RESEARCH HIGHLIGHT

CCHFV entry via LDLR keeps it 'ticking'?

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Endemic in Africa, the Balkans, the Middle East, and Asia, Crimean-Congo hemorrhagic fever virus (CCHFV) is transmitted from a tick vector to humans and the mortality rates can be as high as 40%. In a recent paper in *Cell Research*, Xu et al. reports the discovery of LDLR as the CCHFV entry receptor in humans and mice, which may provide clues to the receptor that the virus uses in its tick vector, a major discovery that opens up new and much needed options for therapeutic development.

Crimean-Congo hemorrhagic fever virus (CCHFV) is a significant cause of disease and death in Africa and Asia. The case mortality rate is high, ranging between 1% and 40%. The infection can be spread by an infected *Hyalomma* tick vector or by human secretions from human to human.[1] There are no vaccines or specific therapeutics licensed to treat CCHFV disease. In a recent paper in *Cell Research*, Xu et al.[2] show that low-density lipoprotein receptor (LDLR) is an entry receptor for CCHFV in endothelial cells (Fig. 1a, b), liver and spleen, a major cell type and organs that are infected in the course of Crimean-Congo hemorrhagic fever. The authors' work also suggests that there remains an as yet discovered receptor that contributes to infection of peripheral blood mononuclear cells (PBMCs) in the blood.

Discoveries of virus entry receptor are important scientific milestones to understand the first requirements of viral replication. Without virus-host receptor interaction, virus infection does not happen; therefore, the cellular entry receptors that viruses must bind are obvious therapeutic targets to prevent and treat infection. This has been realized with the development of the HIV drug maraviroc. This drug inhibits the interaction between HIV and the CCR5 co-receptor and has been licensed by the FDA for the treatment of chronic HIV infections.[3]

LDLR is used as an entry receptor for other viruses. It has been shown that vesicular stomatitis virus, a member of the rabies family and a very different virus from CCHFV, also uses LDLR as an entry receptor.[4] More recently, another low-density lipoprotein receptor family member, LDLRAD3, was reported as an entry receptor for Venezuelan equine encephalitis virus (VEEV).[5]

By using domain deletion mutants of LDLR the authors showed that CCHFV binding relied on the ligand-binding domain of LDLR made up of class A LDL-binding domain repeats (LDLAs) (Fig. 1a). While removal of the intermediate and adjacent EGF-like β propeller domain reduced infection, it did not deny infection completely as did removal of the N-terminal LDLA repeats. The LDLA repeat domain normally interacts with the apolipoproteins of LDL particles, leading to uptake of fats into cells of the body. Xu et al. show that LDLA is bound by the Gc glycoprotein of CCHFV to trigger virus entry into cells. These experiments were important in revealing the entry factors required for infection of humans and may even provide clues for understanding how CCHFV infects its tick vector/reservoir.

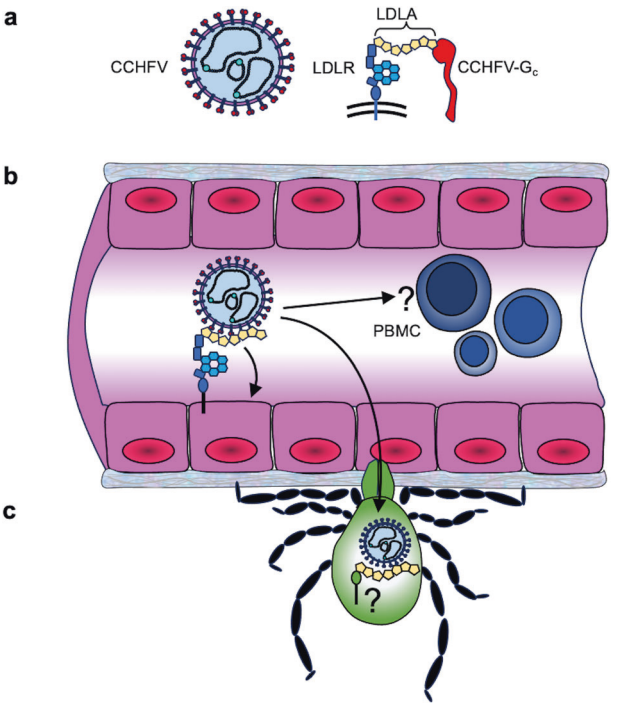

Fig. 1 CCHFV binds to the class A repeat domains of LDLR to infect cells. a, **b** CCHFV-G_C glycoprotein binds to LDLAs on LDLR that normally bind to LDL particles (**a**). This leads to CCHFV infection of hepatocytes in the liver, splenocytes in the spleen, and endothelial cells (**b**) that line blood vessels. **c** LDLA-containing proteins are upregulated on tick gut cells during a blood feeding.

Like many arthropod-borne (arbo) viruses, CCHFV is spread by ticks that bite and feed on blood from the host. Like many other arboviruses like VEEV, West Nile, yellow fever and Zika viruses, they must infect and replicate in the arthropod vector to be further transmitted, and in the case of CCHFV, the *Hyalomma* tick. The host receptors that mediate arthropod infection, remain largely unknown. We read with interest that LDLR-like proteins containing LDLAs that bind to LDL have been identified in ticks (Fig. 1c) and expression is elevated after a tick takes a blood meal.[6,7] We know that ticks, like many other arthropods, cannot synthesize their own cholesterol which must be transported to the

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tick circulation by LDLA-containing proteins.[8] Given the findings of Xu et al., we think that it would be interesting to test whether the insect LDL-binding domains in the tick proteins can confer infectability for CCHFV in tick cells. What better protein evolves as an entry receptor than a protein in the tick that is upregulated upon exposure to the virus during a blood meal? We will watch this area with significant interest as to what receptor mediates infection of the tick.

This is a definitive study that also raises some further important questions about CCHFV receptor usage and cell tropism. It is interesting to note that PBMCs (monocytes, T and B cells) were infectable by CCHFV, but infection could not be blocked to the levels seen in endothelial cells by anti-LDLR therapy. Regardless, the absence of LDLR in *Ldlr*$^{-/-}$ mice or blocking mLDLR caused a significant reduction in serum viremia. This suggests that LDLR is the main receptor for CCHFV, but there may be minor receptors and infection factors that remain to be found.

The study reported by Xu et al. provides significant insight into CCHFV replication with considerable implications for therapeutic development to prevent and treat CCHFV infection in humans. This work may also point toward the tick receptor, responsible for the zoonotic forest-urban/city cycles of CCHFV.

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ADDITIONAL INFORMATION

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