they block the cell entry pathway of influenza virus.”

During COVID-19 pandemic, scientists indicated that SARS-CoV-2 uses the same pathway as influenza virus to enter the host cells.

“We hypothesised that DPUDs should also be able to prevent SARS-CoV-2 infection since they block the common viral entry pathway. We immediately tested the DPUDs against SARS-CoV-2 and found them to almost completely block infection. Of the 23 DPUDs that we developed and tested, five showed extremely potent antiviral effect and we found them to be host-directed,” says Mr. Kumar.

“Compared with Molnupiravir, two DPUD molecules that we tested on animals against SARS-CoV-2 showed better efficacy. Mice challenged with the virus followed by treatment with DPUDs showed better body weight recovery and improvement of lung pathology,” says Indranil Banerjee from the Department of Biological Sciences at IISER Mohali, and one of the corresponding authors of the paper. In the case of influenza virus, one DPUD was tested on mice.

“We mimicked influenza virus evolution in the presence of Tamiflu and DPUD. The virus developed resistance to Tamiflu after prolonged exposure (10 generations) but not to the DPUD tested,” says Dr. Indranil. “The virus remained sensitive to the DPUD despite prolonged exposure and this is the reason why the small molecule was able to inhibit infection.”

Explaining how the small molecules were able to block virus entry into cells, Dr. Indranil says the chloride concentration inside and outside a cell varies. Maintaining equilibrium of chloride concentration inside the cell is critical for endocytosis — cellular process in which substances are brought into the cell.

“These molecules carry chloride ions into the cell, thereby leading to a large accumulation of chloride inside the cell, disturbing the chloride equilibrium. When the chloride equilibrium is disturbed, some endocytic pathways that these viruses depend on to enter cells become non-functional. As a result, the viruses fail to enter the cells and establish infection,” explains Dr. Indranil Banerjee.

However, the precise mechanism by which virus entry into the cell is blocked by DPUDs is not clear. The mechanism of nutrient entry into cells even when the virus entry pathways are blocked needs to be further studied.

“Probably the small molecules target the pathways the viruses use to enter cells while keeping the other pathways open, so the cell health remains unaffected,” Dr. Indranil says.

The small molecules were found to be highly effective when tested against H1N1 and H3N2 influenza virus sub-types and the SARS-CoV-2 Wuhan, Delta, and two Omicron variants of concern.

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