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Selective Autophagy Eats Up Invading Viruses

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Autophagy is a cellular process by which cellular components are engulfed inside distinct double-membrane structures (autophagosomes) and shuttled to the lysosomes for degradation. In addition to non-selective, bulk degradation of cytoplasmic contents, autophagosomes can selectively recycle unwanted organelles, remove protein aggregates, and eliminate invading viruses [1-4]. In recent years, the subject of the pathophysiological function of selective autophagy has received increasing attention.

The adaptor proteins, including p62 (also known as sequestosome 1) and Nbr1 (neighbor of BRCA1 gene 1), have been revealed to be essential in mediating selective autophagy [2,5,6]. They function as autophagy receptors targeting ubiquitinated proteins to autophagosomes for degradation. Despite the difference in length and primary sequence, p62 and Nbr1 share a similar domain structure containing an N-terminal Phox/Bem1p (PB1) domain, an LC3-interacting region (LIR), and a C-terminal ubiquitin association (UBA) domain [2,5,6]. The PB1 domain allows p62 and Nbr1 to interact with the PB1 domain of other proteins and also enables p62 to form self-aggregates. The LIR of p62 and Nbr1 binds directly to the microtubule-associated protein light chain 3 (LC3) located on the forming autophagic membranes, and such interaction is required for their recruitment into the autophagosome. The UBA domain of p62 and Nbr1 interacts with ubiquitin chains. Through binding to both LC3 and ubiquitinated proteins/organelles, p62 acts as a bridge to direct the proteins/organelles for destruction by the lysosomes [2,5,6].

Dysregulation of p62 and Nbr1 is associated with many diseases through formation of toxic protein aggregates, or inactivation of immune system or cellular regulating processes [7-11]. p62 has been identified as a common component of protein aggregates observed in human diseases, especially in neurodegenerative and liver diseases [12]. Mutations of p62 give rise to inherited Paget's disease of bone, characterized by focal increased bone turnover [13]. The role of Nbr1 in the regulation of bone mass and density was also reported in mice with knock in of a truncated form of Nbr1 [14].

Although selective autophagy has been implicated in a wide variety of cellular processes, the potential role of such an autophagic process in viral infection, termed xenophagy in the context of microbial infection, is largely unknown. Study has begun to unravel the involvement of xenophagy in the clearance of Sindbis virus, an enveloped, positive-stranded virus [15]. It has been reported that mice over expressing beclin-1, a protein critical for the formation of autophagosome, display reduced viral loads and diminished neuronal pathogenesis following Sindbis virus infection [16], whereas autophagy-deficient mice established by neuron-specific knockout of Atg5 have impaired elimination of viral capsid protein and increased mortality [15]. Further *in vitro* research has demonstrated that p62 is capable of interacting directly with the capsid protein of Sindbis virus and delivering it to the autophagosomes for autophagic degradation [15]. It has also been observed that autophagy deficiency results in an accumulation of p62-capsid protein aggregates which are toxic and are able to cause host cell death and disrupt normal cellular functions [15]. These results suggest an important role for p62-mediated selective viral autophagy in host anti-viral defense.

The precise mechanisms by which p62 targets Sindbis capsid protein for degradation remain to be elucidated. Although the UBA domain is likely a site responsible for p62 binding to viral capsid protein, direct evidence is still lacking, and whether mono- or poly-ubiquitination, or other post-translational modification of viral protein is required for such an interaction is unclear. It is also unknown whether p62 recognizes assembled or unassembled form of viral capsid. In addition to its function in selective autophagy, p62 also has a dual role as a scaffold protein to regulate multiple signaling pathways by interaction with various signaling proteins. For example, p62 has been shown to activate the NF-κB signaling pathway through binding with atypical PKC, RIP1 kinase, or TRAF6 [7,17]. It needs to be further determined whether these signaling mechanisms of p62 participate in the regulation of host immunity and viral pathogenesis during viral infection. Moreover, as described above that Nbr1 is another key regulator of selective autophagy and it can work independently or collaboratively with p62 [2,5,6], thus it would be interesting to study whether Nbr1 also plays a role in selective autophagic clearance of viral proteins and whether the presence of Nbr1 can compensate for the loss of p62, or vice versa.

Given the significance of selective autophagy in protecting against viral invasion, it is conceivable that viruses may have developed strategies to disrupt this host defense mechanism. p62 and Nbr1 are ubiquitously expressed and their expressions are regulated at multiple levels. They can be degraded by selective autophagy themselves. In response to oxidative stress, p62 has been shown to be transcriptionally upregulated [18]. Post-translational modification of p62 has also been reported recently [19]. It was demonstrated that phosphorylation of p62 at serine 403 within the UBA by casein kinase 2 enhances its affinity with polyubiquitin chain, resulting in efficient autophagic clearance of ubiquitinated proteins/aggregates [19]. *In vitro* protease cleavage assay has shown that p62 can be cleaved by caspase-6 and -8 and calpain 1

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[20]. Therefore, it will be of importance to determine whether virus infection can modulate the expression and function of these adaptor proteins.

In sum, although many issues remain unsolved, selective autophagy appears to represent a novel host anti-viral mechanism against Sindbis viral infection. Future studies will be of significant interest to determine whether such machinery also applies to other viral proteins.

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