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Autophagy promotes cell motility by driving focal adhesion turnover

Ziheng Xu and Daniel J. Klionsky

Life Sciences Institute and Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, MI, USA

ABSTRACT

In eukaryotic cells, cell migration is a dynamic and complex process that involves finely tuned orchestration of a multitude of proteins including, for example, those involved in focal adhesions (FAs). Cell migration plays an indispensable role in particular stages of development and its proper regulation is crucial in various biological processes, from wound healing to the immune response. FAs are transmembrane protein complexes that traverse cytoskeletal infrastructures all the way to the extracellular matrix, producing traction at the leading edge of the cell, thus allowing for motility. The assembly of FAs has been extensively studied, whereas disassembly remains poorly understood. Here, we highlight 2 recent studies (see the corresponding puncta in the previous and current issues of the journal) that demonstrate a requirement for macroautophagy/autophagy in FA disassembly. These studies also provide a deeper understanding of how autophagy can contribute to cell migration among multiple cell types.

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By knocking down different autophagy-related (ATG) proteins, the authors investigate the role of autophagy in cell motility. Results show that in autophagy-deficient cells, migration becomes significantly impaired.[1] In addition, the defect in cell migration results in a substantial reduction in tumor cell metastasis in mice.[2] The change in cell motility is accompanied by an increase in the size of FAs, suggesting that the former phenotype corresponds to a defect in FA disassembly. Moreover in autophagy-deficient 4T1 tumor cells, there is an increase in the protein level of PXN (paxillin), one of the major components of FAs. Quantification of FA dynamics from both studies reveal that the disassembly of FAs is indeed compromised in autophagy-deficient cells, and thus likely accounts for the phenotype of reduced cell motility.

To further substantiate the connection between FA turnover and autophagy, both groups studied the localization of GFP-LC3-labeled autophagosomes with different FA proteins. Various proteins incuding PXN, VCL (vinculin) and ZYX (zyxin) are observed to colocalize with GFP-LC3 in migrating cells. Additionally, Kenific and colleagues report a 40-fold increase of autophagosomes at FA sites at the leading edge of migrating cells compared to nonFA sites.[1] The authors hence conclude that a selective degradation of FA proteins via autophagy is present at the leading edge and this process contributes to the motility of multiple cell types.

Unlike nonselective macroautophagy, the selective process typically requires specific cargo receptors that tether substrates to proteins such as LC3/Atg8.[3] Based on this, Kenific et al. performed a mini-screen of several known cargo receptor candidates including SQSTM1/p62, OPTN and CALCOCO2/NDP52. Among these, they determined that NBR1 plays a role in cell migration: NBR1-depleted cells phenocopy the autophagy-deficient cells; these cells also have a substantial decrease in autophagosome targeting at the leading edge of the cell. Co-immunoprecipitation confirmed the interaction between NBR1 and multiple FA proteins including PXN and ZYX. Moreover, the authors demonstrate that ectopic expression of GFP-NBR1 results in enhanced FA turnover, whereas the expression of GFP-NBR1 without its LC3-interacting region (LIR) does not. Similarly, the absence of a ubiquitin-associated domain in NBR1 also eliminates its effect on FA turnover. Accordingly, these data suggest that NBR1 functions as the primary selective autophagy cargo receptor during FA turnover.

In contrast to data showing the involvement of a specific cargo receptor, highly metastatic 4T1 tumor cells do not exhibit a change in cell motility after depletion of either SQSTM1 or NBR1.[2] Since there is evidence indicating selective autophagy may occur through direct interaction between LC3 and an autophagy substrate,[4] Sharifi and colleagues hypothesized that the degradation of FA proteins, especially PXN, is facilitated at least in part by direct interaction with LC3. The authors first identified a LIR in PXN that is conserved from *Xenopus* to human. They further determined the interaction between PXN and LC3 using co-immunoprecipitation. Knocking down LC3B results in an accumulation of PXN as well as phenocopying ATG5 or ATG7 depletion. In addition, this interaction via the LIR is regulated by oncogenic SRC, which is essential for SRC-stimulated cell motility. Putting all the evidence together, the authors demonstrate that the direct interaction between PXN and LC3 is responsible for autophagy-dependent FA disassembly, downstream of SRC signaling.

In conclusion, these 2 studies have clearly identified an important role for autophagy in orchestrating cell motility through FA turnover. This general autophagy-involved model adds to the diverse pathways by which cells can degrade FAs, including endocytosis and CAPN/calpain cleavage.[5] Despite the fact that the underlying detailed mechanism may vary among different cell types, these studies provide additional evidence that autophagy is

CONTACT Daniel J. Klionsky klionsky@umich.edu University of Michigan, Life Sciences Institute, Rm. 6036, 210 Washtenaw Ave., Ann Arbor, MI, USA.

involved in different stages of cancer, including tumor metastasis. Mechanistic insight into autophagy-dependent FA disassembly described in these studies may indicate the potential to develop novel cancer therapies that target this aspect of cell motility.

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No potential conflicts of interest were disclosed

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