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Signalphagy:

Scheduled signal termination by macroautophagy

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Abstract

A fundamental issue in cell biology is how the activation of a signaling pathway should lead to the appropriate cell response. Because of their oncogenic potential, the abundance, the duration and the localization of key signaling proteins must be carefully controlled. Negative feedback loops that combine transcription and protein–protein interactions are among the strategies by which a cell can turn off signaling. Our recent studies in *Cancer Research* and *Autophagy* show that degradation of key active proteins such as RHOA-GTP by constitutive autophagy represents one safeguard mechanism that limits signaling in a spatially and temporally restricted manner for faithful cytokinesis and directed migration. As a result, all autophagy compromises drive cytokinesis failure, aneuploidy, and motility—three processes that directly have an impact upon cancer progression. We therefore propose the term "signalphagy" to indicate a dedicated type of macroautophagy that degrades and thereby maintains the appropriate level of active signaling proteins to achieve tumor suppression.

Keywords

autophagy; tumor suppression; signaling; active RHOA; cytokinesis; migration

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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and

Belaid A, Ndiaye PD, Cerezo M, Cailleteau L, Brest P, Klionsky DJ, Carle GF, Hofman P, Mograbi B. Autophagy and SQSTM1 on the RHOA(d) again: emerging roles of autophagy in the degradation of signaling proteins. Autophagy 2013; In press

Since its discovery in the 1950s, macro-autophagy was first thought to be a bulk, nonselective “self-eating” process to cope with starvation and other environmental challenges. In response to these emergency states, macroautophagy is dramatically upregulated to provide the supply of energy needed for cell survival. As a result, yeast and mice deficient for auto-phagosome formation rapidly die under nutrient-poor conditions. This has led to the notion that the primary function of autophagy is adaptation to starvation. In contrast, constitutive autophagy was less studied until its defects were recently shown to be involved in a growing list of common devastating human diseases including neurodegeneration, myopathies, and cancers. Emerging evidence suggests now that autophagy occurs continuously at basal levels in rich conditions and degrades selectively damaged and unneeded proteins/organelles that would otherwise accumulate during a cell’s life.

The Pandora’s box of constitutive autophagy is open: the substrates that are selectively degraded by autophagy include, as expected, organelles such as mitochondria (mitophagy), peroxisomes (pexophagy), large protein aggregates (aggrephagy), invading bacteria (xenophagy), and even portions of the nucleus and micronuclei (nucleophagy). Far from being simply a housecleaner, a pioneering study by Gao et al. provides the evidence that autophagy also negatively regulates WNT (wingless-type MMTV integration site family) signaling by degrading DVL (disheveled segment polarity protein); however, this occurs under nutrient starvation. Other fascinating observations report signaling molecules, kinases, cell-cycle regulators, and transcription factors among the autophagy substrates. However, similarly to DVL, this occurs under stressful conditions such as extracellular matrix detachment, infections, and treatment with chemotherapy drugs.

One key step in understanding the tumor suppressive function of autophagy will be to better characterize its substrates. We assume that constitutive autophagy keeps in check cell growth by degrading a signaling protein. To identify such a signaling protein, a feature of our strategy was to block the autophagy pathway, at the degradation step, within the autolysosome. For this purpose, we made a targeted disruption of the *TCIRG1/A3* subunit of the v-ATPase proton pump in order to raise the pH and thereby completely block the acidic proteases and autophagic degradation, leading to the accumulation of the substrates within the autolysosomes.

By analyzing the phenotype of the *Tcirg1*-null cells we made the surprising demonstration that autophagy controls the RHOA pathway, a pathway critical for cancer progression. As with other autophagic substrates, the active form of RHOA is a long-lived protein, whereas the inactive form has a substantially shorter half-life. Strikingly, the difference in stability stems from the fact that the inactive form of RHOA is degraded by the proteasome, whereas the active form is degraded by autophagy. By contrast to starvation-induced macroautophagy, the degradation of RHOA is a highly selective process that occurs under basal conditions and involves ubiquitination. Mechanistically, a new paradigm is emerging: we propose that there are two types of autophagy, that is, constitutive and starvation-induced autophagy, which do not fulfill the same function and target the same type of cargo for degradation. The substrates that are selectively degraded by autophagy, irrespective of their

nature—aggregates, organelles and signaling proteins—are all ubiquitinated. Ubiquitination helps recruit the autophagy adaptor SQSTM1/p62 that binds simultaneously to LC3/GABARAP on the nascent autophagosome, thereby ensuring the selective sequestration and degradation of the targeted substrates.

Perspectives, Promises, and Challenges

We are rapidly gaining insight into how autophagy is regulated by signaling pathways, and how autophagy in turn controls signaling. Such intricate interplay between autophagy and signaling allows a cell to respond appropriately to its environment. Yet, many questions remain: for instance to date, there are over 70 RHO guanine nucleotide exchange factors (RHO-GEFs) that activate RHOA, 60 RHO GTPase-activating proteins (RHO-GAPs) that inactivate it, 3 GDIs that sequester RHOA in concert with several kinases that phosphorylate it. Therefore, what are the reasons for using selective autophagy instead of transcription, or reversible GEF, GAP and phosphorylation events to modulate RHOA activity? We should keep in mind that upon activation, not all the RHOA molecules are turned on simultaneously. Instead, only a small fraction of RHOA is activated in highly dynamic zones: the midbody during cytokinesis, and the lamella during migration. In both cases, RHOA appears to be degraded by autophagy to ensure signaling efficiency—that is, restricted activation of RHOA allowing irreversible exit of mitosis and directed migration. Undoubtedly, this timely and irreversible degradation by autophagy contrasts with gradual and reversible enzymatic events (such as phosphorylation, the action of GEFs, GAPs, etc.). We therefore postulate that signal termination by autophagy, which we call “signalphagy,” achieves signaling specificity; compartmentalization and dynamic modulation. We guess that the next years are going to be as exciting as the previous with regard to our gaining further insight into the role of autophagy in regulating cellular physiology.

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