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Titolo	A SELECTIVE ER-PHAGY EXERTS PROCOLLAGEN QUALITY CONTROL VIA A CALNEXIN-FAM134B COMPLEX [Tesi di dottorato]
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Sommario	The endoplasmic reticulum (ER) is the largest cellular organelle adapting dynamically to cope with cellular stress and high demand of newly synthesized proteins. Protein misfolding eventually occurs in the ER and leads to protein aggregation and ER dysfunction. Mammals have developed evolutionary-conserved quality control mechanisms at the ER. ER-phagy is a novel identified pathway targeting ER portions via autophagy for lysosomal degradation. This process occurs through ER-phagy receptors, ER proteins that bind autophagosomal LC3 protein via a cytosolic LC3 interacting domain. However, the importance of ER-phagy in maintaining cellular homeostasis is still undiscovered. Moreover, the molecular mechanisms that regulate ER-phagy according to cellular needs are still largely unknown. Chondrocytes and osteoblasts are highly secretory cells with an abundant ER, producing predominantly procollagen (PC) molecules in the extracellular matrix during endochondral ossification. They reside in a poorly vascularized tissue as the growth plate with scarcity of nutrients, representing a good cellular model to study ER-phagy. We have characterized ER- phagy in PC producing cells, serving as a cellular pathway that selectively recognizes misfolded PC in the ER lumen. Specifically we found that the ER chaperone CALNEXIN acts as co-receptor that recognizes ER-

	luminal misfolded PC and interacts with the ER- phagy receptor FAM134B. In turn, FAM134B binds the autophagosome membrane-associated protein LC3 and delivers a portion of ER containing both CALNEXIN and PC to the lysosome for degradation. Moreover, we identified ER-phagy as a transcriptionally induced mechanism by induction of FAM134B expression during starvation and upon FGF signaling, a critical regulator of chondrocyte differentiation. In vivo, FAM134B knock-down in Medaka fish dampened cartilage growth and bone formation, suggesting a physiological function of ER-phagy during skeletogenesis. Taken together, these data unveil a role for FAM134B-dependent ER-phagy in maintaining cellular fitness in PC producing cells and suggest potential therapeutic approaches for the treatment of skeletal features in multiple human diseases.
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