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# New targets for controlling Ebola virus disease

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EBOV infects multiple different cell types and replicates rapidly *in vivo* [1]. Due to its long filamentous structure, EBOV is internalized by macropinocytosis after cell surface receptor binding by the viral glycoprotein (GP). Unlike many other enveloped viruses, EBOV entry process involves multiple steps of traversing of the virion through endosomal vesicle route before its nuclear core is released into cell cytoplasm for replication [2]. In an attempt to systematically delineate the complex process how EBOV enters host cells, Sakurai *et al.* has recently revealed that two previous unknown calcium channels belonging to two-pore channel (TPC) family play the central role in the late steps of EBOV entry process [3]. TPCs are the major calcium channels activated by NAADP (nicotinic acid adenine dinucleotide phosphate) as well as phosphatidylinositol 3,5-biphosphate (PI(3,5)P2) in the late endosomes required for their acidification and maturation. In the absence of TPCs or when their channel activity is blocked, even though EBOV virion can still travel to the late endosomal/lysosomal compartment, it cannot penetrate into the cytoplasm. Interestingly, this impairment is not due to the failure of cleavage of EBOV GP by cathepsin B/L or trafficking of the GP-cleaved viral particles to the NPC1+ endosome compartments, but is caused by blockage of viral–host membrane fusion [3]. One of the most significant findings of this work is that small molecule compound Tetrandrine, originally from Chinese herb medicine (such as *Stephania tetrandra*) can potently and selectively block EBOV entry through its inhibition on TPC channels, with IC50 as low as 55 nM [3]. Thus, the lengthy entry process is EBOV's Achilles' heel; like TPCs, other host factors required for this process are good candidates to be targeted by small molecule inhibitors; however, further tests need to be performed in animal models infected with wild-type Ebola viruses.

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As oppose to the pro-viral host factors, a number of proteins produced by host cells can strongly antagonize EBOV infection. Interferon-stimulated gene (ISG) encoded host factors are well known for their role in antiviral function [4]. Among them, IFITM1,2,3 are highly effective in inhibiting EBOV entry by blocking membrane fusion in late endosome/lysosome [2].

Cholesterol-25-hydroxylase (CH25H) is another ISG protein that can potently inhibit EBOV infection, which was initially identified by our high-throughput overexpression screening [5]. CH25H encodes an enzyme catalyzing the hydroxylation of cholesterol at position 25 in host cells, thus forming and releasing 25-hydroxyl cholesterol (25HC) into the circulation [4,6].

Importantly, our work shows that it is 25HC responsible for the antiviral activity of CH25H [5]. Indeed, other oxysterols (hydroxylated cholesterols) can also effectively inhibit EBOV infection. In fact, antiviral activity of some synthetic 25HC oxysterol is even much stronger that the naturally existing 25HC [5,6]. Mechanistic studies further show that 25HC also operates at viral entry step, blocking the viral–host membrane fusion [6]. It will be interesting to see whether 25HC can act synergistically with IFITM1,2,3 in antagonizing EBOV entry in late endosome/lysosome compartment, as both affect the curving and synapse formation in the final step of membrane fusion. No doubt, better understanding of the molecule events that control viral–host membrane fusion would aid the development of more potent and specific drugs inhibiting EBOV entry.

Apart from targeting entry, blocking viral particle budding and release from host cells also should also be a valid strategy for controlling EBOV infection and pathogenesis [1,2]. In this regard, another ISG protein, Tetherin, has been shown to effectively inhibit EBOV budding. Intriguingly, EBOV GP can antagonize this function. GP interacts with Tetherin in the viral budding raft, and such interaction prevents the formation of multimeric complex of Tetherin, which is required for blocking EBOV virion release [7,8]. Thus, it is feasible that compounds targeting GP– Tetherin interaction can boost up Teth-erin's anti-EBOV activity.

In addition to the intracellular functions, soluble forms of EBOV GP released from the infected cells can thwart the neutralization activity of the antiviral antibodies and dampen adaptive immune responses in general [2]. More recently, work by Sheng *et al.* has revealed another danger nexus of EBOV GP in blood vessel pathogenesis [9]. The study shows that GP can induce high-level expression of mi-RNAs hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p in endothelial cells, which in turn downregulates protein levels of adhesion-related molecules tissue factor pathway inhibitor (TFPI), dystroglycan1 (DAG1) and the caspase 8 and FADD-like apoptosis regulator (CFLAR) [9]. Such alteration leads to severe apoptosis of endothelial cells and thus damage of blood vessels, which is associated with hemorrhagic fever syndrome.

As discussed above, EBOV GP clearly plays a central role in viral life cycle and host–pathogen interaction, and therefore is a high-value target for disease intervention. Indeed, our recent computational modeling work has put this view in another perspective. We show that GP forms a major node of comutation network for EBOV evolution, one of the key

contributing factors to its case fatality rate, i.e. the pathogenicity power of the virus [10]. Furthermore, the study has also revealed a high degree of connectivity of GP with the viral NP and L proteins in the comutation network, which is entirely unexpected, suggesting potentially important functional relevance [10]. Experiments are under the way in testing whether paired comutations are involved in physical interactions and whether such interactions can be exploited for drug targeting to control viral infection, replication or pathogenesis.

In summary, as EBOV can infect and replicate rapidly once inside the human body, a systems approach should be implemented to identify multiple drug targeting sites to hit this deadly virus from head to toe all around its way (Fig. 1). Recent progress in the feld has shown that such systematic research effort is highly promising and will lead to the development of effective therapeutics to intervene Ebola viral disease in near future.

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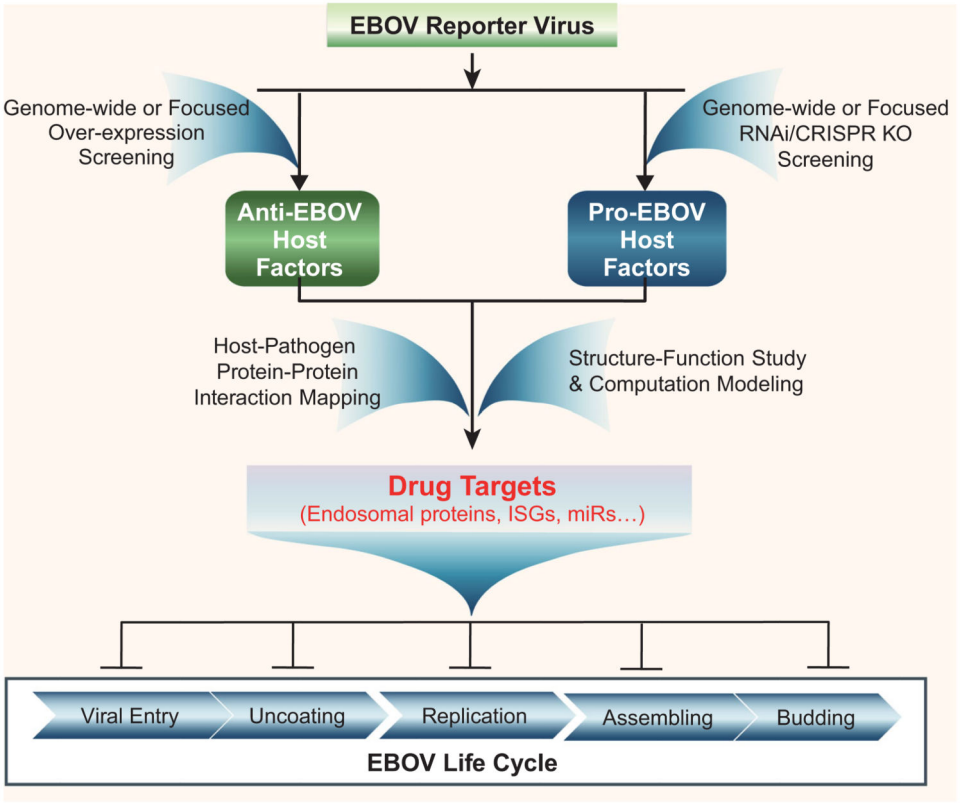


**Figure 1.**

A systems approach to identify host factors which can serve as novel drug targets for Ebola viral disease intervention. Genome wide or focused overexpression or RNAi/CRISPR gene knockdown/knockout screenings are carried out *in vitro* using EBOV reporter virus systems. Both anti- or pro-EBOV host factors can be identified through such functional screenings. Genes encoding anti- or pro-EBOV host factors will be further characterized by host–pathogen protein–protein interaction mapping, structure-function analysis and computational modeling to reveal potential drug targets. We anticipate the drug targets will include host endosomal proteins (such as TPCs), ISGs (like IFITMs) and miRNAs, which play pivotal roles in controlling the key steps of EBOV life cycle.