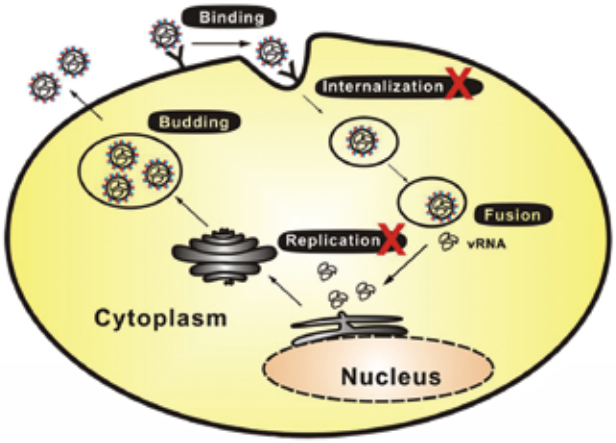
Scientists Repurposing FDA-Approved Drugs to Fight against Viruses

In a study published in *Cell Research* on August 23, researchers from the CAS Wuhan Institute of Virology/Center for Biosafety Mega-Science, Chinese Academy of Sciences, together with their collaborator from State Key Laboratory of Pathogen and Biosecurity discovered a new talent for two molecules of calcium channel blockers (CCBs), a group of widely used anti-hypertensive and anti-atherosclerotic agents. These two CCB molecules were found to inhibit the replication of a certain virus that causes severe fever with thrombocytopenia syndrome (SFTS).

SFTS is an emerging tick-borne infectious disease caused by a novel phlebovirus (SFTS virus, SFTSV), which was listed among the top 10 priority infectious diseases by the World Health Organization due to its high fatality and pandemic risk. Currently, there is no medicine marketed specifically against SFTSV. In the face of a growing threat to public health imposed by SFTSV, a fight back against SFTSV is highly demanded.

To meet the demanding need, researchers resorted to screen FDA-approved drugs for anti-viral compounds. This is an effective strategy to repurpose drug application as it eases one's mind on the safety concerns of the identified drug candidates. By screening a library of FDA-approved drugs for anti-SFTSV activity, they found that a particular small molecule benidipine hydrochloride, a calcium channel blocker (CCB), strongly inhibited SFTSV replication *in vitro*.

Researchers then sought to investigate the inhibitory mechanism of benidipine hydrochloride against SFTSV infection. They firstly ruled out the possibility that benidipine hydrochloride kills SFTSV in a direct way. Then they inspected whether benidipine hydrochloride affects SFTSV infection at the stage of entry. After precautious analyses, they confirmed that benidipine hydrochloride inhibits virus infection through impairing virus internalization and genome replication through reducing the intracellular Ca^{2+} level.



A proposed model for the anti-SFTSV activity of the two calcium channel blockers that inhibit viral internalization and replication through reducing the intracellular Ca^{2+} concentration. (Credit: Prof. PENG Ke's group)

They also tested a broad panel of CCBs to see whether inhibition of SFTSV replication is a general feature of these drugs. They tested and found another CCB molecule (termed nifedipine) could also inhibit SFTSV infection. The anti-SFTSV effect of these two CCBs was further analyzed in a humanized mouse model in which CCB treatment resulted in reduced viral load and decreased fatality rate. Importantly, by performing a retrospective clinical investigation on a large cohort of 2,087 SFTS patients, it revealed that nifedipine administration enhanced virus clearance, improved clinical recovery, and remarkably reduced the case fatality rate.

In short, their study is highly valuable for developing potential host-oriented therapeutics for SFTS and other

lethal acute viral infections known to be inhibited by CCBs *in vitro*. The evidence clearly indicates the potential therapeutic effect of nifedipine in treating SFTS patients and strongly supports the design of future clinical trials to evaluate the safety and efficacy of CCB therapy for SFTS patients, for both benidipine hydrochloride and nifedipine, two CCBs that are commonly used in clinics. Could other FDA-approved drugs be repurposed to treat diseases or fight against pathogens that are not listed in their indications. It is an open question.

(By YAN Fusheng)

Reference

Hao Li *et al.*, Calcium Channel Blockers Reduce Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV) Related Fatality. *Cell research* 29, 739 (2019). doi: 10.1038/s41422-019-0214-z.