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SPOTLIGHT

Go for the Golgi: Eating selectively with Calcoco1

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Degradation by macroautophagy can be highly selective, but given the promiscuity of cargo receptors, questions remain surrounding how this selectivity is achieved. In this issue, Nthiga et al. (2021. *J. Cell Biol.* https://doi.org/10.1083/jcb.202006128) show how the adaptor Calcoco1 distinguishes cargo by how it binds.

The recycling of intracellular materials is critical to maintain cellular health, and the lysosome-mediated macroautophagy degradation pathway plays a central role in this process. Macroautophagy, one of several autophagy pathways, traffics cytosolic cargoes to the lysosome by first packaging them into a multilamellar vesicle known as the autophagosome. These can range from hundreds of nanometers to tens of microns in diameter, permitting a wide range of cargoes to be captured and delivered.

Although first hypothesized to be solely a bulk degradation pathway evoked by emergent conditions such as prolonged nutrient deprivation or nerve injury, it is now clear that macroautophagy is essential not only as a constitutive process, but also to maintain homeostasis by selective uptake of discrete cargoes in an adaptor protein–dependent manner. Modeled after the cytoplasm-to-vacuole targeting pathway in *Saccharomyces cerevisiae* (1), cargo capture relies on adaptor proteins known as autophagy receptors that work in concert to identify cargo, traffic it to the site of autophagosome biogenesis, and then scaffold it to the growing autophagosomal membrane. The adaptor proteins are often degraded in conjunction with the intended cargo, permitting what is modeled to be an exclusive form of degradation. From organelles ranging from ER to lipid droplets, to invading pathogens and proteinaceous inclusions, the breadth of cargoes identified to be degraded in this manner continues to grow.

Adaptor protein–dependent pathways are collectively known as selective macroautophagy, but the mechanism of how selectivity is achieved globally is unclear. These pathways are often studied and referred to in a cargo-specific manner by the addition of the suffix "-phagy," such as mitophagy for mitochondria and ER-phagy for ER. Although the discrete terminology offers a convenient shorthand to denote which cargo is under study, the terminology has had the unintended outcome of creating silos; the study of a specific -phagy often occurs alone. As a result, observations across multiple studies have revealed that many of the cargo receptors are not exclusive to one type of cargo but shared by many. For example, the most commonly studied adaptor protein, p62/SQSTM1, has been implicated in the turnover of a broad range of cargoes from peroxisomes, ER, and mitochondria to protein aggregates and bacteria (1, 2, 3). This is not unique to p62/SQSTM1, as Optineurin and Calcoco2/NDP52 have been shown to coordinate the turnover of not only multiple cargoes, but in some instances, the same type of cargo. Given this landscape, it muddles whether and how selective cargo capture could be achieved.

In this issue, the findings by Nthiga et al. suggest that despite the apparent promiscuity of a cargo receptor, specificity for discrete cargo can still be maintained (4). At the heart of this study, the authors identify a new -phagy, Golgiphagy, building upon the observation that nutrient deprivation leads to a lysosome-dependent reduction in resident Golgi proteins. The authors identify the adaptor protein Calcoco1, a paralogue of two previously described adaptor proteins, Calcoco2/NDP52 and Calcoco3/TAXBP1, as the autophagy receptor for turnover of the Golgi, whose degradation by macroautophagy had not yet been fully defined. Using alanine-scanning mutagenesis to determine the molecular determinants of uptake, the authors found that Calcoco1 binds to the Golgi-resident protein ZDHHC17 via a defined binding motif in its ankyrin repeat domain (zDABM). This binding then traffics Golgi fragments into the autophagosome, carrying other Golgi-resident proteins such as TMEM165 and GM130.

Although the authors implicate Calcoco1 in the turnover of Golgi, it was notable that they, as well as others, had also previously reported that this autophagy receptor is required for the turnover of ER (5, 6). These previous studies found that Calcoco1 binds to the ER tethering proteins VAPA and VAPB (5). Although the two phenylalanines (FF) in an acidic tract (FFAT) domain of Calcoco1 was suggested to mediate binding in this case, the newer observation in Golgi gave rise to the inevitable question: are these events truly specific for the cargoes as they claimed?

It turned out that although Calcoco1 is shared by two different cargoes, specificity was indeed dictated by the different binding domains within the adaptor protein. The zDABM and FFAT domains work

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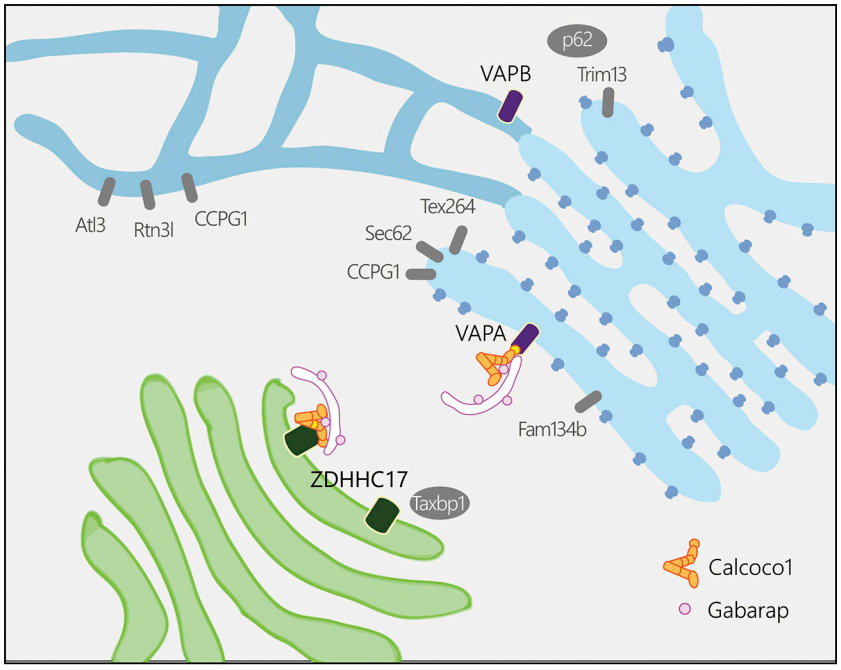

Figure 1. **Calcoco1 distinguishes cargo by binding selectively.** Schematic representation of a cell undergoing Calcoco1-mediated degradation of Golgi fragments and ER. Under conditions of stress, Calcoco1 identifies Golgi fragments through its zDABM to the resident Golgi protein ZDHHC17 or through its FFAT domain to the ER-tethering proteins VAPA or VAPB. The binding domains of Calcoco1 is schematically represented in yellow. Calcoco3/TAXBP1 can also bind ZDHHC17 and thereby may be able to help coordinate Golgiphagy, whereas FAM134B, RTN3L, CCPG1, SEC62, ATL3, and TEX264 are known players in ER-phagy that may or may not work with Calcoco1 (7). Also noted is TRIM13, which has recently been shown to engage the N-end rule and work with p62 as another potential pathway involved (11).

independently of one another; this allowed authors to separate the turnover of Golgi and ER but still demonstrate their mutual dependence on Calcoco1 (Fig. 1). Thus, by examining the fate of both cargoes in the same study, they provide an additional level of clarity that would not have been normally achieved. Calcoco1 can differentially scaffold these very different cargoes, and can do so independently.

These findings raise a subsequent question of how Calcoco1 chooses one cargo over the other. The authors may have provided a hint when they found that Calcoco3/TAXBP1 can also bind ZDHHC17 through a zDABM, although it cannot bind VAPA or VAPB as it does not contain a FFAT domain. Perhaps it is the coincidence of these two adaptor proteins that drive Golgiphagy, whereas Calcoco1 works with others (e.g., FAM134B, RTN3L) to drive ER-phagy (7). This suggests a growing model of key resident proteins recruiting multiple adaptors, the combination of which amplifies signal and promotes autophagosome building (8, 9, 10). How this signal is initiated and propagated locally may allow us to gain greater appreciation of how macroautophagy is deployed constitutively, which will offer much-needed clues as to how these pathways play a central role in health and disease. Nonetheless, by simply considering their work across different cargo, Nthiga et al. highlights the 15-yr evolution of the field, from merely identifying that macroautophagy goes beyond degradation en masse to refining our understanding of how selectivity is actually achieved.

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