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Review

Chaperone-mediated autophagy: Molecular mechanisms and physiological relevance

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ABSTRACT

Chaperone-mediated autophagy (CMA) is a selective lysosomal pathway for the degradation of cytosolic proteins. We review in this work some of the recent findings on this pathway regarding the molecular mechanisms that contribute to substrate targeting, binding and translocation across the lysosomal membrane. We have placed particular emphasis on the critical role that changes in the lipid composition of the lysosomal membrane play in the regulation of CMA, as well as the modulatory effect of other novel CMA components. In the second part of this review, we describe the physiological relevance of CMA and its role as one of the cellular mechanisms involved in the response to stress. Changes with age in CMA activity and the contribution of failure of CMA to the phenotype of aging and to the pathogenesis of several age-related pathologies are also described.

Contents

1. Introduction: intracellular protein degradation and the lysosomal system

Maintaining a balance between protein synthesis and degradation is absolutely essential for proper cellular functioning, cellular homeostasis, and cell survival in a changing extracellular environment [1,2]. Protein degradation thus wears several hats in cells: First, as a recycling system, it mediates the breakdown of proteins that are no longer needed into constitutive amino acid components, which can then be used in the synthesis of new proteins

Abbreviations: AD, Alzheimer's disease; CMA, chaperone-mediated autophagy; HD, Huntington's disease; hsc70, heat shock cognate protein of 70 kDa; hsp, heat shock protein; LAMP, lysosome-associated membrane protein; LSD, lysosomal storage disorders; PD, Parkinson's disease.

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[1]. Second, protein degradation serves also as a quality control mechanism, ensuring that proteins damaged or incorrectly synthesized are removed from the cells by degradation, preventing thus the devastating cellular consequences associated with accumulation of malfunctioning proteins inside cells [3]. Third, recent studies have identified the important role of protein degradation in cellular defense, as it contributes to the proteolytic breakdown of components of invading pathogens and other types of biological cell aggressors [4]. Fourth, protein degradation acts as a cautious controller of cellular homeostasis, because continuous degradation of most intracellular proteins limits the amount of time a given protein is exposed to the sometimes harsh and potentially altering cellular environment, thereby offering a preventative strategy against possible protein damage and dysfunction [3]. Finally, the cellular ability to rapidly change the rate of a particular protein's degradation allows fast modulation of individual components of the proteome in response to stress or the changing extracellular millieu, making protein degradation a key player in cellular adaptation [2,4].

Two major systems, present in almost all cell types, mediate complete degradation of intracellular proteins into their constitutive amino acids. The ubiquitin–proteasome system is a multi-subunit protease complex in the cytosol which permits entry and subsequent degradation of proteins tagged with one or more covalently bound ubiquitin molecules [5]. Subunits of the regulatory complex of the proteasome recognize the ubiquitin tag, remove it, and mediate the unfolding of the substrates required to gain access to the catalytic region of the proteasome barrel. With certain exceptions, most proteasome substrates are short-half life proteins such as newly synthesized, misfolded, and critical regulatory proteins involved in cell division, signaling, and transcription [1,3,5]. Post-translational modifications such as phosphorylation or oxidation also favor degradation through this cytosolic protease.

The autophagic/lysosomal system is the other major mechanism for intracellular proteolysis [6,7]. Lysosomes are single membrane organelles dedicated to degradation of both intracellular and extracellular components. Their acidic pH and the large variety of hydrolases present in the lysosomal lumen (including proteases, lipases, glycosidases, and nucleases) mediate complete breakdown of all types of molecules and confer upon this organelle its high degradative capacity [8]. Substrates can reach lysosomes via heterophagy (including endocytosis and phagocytosis), in which the cargo to be degraded originates at the plasma membrane or extracellularly, or via autophagy, for cargo located in the cytosol, which is the main focus of this special issue of SCDB. Autophagy or "self-eating" refers to the complete degradation of intracellular macromolecules (long-lived proteins and organelles) in lysosomes. Autophagy serves a variety of important cellular purposes, many related to the functions of intracellular proteolysis described above, which include, among others, constitutive protein and organelle recycling under basal conditions, generation of essential components (amino acids, free fatty acids, sugars) during conditions of nutritional stress or starvation, tissue remodeling during development and embryogenesis, antigen presentation and pathogen destruction as part of the acquisition of innate immunity, removal of altered or damaged cellular components, and it even participates in a type of cell death and in the removal of residual apoptotic bodies [6,7].

There are three main types of autophagy in mammals. Macroautophagy (extensively reviewed in other articles of this *special issue*), involves the formation of a double-membrane structure (termed the phagophore or limiting membrane) which sequesters portions of the cytoplasm, including entire organelles and proteins, and seals to form a double-membrane vesicle or autophagosome. More than 30 gene products—generically known as autophagy-related, or Atg proteins—participate in the formation of the autophagosome, which acquires the necessary hydrolytic enzymes to degrade its cargo upon fusion with lysosomes [6]. Like macroautophagy, microautophagy also involves nonspecific engulfment of cytoplasm, although in this case via direct invaginations of the lysosomal membrane itself to form intralysosomal vesicles which "pinch off" into the lumen and are degraded there by the lysosomal hydrolases [9]. A third type of autophagy, described so far only in mammalian cells, is chaperone-mediated autophagy (CMA), which constitutes the main focus of this review.

2. Chaperone-mediated autophagy: general properties

CMA is a uniquely selective form of autophagy by which specific cytosolic proteins are transported one-by-one across the lysosomal membrane for degradation [10,11]. Unlike the other forms of autophagy, in which portions of the cytoplasm are typically engulfed in bulk (although there are specific types of micro- and macroautophagy), CMA is extremely selective for a subset of cytosolic soluble proteins, whereas this pathway cannot degrade organelles. CMA is constitutively active in many cell types, but, like macroautophagy, CMA is maximally activated under stress conditions (inducible CMA) such as nutritional stress or starvation and cellular stresses leading to protein damage [11]. Very often, both macroautophagy and CMA act in a synchronized or sequential manner. For example, during starvation, macroautophagy is first activated, and then, as starvation persists, cells switch from this bulk degradation to CMA, which mediates selective targeting of non-essential proteins for degradation to obtain the amino acids required for the synthesis of essential proteins [12,13]. The intrinsic selectivity of CMA is also well suited for the removal of proteins damaged during stress without perturbing nearby normally functioning forms of the same protein. This selectivity is achieved by making the CMA-tag accessible to the chaperone in the altered protein but inaccessible when it is properly folded. Furthermore, during stress the selective removal by CMA of endogenous inhibitors of transcription factors known to contain the KFERQ-related motif, such as IκBα and c-Fos, also favors transcriptional activation of stress-related proteins, acting thus as a modulator of the severity of the cellular response to stress.

In addition to the involvement of CMA in basal cellular homeostasis and in the stress response, this autophagic pathway also bears specialized functions such as the recently proposed participation of CMA in antigen presentation [14]. Experimental reduction of CMA activity in cultured cells compromises their viability when exposed to different stressors and it is probably responsible, at least in part, for the accumulation of damaged proteins in their cytosol, highlighting the physiological importance of this pathway. In addition, improper CMA function has been identified in several nephropathies, some neurodegenerative disorders, and certain lysosomal storage diseases, and it is also a common characteristic of most cell types and tissues in aging organisms [11].

3. Molecular dissection of CMA

The distinctive characteristic of CMA – the selectivity for the degradation of a subset of soluble cytosolic proteins – is directly determined by two factors: the presence of a recognition-targeting motif in the amino acid sequence of the substrate proteins, and the fact that proteins access the lysosomal lumen one-by-one after unfolding [10]. The cytosolic and lysosomal molecular machineries that mediate this process are organized on the basis of these important features. They include the recognition of the substrate protein, mediated by the targeting signal and the complex of cytosolic chaperones that recognize this signal, and the translocation complex at the lysosomal membrane, which takes