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AUTOPHAGIC PUNCTUM

Developmentally regulated selective autophagy determines ER inheritance by gametes

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ABSTRACT

The endoplasmic reticulum (ER) carries out essential cellular functions ranging from protein trafficking to metabolite signaling. ER function is maintained in part by quality control pathways including ER degradation by selective autophagy (reticulophagy) during conditions of cellular stress. Reticulophagy is known to be important for cellular responses to starvation and protein folding stress, but no natural role during development had been identified. While investigating ER remodeling during the conserved cell differentiation process of meiosis in budding yeast, we unexpectedly observed developmentally regulated reticulophagy that was driven by expression of the autophagy receptor Atg40. This reticulophagy was coordinated with massive morphological rearrangement of the ER, including movement of most cortical ER away from the cell periphery. As meiotic reticulophagy prevents specific ER subpopulations from being inherited by gametes, we propose that it serves a quality control role, preventing deleterious material from being passed on to subsequent generations.

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The ER is a membrane-bound organelle tasked with diverse functions that include protein synthesis and trafficking, lipid metabolism, and calcium signaling. ER structure and function are highly adaptable and vary dramatically depending on cell type and environmental conditions. Pathways must therefore exist to shape ER structure and function in response to changing cellular conditions. One such pathway is ER degradation by reticulophagy, in which an ER-localized autophagy receptor binds to Atg8 family proteins on nascent autophagosomes, driving capture of ER fragments and subsequent targeting to the lysosome (vacuole in yeast) for degradation. Reticulophagy is triggered across diverse organisms by nutrient starvation, ER stress, and protein aggregation. While the role of reticulophagy in promoting proteostasis and cell survival during harsh stress conditions is clear, it was unknown whether reticulophagy also occurs naturally during development.

Meiosis produces specialized reproductive cells called gametes through a conserved program of cell differentiation. Gametes are a bottleneck through which new generations of life are established, and meiotic quality control mechanisms are thus crucial for ensuring gamete and organismal fitness. Despite extensive study of the mechanisms regulating meiotic chromosome segregation, little is known about organelle inheritance and quality control during gametogenesis. We set out to characterize the fate of the ER during meiosis in budding yeast and uncovered extensive ER remodeling, including the first known case of reticulophagy in a developmental context [1].

Using live-cell fluorescence microscopy, we observed dramatic and temporally regulated reorganization of the ER as cells progressed through meiosis, culminating in the collapse of most cortical ER away from the cell periphery and delivery into gametes (Figure 1). Small fragments of ER persist at the cell periphery, exempt from ER collapse due to the presence of the specific ER-plasma membrane (PM) tethering proteins Tcb1, Tcb2, Tcb3 and Ist2. These cortically retained ER fragments are physically excluded from gametes and subsequently degraded after meiosis, during gamete maturation (Figure 1).

We found that selective autophagy is also leveraged by meiotic cells to degrade a distinct subset of ER (Figure 1). Western blotting of several GFP-tagged ER proteins shows accumulation of a distinct GFP-only band as cells progress through meiosis owing to the resistance of GFP to vacuolar proteases, even as the endogenous portion of the fusion protein is degraded. Microscopy experiments show diffuse GFP signal within the vacuole in late meiosis, further confirming that reticulophagy takes place during this process. Meiotic reticulophagy is dependent on the central autophagy regulator kinase Atg1, and Atg40, a reticulophagy receptor that specifically targets tubular ER. *ATG40* mRNA and protein expression spike in late meiosis, coinciding precisely with the onset of reticulophagy. Cells arrested just prior to meiotic entry fail to express Atg40 or carry out reticulophagy, but ectopically expressing Atg40 drives robust ER degradation. Together these results show that cells are primed for reticulophagy from the onset of meiosis but withhold doing so until a later developmental stage, using Atg40 expression as a trigger.

Conditions that prevent meiotic ER collapse also show reduced reticulophagy, leading us to hypothesize that autophagy primarily acts on collapsed ER. Indeed ER-PM tethers, which are strictly retained at the cell cortex are not subject to autophagic degradation like the rest of the ER. Moreover, introduction of an

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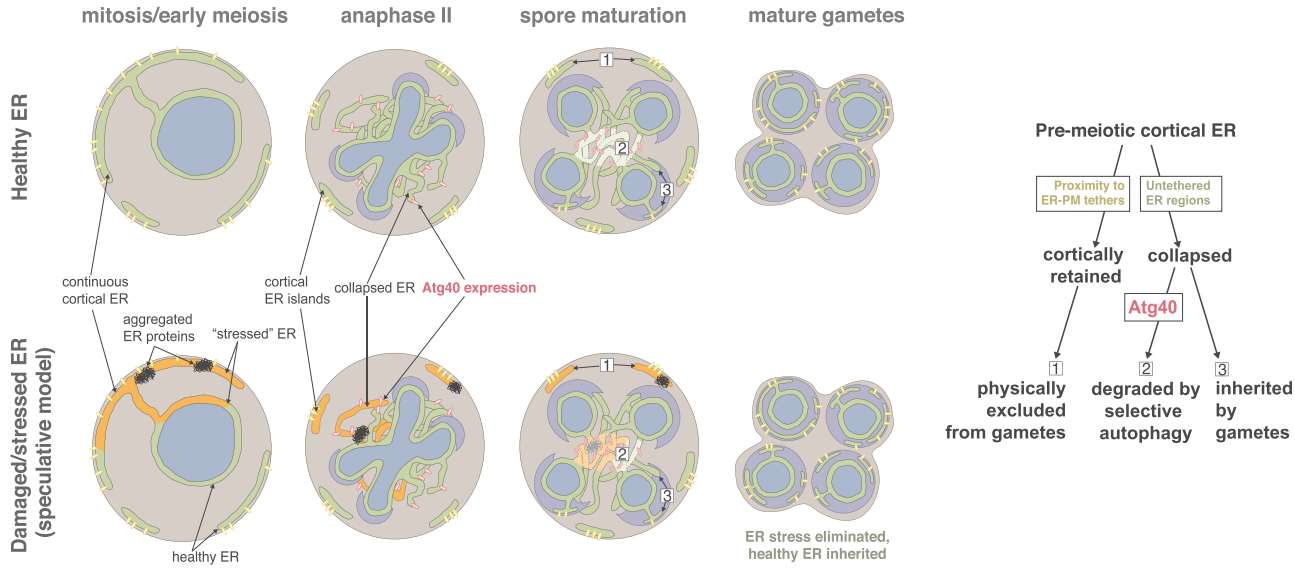

Figure 1. Model of ER inheritance and degradation during meiosis. Top: During meiosis, the cortical ER undergoes a transition from continuous to fragmented, leading to the collapse of most cortical ER. ER fragments that are closely associated with ER-plasma membrane tethers are retained at the cell cortex and excluded from gametes (1). Developmentally timed Atg40 expression mediates the degradation of a subset of collapsed ER by selective autophagy (2), and a subset of collapsed ER is inherited by gametes (3). Bottom: Speculative model for ER quality control during meiosis. We propose that markers of damaged or stressed ER, including lumenal protein aggregates, can be eliminated by selective targeting to cortically retained ER fragments (1) and/or degradation by selective autophagy (2), ensuring that only healthy ER is passed on to gametes (3). Right: Outline of three distinct ER fates during meiosis, highlighting key mediators. Figure adapted from reference 1.

artificial ER-PM tether that dramatically increases cortical ER retention and reduces ER collapse also result in reduced reticulophagy. We therefore conclude that cortical ER retention and reticulophagy are two mutually exclusive mechanisms by which cells prevent inheritance of distinct ER subsets by gametes, and that morphological ER remodeling during meiosis is integral to its regulated inheritance and degradation (Figure 1).

Our findings represent the first identified instance of developmentally programmed reticulophagy, allowing us to study how this conserved phenomenon is regulated in a natural context without use of external stressors. We found that Atg40 expression triggers reticulophagy with precise developmental timing, though what controls *ATG40* transcription remains to be determined. Identification of these putative regulators will be crucial for understanding the developmental role of reticulophagy and how it is coordinated with meiotic cellular remodeling more broadly. Nonetheless, the precise meiotic regulation of reticulophagy suggests functional importance for this process. Indeed, cells lacking Atg40 show reduced gamete formation, an effect that is exacerbated by the absence of the reticulophagy receptor Atg39, which targets nuclear and perinuclear ER. One tempting hypothesis is that reticulophagy ensures the degradation of damaged or toxic ER components during meiosis. This model (Figure 1) is analogous to recent reports that cytosolic protein aggregates and other markers of cellular senescence are sequestered in an uninherited nuclear compartment during meiosis. Together these findings suggest that extensive cellular quality control pathways act in parallel during meiosis l to eliminate harmful material and shield the next generation from accrued damage. Our findings motivate further investigation of the relationship between age, ER dysfunction, and ER quality control in meiosis.

A key question in this and other reticulophagy studies is how cargo specificity is achieved. In meiosis, cortical ER collapse produces the pool of ER eligible for reticulophagy, and we found this to be controlled by ER-PM tether proximity as well as rapid separation of retained and collapsed ER pools, which we propose is achieved by reticulon-mediated ER fragmentation. How this separation is regulated is an interesting open question. Among the pool of collapsed ER, only a subset is targeted for reticulophagy. Reticulophagy receptors like Atg40 localize to specific ER subdomains, though whether there is any additional specificity to what cargo is packaged within autophagosomes is unknown. For example, lumenal protein aggregates are degraded by Atg40-mediated reticulophagy, though it is unclear whether Atg40 targets aggregates directly through a specific recognition mechanism or indirectly through bulk ER degradation. Identifying naturally occurring reticulophagy substrates will be crucial for understanding its role in developmental quality control.

Disclosure statement

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