Picornavirus VP3 protein induces autophagy through the TP53-BAD-BAX axis to promote viral replication

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Background: Viral infection frequently induces both apoptosis and autophagy, which are tightly interconnected processes shaping host–pathogen interactions. While many viruses manipulate these pathways for their own benefit, the precise mechanisms by which host apoptosis and autophagy regulate picornavirus replication remain largely unclear.

Objective: This study aimed to elucidate how the structural protein VP3 of picornaviruses modulate apoptosis and autophagy to promote viral replication and pathogenesis.

Results: This study demonstrated that VP3 proteins of foot-and-mouth disease virus (FMDV), poliovirus (PV), and Seneca Valley virus (SVA) trigger both autophagy and apoptosis *in vitro* and *in vivo*. VP3 facilitates the phosphorylation and mitochondrial translocation of TP53, which in turn interacts with the pro-apoptotic protein BAD to activate the classical TP53–BAD–BAX apoptotic pathway. Concurrently, TP53 activation drives autophagic responses, marked by LC3B lipidation, which is essential for sustaining autophagic flux. Functional mapping identified Gly129 within VP3 as a critical residue mediating its interaction with TP53. Mutation of this residue abrogated VP3-induced autophagy and apoptosis and drastically reduced viral replication and pathogenicity. Importantly, Gly129 is highly conserved among diverse picornaviruses, suggesting a universal regulatory mechanism. Moreover, VP3-induced apoptosis and autophagy predominantly occur at the middle to late stages of infection, thereby facilitating viral replication and enhancing pathogenesis.

Conclusion: This study identifies simultaneous induction of autophagy and apoptosis via the classical TP53–BAD–BAX mitochondrial pathway as a novel feature of picornavirus VP3 proteins. This mechanism highlights how picornaviruses hijack host autophagy to potentiate viral replication and virulence, offering new insights for the development of broad-spectrum antivirals and rationally designed attenuated vaccines.