Eating Twice for the Sake of Immunity: A Phagocytic Receptor that Activates Autophagy

Shahab Shahnazari1,2 and John H. Brumell1,2,3,*

1Cell Biology Program, Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
2Department of Molecular Genetics
3Institute of Medical Science
University of Toronto, Toronto, ON M5S 1A8, Canada
*Correspondence: john.brumell@sickkids.ca
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The mechanism by which the cell responds to invading pathogens is an area of intense research. Joubert et al. (2009) have found that the phagocytic receptor CD46 is able to activate autophagy through a tripartite interaction between itself, a scaffold protein GOPC, and the autophagy inducer complex of Beclin1-VPS34.

Macroautophagy (hereafter referred to as autophagy) was initially characterized as a general lysosome-dependent pathway by which cytoplasmic components are recycled in response to stress and starvation (Xie and Klionsky, 2007). More recently, this degradative pathway has been found to be involved in a wide variety of processes, including innate and adaptive immune responses to pathogens, promoting both cell survival and antigen presentation (Virgin and Levine, 2009). Autophagy has been found to selectively target cytosolic or membrane-bound pathogens, including a variety of bacteria, parasites, and viruses (Virgin and Levine, 2009). The mechanism by which autophagy is specifically activated for targeted degradation of pathogens remains to be fully elucidated.

Recent work has suggested that Toll-like receptors (TLRs) activate autophagy in response to binding by their respective pathogen-associated molecular patterns (PAMPs) (Sanjuan et al., 2007; Xu et al., 2007). Members of the Nod-like receptor family (NLRs) may also target pathogens to the autophagy pathway (Yano et al., 2008). However, the mechanism by which these receptors induce autophagy is not clear.

CD46 is a broadly expressed C3b- and C4b-binding protein, the activation of which can trigger downstream signaling events, including Vav, Rac, and Erk activation. At its C terminus, CD46 can have one of two signaling motif-containing tails: Cyt1 or Cyt2. CD46 has been shown to be constitutively internalized via clathrin-coated pits and is internalized by macropinocytosis upon antibody-mediated cross-linking (Liszewski et al., 2005). CD46 has been identified as the receptor for a group of pathogens that includes viruses and bacteria. Pathogen/CD46 interaction has been sufficient to induce autophagy in a manner requiring the key autophagy components Atg5 and Atg7. Induction of autophagy was also found to be sensitive to the autophagy inhibitor 3-methyladenine (a PI3-kinase inhibitor). This autophagic induction was not due to any secondary effects on autophagosome maturation but was rather due to de novo formation of these structures.

How does CD46 initiate autophagy? Using a yeast two-hybrid screen, Joubert et al. found that the CD46-Cyt1 isoform interacts with the class I PDZ domain of the scaffold protein GOPC. Of interest, a murine neuron-specific isoform of GOPC had been previously shown to interact with Beclin 1, a key component of the core autophagic machinery (Yue et al., 2002). Coaffinity purification showed that this interaction also occurs in human cells and that the interaction requires GOPC’s coiled-coil (CC) domain. Beclin 1 is itself also a scaffold protein that interacts with VPS34 to form a complex that is required for autophagy (Xie and Klionsky, 2007).

With an siRNA strategy, Joubert et al. found that starvation-induced autophagy was not affected in cells treated with siRNA against CD46-Cyt1 or GOPC, indicating that these factors are not components of the general autophagic machinery.

Different pathogens, including measles virus (MeV) and certain serotypes of group A Streptococcus (GAS), have been found to bind CD46 (Liszewski et al., 2005). Joubert et al. found that the Edmonston strain of MeV and emm6* GAS were both able to induce autophagy in a CD46-Cyt1- and GOPC-dependent manner. Of interest, the authors also looked at the autophagic targeting of a non-CD46-binding strain of GAS (emm49*) and observed a significant delay in degradation of the bacteria, indicating that CD46 binding is an early signal to specifically target the bacteria for degradation by autophagy.

Joubert et al. have shown that the phagocytic receptor CD46 interacts with Beclin1-VPS34 via GOPC and that this interaction is required for the autophagic response to GAS and MeV binding. Whether this has an impact on other pathogens that are internalized through CD46 binding remains to be determined. Additionally, this work suggests the possibility of a wider role for GOPC wherein it could potentially interact with other cell surface proteins to induce autophagy. Of interest, the cystic fibrosis transmembrane conductance regulator CFTR has been shown to be targeted for lysosomal degradation when bound to GOPC, a process that likely involves autophagy (Cheng et al., 2004).
The downstream events following activation of the CD46-Cyt1/GOPC/Beclin1-VPS34 pathway remain to be fully determined. Does recruitment of Beclin1-VPS34 by GOPC induce production of PI3P by this complex? If so, is this sufficient to induce autophagy, or are other concomitant factors (presumably CD46 receptor dependent) required for this process? Is the induction of autophagy general (i.e., throughout the cell) or targeted predominantly to the pathogen-containing phagosome (Figure 1, pathway 1)? General induction of autophagy by CD46-Cyt1/GOPC/Beclin1-VPS34 can, upon receptor crosslinking with antibody, result in a pool of preformed autophagosomes, as demonstrated by Joubert et al. The authors suggest that this pool can then sequester and degrade internalized pathogens by an as yet undetermined mechanism. On the other hand, targeted induction of autophagy could occur at the phagosomal membrane itself via recruitment of autophagy factors in a Beclin1-VPS34-dependent manner. In fact, phagosomes have been previously found to recruit autophagy components, including Beclin1 and Atg5/12, targeting them to lysosomes (Huang et al., 2009; Sanjuan et al., 2007). Some pathogens exploit autophagy in host cells, so it will be intriguing to see whether the CD46-Cyt1/GOPC/Beclin1-VPS34 pathway can serve as both a host defense and an “Achilles heel” for different pathogens (Virgin and Levine, 2009).

The mechanism by which cells detect and specifically identify targets for degradation by selective autophagy remains to be fully determined, but the characterization of this pathway by Joubert et al. provides important evidence for a receptor used for pathogen internalization that directly links with known autophagy components. Whether other CD46-interacting pathogens or GOPC-interacting membrane proteins induce autophagy in a similar manner remains to be determined.

REFERENCES


Figure 1. Model of Cellular Pathways for CD46-Mediated Induction of Autophagy

(Pathway 1) Autophagy targeted to the pathogen-containing phagosome.

(Pathway 2) General autophagy throughout the cell.