Autoimmunity Reviews 16 (2017) 856–874

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autophagy in neuroinflammatory diseases

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ARTICLE INFO

Article history:
Received 16 May 2017
Accepted 20 May 2017
Available online 29 May 2017

Keywords:
CMA-mediated autophagy
Neuropsychiatric lupus
Chronic inflammatory demyelinating polyradiculoneuropathy
Amyotrophic lateral sclerosis
Therapeutic peptide

ABSTRACT

Autophagy is a metabolically-central process that is crucial in diverse areas of cell physiology. It ensures a fair balance between life and death molecular and cellular flows, and any disruption in this vital intracellular pathway can have consequences leading to major diseases such as cancer, metabolic and neurodegenerative disorders, and cardiovascular and pulmonary diseases. Recent pharmacological studies have shown evidence that small molecules and peptides able to activate or inhibit autophagy might be valuable therapeutic agents by down- or up-regulating excessive or defective autophagy, or to modulate normal autophagy to allow other drugs to repair some cell alteration or destroy some cell subsets (e.g. in the case of cancer concurrent treatments). Here, we provide an overview of neuronal autophagy and of its potential implication in some inflammatory diseases of central and peripheral nervous systems. Based on our own studies centred on a peptide called P140 that targets autophagy, we highlight the validity of autophagy processes, and in particular of chaperone-mediated autophagy, as a particularly pertinent pathway for developing novel selective therapeutic approaches for treating some neuronal diseases. Our findings with the P140 peptide support a direct cross-talk between autophagy and certain central and peripheral neuronal diseases. They also illustrate the fact that autophagy alterations are not evenly distributed across all organs and tissues of the same individual, and can evolve in different stages along the disease course.

Contents

Abbreviations: Aβ, amyloid-β; Ab, antibody; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APC, antigen-presenting cell; APP, amyloid precursor protein; ATG, autophagy-related; ATG1/ULK, unc-51 like autophagy activating kinase-1; ATG6/Beclin-1, Bcl-2 interacting myosin/moesin-like coiled-coil protein-1; ATG18/WIPI, WD-repeat protein interacting with phosphoinositides; BBB, blood brain barrier; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMA, chaperone-mediated autophagy; EAE, experimental autoimmune encephalomyelitis; EAN, experimental autoimmune neuritis; ER, endoplasmic reticulum; HD, Huntington's disease; HSPA8/HSC70, heat shock 70-kDa protein 8; Htt, huntingtin; IL, interleukin; LAMP2A, lysosome-associated membrane protein 2A; lpr, lymphoproliferation; MAP1LC3B/LC3, microtubule-associated protein 1 light chain 3β; MHC, major histocompatibility complex; mHtt, mutated Htt; MRL, Murphy Roths large; mTOR, mammalian target of rapamycin; MS, multiple sclerosis; NMDAR, *N*-methyl-D-aspartate receptor; NP, neuropsychiatric; NPSLE, neuropsychiatric systemic lupus erythematosus; OS, oxidative stress; PD, Parkinson's disease; PE, phosphatidylethanolamine; PINK1/PARK6, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; PI3KC3, phosphatidylinositol triphosphate kinase complex 3; PtdIns3/PI3P, phosphatidylinositol-3-phosphate; SLE, systemic lupus erythematosus; SNCA, α-synuclein; SOD1, superoxide dismutase-1; SQSTM1/p62, sequestosome-1/ubiquitin-binding protein p62; TCR, T cell receptor; TDP-43, transactive response DNA binding protein 43 kDa; TLR, Toll-like receptor; TREM, triggering receptors expressed on myeloid cells; UPS, ubiquitin-proteasome system.

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http://dx.doi.org/10.1016/j.autrev.2017.05.015
1568-9972/

1. Introduction

1.1. Neuronal autophagy

Autophagy is a vital, finely-regulated and evolutionary-conserved intracellular pathway that continuously degrades, recycles and clears unnecessary or dysfunctional cellular components (e.g. damaged organelles, proteins abnormally folded or produced in excess) [1]. This dynamic, self-recycling process is crucial for adaptation to the environment and to maintain cell homeostasis, especially under stress conditions, such as nutrient deprivation, hypoxia, oxidative stress (OS), changes of intracellular level of Ca^{2+}. Autophagy is thus particularly involved in cellular processes, such as development, lineages differentiation [1,2], as well as in many aspects of lymphocyte development, activation and differentiation [3]. In macroautophagy, the most extensively studied form of autophagy, cellular cargo are sequestered within double-membrane vesicles called autophagosomes (Fig. 1). The latter are formed de novo upon induction of autophagy and initially appear as small membrane structures referred to as isolation membranes or phagophores. The highly conserved machinery leading to the formation of autophagosome is timely coordinated by a "battery" of autophagy-related (*ATG*) genes and regulators (Fig. 2). At an upstream stage, the latter involves mammalian target of rapamycin (mTOR) complex 1, a multiprotein complex that contains different protein partners, namely RAPTOR/KOG1 and SEC13 protein 8, the ATG1/unc-51 like autophagy activating kinase (ULK)-1 complex, the class III phosphatidylinositol triphosphate kinase (PI3KC3) complex 1, ATG9, the ATG18/WIPIs, and the ATG12-ATG5-ATG16 and microtubule-associated protein-1 light chain-3β (MAP1LC3B)/LC3-γ-aminobutyric acid receptor-associated protein conjugation systems, which reside in the isolation membrane at some stages of autophagosome formation. Subsequently, the outer membrane of the autophagosome fuses with the lysosome membrane, giving rise to autolysosomes, and the autophagosome inner membrane and autophagosome cargo are degraded by acidic lysosomal proteases and recycled (Fig. 2).

Two other major forms of autophagy co-exist along with macroautophagy (the latter is often just mentioned as "autophagy", leading sometimes to confusion in the discussions), namely microautophagy, which directly engulfs cytosolic material into lysosomes via the formation of characteristic invaginations of the lysosomal membrane [4], and chaperone-mediated autophagy (CMA; Fig. 1), which involves the recognition of substrate proteins containing a KFERQ-like motif by a HSPA8/HSC70-containing complex [5]. This pentapeptide motif, found in ~30% of cytosolic proteins, is normally buried in native proteins but can become exposed on the surface of misfolded proteins [6]. Targeted proteins recognized by HSPA8 then undergo