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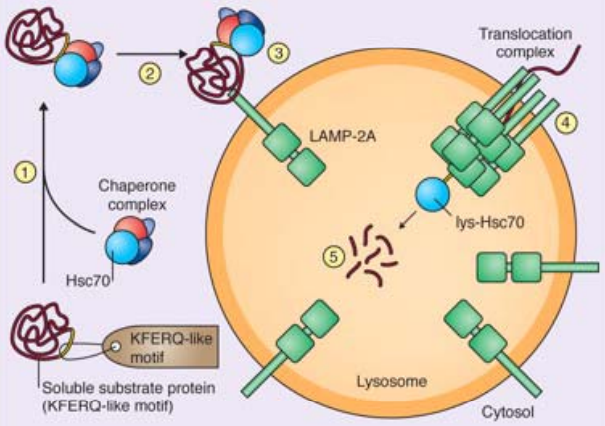
Chaperone-mediated Autophagy at a Glance

Susmita Kaushik, Urmi Bandyopadhyay, Sunandini Sridhar, Roberta Kiffin, Marta Martinez-Vicente, Maria Kon, Samantha J. Orenstein, Esther Wong and Ana Maria Cuervo

What is CMA?

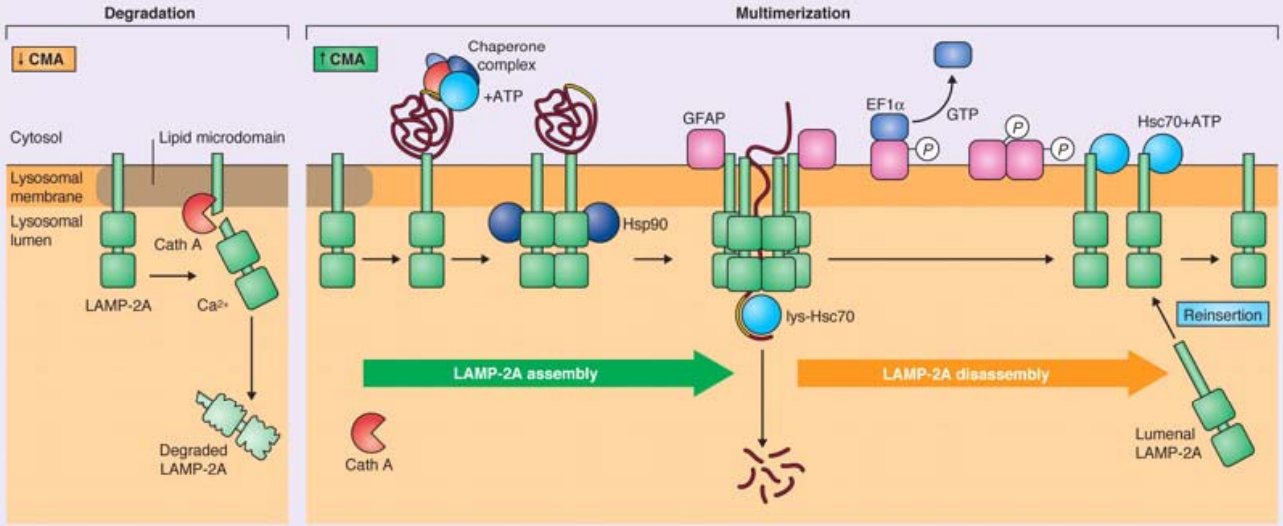


CMA is a selective form of autophagy by which single soluble proteins are directed one-by-one to lysosomes for degradation.

The steps in CMA are:

1. Binding of Hsc70 to the targeting motif in the substrate protein
2. Delivery to LAMP-2A, the CMA receptor at the lysosomal membrane
3. Unfolding of substrate protein
4. Translocation across the lysosomal membrane assisted by the lysosomal resident form of Hsc70
5. Degradation by the lysosomal proteases

Dynamics of the CMA receptor



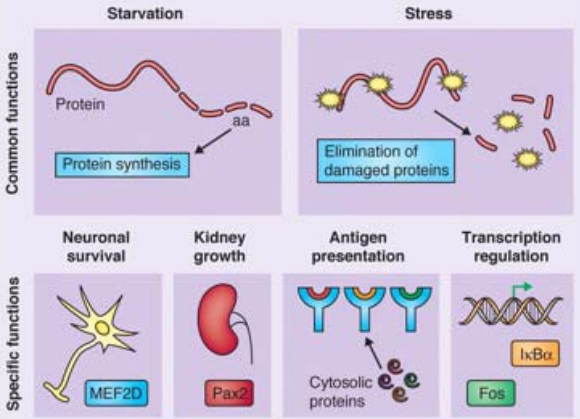
LAMP-2A at the lysosomal membrane undergoes continuous cycles of assembly and disassembly to assure substrate binding (that only occurs to monomers of LAMP-2A) and translocation (that requires the formation of a multimeric translocation complex).

Validated CMA substrates

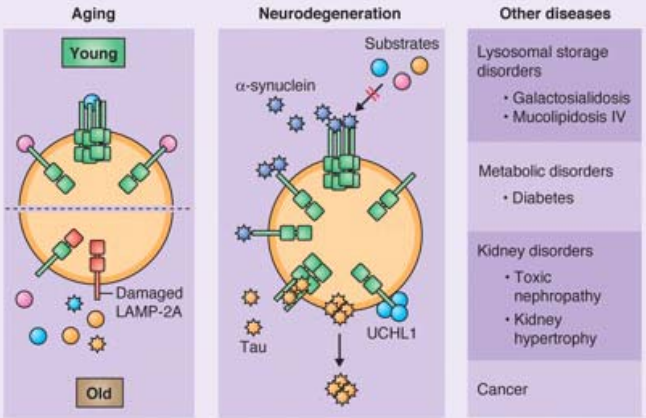
Aldolase B	GAPDH	Pax2
Annexins I, II, IV and VI	Hemoglobin (β-chain)	Phosphoglycerate mutase
Aspartate aminotransferase	Hsc70	Pyruvate kinase
Ataxin 7*	IκBα	Regulator of calcineurin 1
Fos	MEF2D	α-synuclein
C8 subunit (26S proteasome)	α2-microglobulin	Tau
Eps8	MDM2*	RNase A
Galectin 3*	Subunits of the 20S proteasome	Ubiquilin

*Association with CMA components demonstrated but degradation through CMA still pending validation

CMA: Physiology



CMA: Pathology



Abbreviations: cath A, cathepsin A; CMA, chaperone-mediated autophagy; EF1α, elongation factor 1α; Eps8, epidermal growth factor receptor kinase substrate 8; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFAP, glial fibrillary acidic protein; Hsc70, heat-shock cognate protein of 70 kDa; hsp, heat shock protein; IκBα, inhibitor of the nuclear factor κB; LAMP-2A, lysosome-associated membrane protein type 2A; lys-Hsc70, lysosomal Hsc70; MDM2, murine double minute; MEF2D, myocyte-specific enhancer factor2D; Pax2, paired box 2; RNase A, ribonuclease A; UCHL1, ubiquitin carboxyl-terminal hydrolase isozyme L1.

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