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All viruses are gene poor relative to their hosts: even the largest viral genomes only encode hundreds of genes, while those of host cells typically encode tens of thousands of genes. Thus, most steps in viral pathogenesis involve interactions between relatively few different types of viral proteins with much more complex pools of host factors. This pool of host factors represents both the essential milieu to which viruses must adapt for survival and a tremendous, manipulatable resource for gene-poor viruses. Accordingly, host factors play important roles in most, if not all, steps of viral infection. Moreover, host factors are targeted by the viruses to modulate host gene expression and defenses and identifying such host factors and their contributions have long been recognized as an important frontier from the perspective of not only basic biology but also to provide impetus to development of better therapeutics.

Hepatitis E virus is an important human pathogen. The properties and functions of its individual gene products, ORF1, ORF2 and ORF3 are not fully understood. Earlier studies in the lab were directed to define the roles of these individual proteins in viral life cycle by trying to identify the host factors and biochemical processes modulated by them. The physiological functions of the ORF3 protein remain obscure, although several studies using subgenomic expression of ORF3 in transfected cells have shown its importance as a viral regulatory protein.

The salient points of this work are as follows:

- Yeast two-hybrid analysis revealed the wide spectrum of host proteins interacting with ORF3, which are involved in different cellular functions. These include α1 microglobulin bikunin precursor, fibrinogen Bβ, hemopexin, START domain containing 5 protein (STARD5), eukaryotic translation initiation factor 5 (EIF5) and sulfatase modifying factor 2 (SUMF2).
- ORF3 was found to interact with hemopexin both in vitro and in vivo. The interaction was found to involve the N-terminal hydrophobic domain II of ORF3, spanning amino acids 37-62, and the N- and C-terminal regions of hemopexin (the two conserved hemopexin domains) spanning amino acids 1-250 and 251-462.
ORF3 interacts with fibrinogen Bβ, a component chain of the acute phase fibrinogen protein, both \textit{in vitro} and \textit{in vivo}. The interaction was found to involve the C-terminal half of ORF3, spanning amino acids 63-123, and the N-terminal half of Bβ, spanning region 1-266, which is critical for fibrinogen assembly.

ORF3-Bβ interaction leads to decreased fibrinogen secretion from ORF3 expressing human hepatoma cells. ORF3 mediates this decrease by transcriptional downregulation of the three fibrinogen chains Aα, Bβ and γ without affecting the half-life of individual components and the secretion machinery.