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COMMENTARY

Galectins control MTOR and AMPK in response to lysosomal damage to induce autophagy

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ABSTRACT

The Ser/Thr protein kinase MTOR (mechanistic target of rapamycin kinase) regulates cellular metabolism and controls macroautophagy/autophagy. Autophagy has both metabolic and quality control functions, including recycling nutrients at times of starvation and removing dysfunctional intracellular organelles. Lysosomal damage is one of the strongest inducers of autophagy, and yet mechanisms of its activation in response to lysosomal membrane damage are not fully understood. Our recent study has uncovered a new signal transduction system based on cytosolic galectins that elicits autophagy by controlling master regulators of metabolism and autophagy, MTOR and AMPK, in response to lysosomal damage. Thus, intracellular galectins are not, as previously thought, passive tags recognizing damage to guide selective autophagy receptors, but control the activation state of AMPK and MTOR in response to endomembrane damage.

Abbreviations: MTOR: mechanistic target of rapamycin kinase; AMPK: AMP-activated protein kinase / Protein Kinase AMP-Activated; SLC38A9: Solute Carrier Family 38 Member 9; APEX2: engineered ascorbate peroxidase 2; RRAGA/B: Ras Related GTP Binding A or B; LAMTOR1: Late Endosomal/Lysosomal Adaptor, MAPK and MTOR Activator 1; LGALS8: Lectin, Galactoside-Binding, Soluble, 8 / Galectin 8; LGALS9: Lectin, Galactoside-Binding, Soluble, 9 / Galectin 9; TAK1: TGF-Beta Activated Kinase 1 / Mitogen-Activated Protein Kinase Kinase Kinase 7 (MAP3K7); STK11/LKB1: Serine/Threonine Kinase 11 / Liver Kinase B1; ULK1: Unc-51 Like Autophagy Activating Kinase 1.

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The ability to recognize, repair or replace damaged endomembranes or whole organelles is essential for cytoplasmic homeostasis and cell survival. Whereas it is likely that endomembrane perturbations occur at a basal level at all times due to thermodynamic reasons, diverse physiologically and medically relevant exogenous and endogenous agents can deliberately or incidentally damage endomembranes. For example, intracellular pathogens, organic or inorganic cytoplasmic or ingested extracellular aggregates or crystals can affect endosomal, lysosomal and phagosomal integrity. Plasma membrane and delimiting membranes of other organelles can also be physically compromised. Despite the physiological significance for normal cellular and tissue maintenance and function, cellular systems involved in homeostatic repair, removal and replacement of damaged endomembranes are not fully understood. One response to membrane damage is autophagy, a process that plays a general role in maintaining cytoplasmic homeostasis. Autophagy, in its role of quality control, clears cell-damaging sterile irritants or invading pathogens, removes protein aggregates and disposes of dysfunctional or disused organelles. Autophagy, in its metabolic role, plays a key role in maintaining nutrient and energy homeostasis. Metabolic autophagy is regulated by the Ser/Thr protein kinases MTOR and AMPK, best known for orchestrating anabolic and catabolic pathways in general, inclusive of autophagy. Whether signals from endomembrane damage are transmitted to MTOR and AMPK to orchestrate autophagic quality control responses and possibly other processes such as metabolic switching is not known.

We found that during lysosomal damage MTOR is inactivated and that it translocates from the lysosomal membrane to the cytosol, similar to what happens during starvation [1]. Cytosolic lectins termed galectins, recognize membrane damage by binding to lumenal glycans upon their exposure to the cytosol as a consequence of endomembrane damage. We found that of all human galectins, LGALS8 (galectin 8), plays a critical role in MTOR inactivation during lysosomal damage. Active MTOR and its regulators, RRAGA/B GTPase and their guanine nucleotide exchange factor Ragulator, are localized together with the glycosylated lysosomal transmembrane protein SLC38A9 on the lysosome. Using APEX2 proximity biotinylation and LC-MS/MS proteomics in conjunction with other methods, we identified a set of dynamic changes between LGALS8 and components of the SLC38A9-Ragulator-RRAGA/B-MTOR complex occurring during lysosomal damage. In resting cells, LGALS8 is proximal to MTOR but is not near SLC38A9, Ragulator, or RRAGA/B. However, following lysosomal damage, LGALS8 moves into close

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proximity of SLC38A9 and the Ragulator component LAMTOR1/p18 and the RRAGA/B GTPases. Conversely, the proximity between LGALS8 and MTOR is lost during lysosomal damage, as MTOR becomes inactivated and desorbs from the lysosomal membrane to the cytosol. LGALS8 imparts these changes by recognizing exposed lumenal glycans such as the glycosylated residues on SLC38A9. LGALS8 is required specifically for efficient inactivation of MTOR in cells subjected to lysosomal damage but not in cells subjected to starvation. The LGALS8-imparted changes are likely transduced to the activation state of RRAGA/B GTPases, because the entire process of MTOR inactivation and translocation to the cytosol in cells with damaged lysosomes can be rescued by overexpressing a constitutively active form of RRAGB. The above galectin-based system controlling SLC38A9-Ragulator-RRAGA/B-MTOR status and MTOR activity in response to lysosomal damage is termed GALTOR (Figure 1).

In this study, we also discovered that AMPK is responsive to lysosomal damage. AMPK is best known as a protein kinase that responds to cell energy crisis by boosting energy-yielding catabolic pathways while downregulating energy-consuming biogenesis processes. Here, we found that AMPK also responds to lysosomal damage. However, in contrast to MTOR, which is inactivated when lysosomal integrity is compromised, AMPK is activated during lysosomal damage. We next found that LGALS9 (galectin 9), a galectin different from the one controlling MTOR, is responsible for AMPK activation. We detected PRKAA/AMPKα in complexes specifically with LGALS9 in coimmunoprecipitation analyses. This was confirmed using an APEX2-LGALS9 proximity biotinylation assay. Following lysosomal damage LGALS9 associates with TAK1, one of the upstream activating kinases of AMPK. LGALS9 and TAK1 are both required for activation of AMPK in response to lysosomal damage (Figure 1). Another key kinase controlling AMPK, STK11/LKB1, contributes to AMPK activation although it is not specifically detected in LGALS9 complexes. AMPK stimulation by compromised lysosomal integrity is reflected in increased phosphorylation of PRKAA/AMPKα T172, and phosphorylation of AMPK's downstream targets such as ACACA/B (acetyl-CoA carboxylase alpha/beta) at S79, which blocks ACACA/B activity and stops de novo fatty acid synthesis. Importantly, AMPK's target ULK1 shows increased phosphorylation at the AMPK-activating site S317, associated with autophagy activation. In contrast, the MTOR-inactivating phosphorylation of ULK1 on S757, is reduced. This pattern is reversed in LGALS9 knockout cells. Finally, AMPK contributes to MTOR inactivation during lysosomal damage, because knockdowns of AMPK partially relieve inhibition of MTOR activity elicited by lysosomal damage.

In the context of autophagic response, these findings fit the model that AMPK and MTOR reciprocally and antagonistically control autophagy. Furthermore, these studies provide an example showing that AMPK and MTOR are engaged during quality control autophagy. The 2 galectins studied, LGALS8 and LGALS9, act to transmit signals and coordinately regulate these 2 master regulators of autophagy. It is likely that LGALS8 and LGALS9 act more broadly, and at least transiently affect cellular metabolism, a point that remains to be investigated. In addition to metabolic implications that beckon further study, many new questions are opened by this work. Of particular interest is the role of other galectins as well as the relationship of the galectin system relative to the nearly simultaneously reported ESCRT-based lysosomal repair system that seems to act by repairing minor damage and precedes galectin engagement.

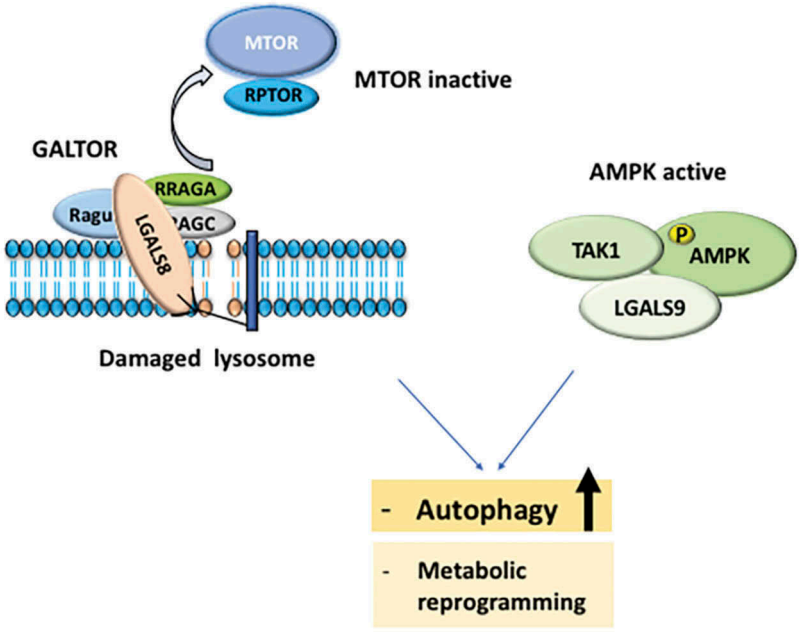

Figure 1. Model depicting how galectins control MTOR and AMPK. Lysosomal damage causes MTOR inhibition through a system termed GALTOR. LGALS8 recognizes lumenal glycans (depicted as an antennary structure) and inhibits MTOR via interactions with the Ragulator-RRAG-SLC38A9 system. Lysosomal damage activates AMPK through LGALS9 with the engagement of TAK1. Galectins control autophagy, and possibly metabolic reprograming, in response to lysosomal damage via MTOR and AMPK.

In conclusion, this study shows that MTOR and AMPK are coordinately influenced by lysosomal damage and that galectins play significant regulatory function in these processes, complementing the previously appreciated role of LGALS8 as a membrane-tear tag binding to a selective autophagy receptor. LGALS8 and LGALS9 recognize lysosomal damage and transduce this signal to control AMPK and MTOR. LGALS8 does this through the GALTOR system resulting in downstream responses including autophagy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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