FEBS Letters xxx (2015) xxx–xxx

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

Autophagy and proteins involved in vesicular trafficking

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ARTICLE INFO

Article history:
Received 14 August 2015
Revised 19 September 2015
Accepted 22 September 2015
Available online xxxx

Edited by Wilhelm Just

Keywords:
Autophagy
Rab GTPase
SNAP receptor
Autophagosome biogenesis
Autophagosome–lysosome fusion

ABSTRACT

Autophagy is an intracellular degradation system that, as a basic mechanism it delivers cytoplasmic components to the lysosomes in order to maintain adequate energy levels and cellular homeostasis. This complex cellular process is activated by low cellular nutrient levels and other stress situations such as low ATP levels, the accumulation of damaged proteins or organelles, or pathogen invasion. Autophagy as a multistep process involves vesicular transport events leading to tethering and fusion of autophagic vesicles with several intracellular compartments. This review summarizes our current understanding of the autophagic pathway with emphasis in the trafficking machinery (i.e. Rabs GTPases and SNAP receptors (SNAREs)) involved in specific steps of the pathway.

1. Introduction to autophagy

Three major types of autophagy have been described in mammalian cells so far: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). These autophagic processes differ not only in terms of mechanistic and morphological characteristics but also in the factors involved. Among these types, macroautophagy (hereafter autophagy) is the most comprehensively studied and best characterized process (for a review see [1]). This evolutionarily conserved "autodigestion program" has a critical role in the maintenance of the cellular metabolism according to the cellular nutritional status. Another critical role of autophagy is the removal of dysfunctional organelles in a fast and efficient way as well as to participate actively as a defense mechanism against invading pathogens [2–5] (see Fig. 1).

Upon autophagy induction, proteins and cytoplasmic components are trapped in double membrane structures known as autophagosomes which fuse with lysosomes to generate autolysosomes. The cargoes are subsequently broken down and the generated molecules (i.e. amino acids, nucleic acids, free fatty acids, cholesterol) are recycled back to the cytoplasm to be used by the cell in anabolic reactions.

The autophagosome biogenesis can be divided into three sequential steps: phagophore formation, elongation, and sealing of the isolation membrane to generate a double membrane compartment. The phagophore is believed to originate from specialized regions of the endoplasmic reticulum (i.e. endoplasmic reticulum exit sites, ERES, [6–8]); (for a recent review see [9]) as well as from endoplasmic reticulum–mitochondria contact sites [10]. Although the origin of the phagophore membrane is still a matter of debate, a bulk of evidence indicates that the growing phagophore takes up membrane inputs from more than one source. In fact, several membrane compartments including the endoplasmic reticulum (ER), mitochondria, the Golgi apparatus and the plasma membrane

Abbreviations: AMD, age-related macular degeneration of the eye; AMPK, AMP-activated protein kinase; ATG, autophagy-related protein; CMA, chaperone-mediated autophagy; COPII, coat protein complex II; DFCP1, double FYVE domain-containing protein 1; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERES, endoplasmic reticulum exit sites; FIP200, 200 kD focal adhesion kinase family-interacting protein; FYCO1, FYVE and coiled-coil domain-containing 1; GAP, GTPase activating protein; GAS, Group A *Streptococcus*; GcAVs, GAS-containing autophagosome-like vacuoles; GDP, guanosine diphosphate; GEF, guanosine nucleotide exchange factor; GTP, guanosine triphosphate; HCV, Hepatitis C virus; HD, Huntington disease; LC3, light chain 3; LRRK1, leucine-rich repeat kinase 1; mTOR, mechanistic target of rapamycin; MVB, multivesicular body; MW, molecular weight; NS4B, non-structural protein 4B; NSF, N-ethyl-maleimide-sensitive factor; PAS, phagophore assembly site; PE, phosphatidylethanolamine; PIK3C3, class III phosphatidylinositol 3 kinase; PKA, cAMP-dependent protein kinase; PtdIns3P, phosphatidylinositol 3-phosphate; RE, recycling endosome; SNAP, soluble N-ethyl-maleimide attachment proteins; SNARE, SNAP receptor; SQSTM1, sequestosome 1; STX, Syntaxin; TRAPP, transport protein particle; ULK1, unc-51 like autophagy activating kinase 1; VPS, vacuolar protein sorting; WIPI, WD-repeat-interacting phosphoinositide proteins.

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http://dx.doi.org/10.1016/j.febslet.2015.09.021
0014-5793/

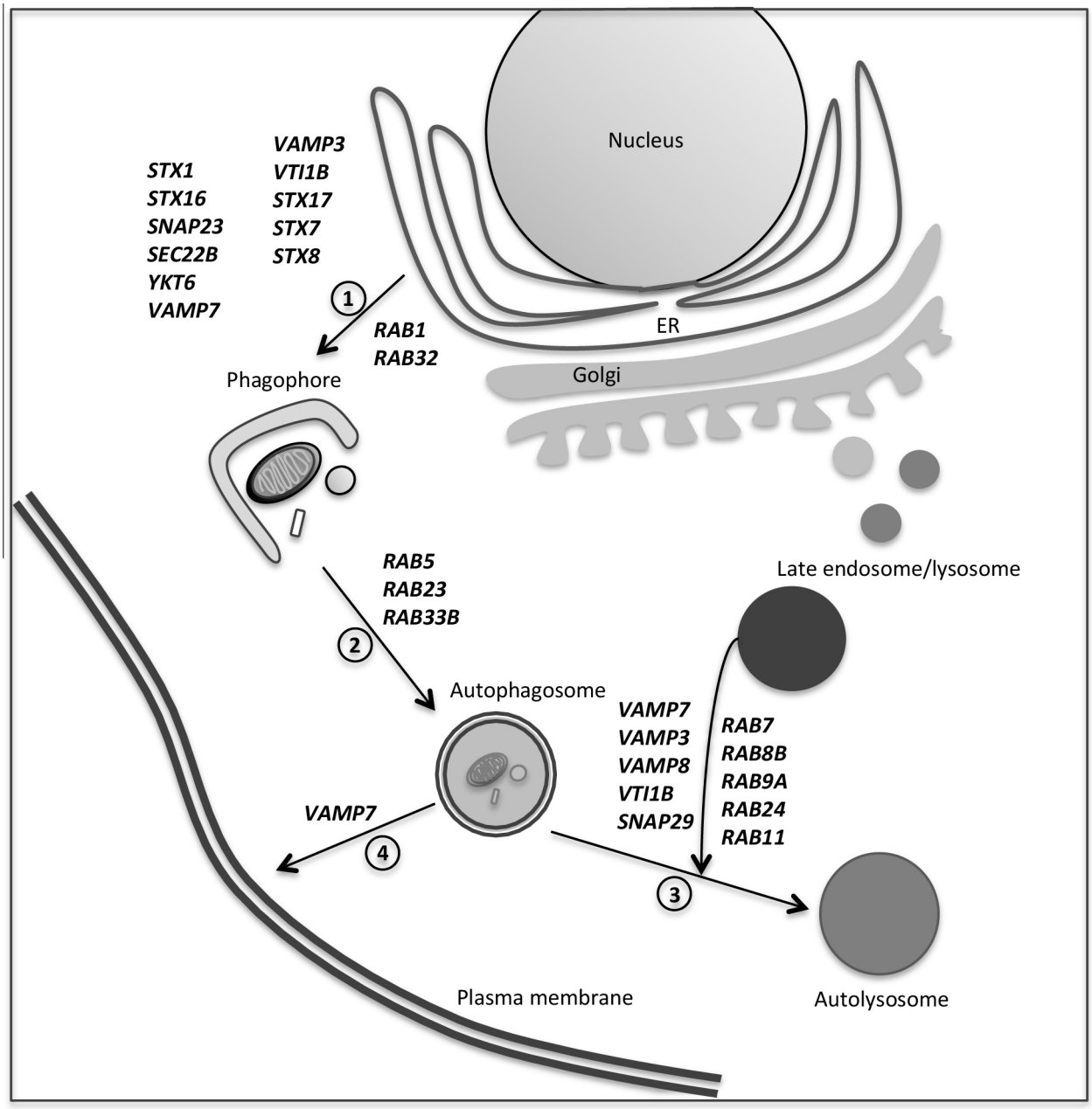

Fig. 1. Model: Regulation of autophagy by Rab GTPases and SNAREs. Participation of different proteins in the general autophagic process schematized in (1) phagophore formation from specialized regions of the endoplasmic reticulum; (2) phagophore elongation and sealing of the isolated membrane to generate a doublemembrane compartment called autophagosome; and (3) autophagosome maturation through interactions with late endosomes and lysosomes. (4) Autophagosomes may also fuse with the plasma membrane in order to release their content to the extracellular space.

seem to contribute to the formation of the phagosome (for a review see [11–14]). Subsequently, the newly formed autophagosome matures through interactions with late endosomes and lysosomes.

2. Critical core machinery involved in autophagy

As a cellular degradation process, the autophagic pathway is delicately controlled, and numerous critical factors and regulatory kinases have been identified (for a review see [1,15]). A number of factors known as ATGs (for "autophagy-related proteins") are the main components involved in autophagy [16,17]. The large majority of these proteins are conserved from yeasts to humans with many yeast orthologs having been identified in mammalian cells.

One of the initial kinase complexes involved in autophagy is the ULK1 (UNC-51-like kinase complex 1) [18], which comprises ULK1, FIP200/RB1CC1 (the 200 kD focal adhesion kinase family-interacting protein), ATG13, and ATG101. The ULK1 kinase can be modulated by signals such as amino acid starvation via mTORC1 (mechanistic target of rapamycin complex 1), which senses amino acids availability and suppresses autophagy, or by glucose deprivation/ATP depletion via the AMP-activated protein kinase (AMPK). Low levels of ATP activate AMPK which, in turn, inhibits mTORC1 through phosphorylation and activation of the TSC1/2 complex and the GTPase Rheb [19], stimulating autophagy (for a more comprehensive analysis of these signalling pathways, please see [20–22]).

Please cite this article in press as: Amaya, C., et al. Autophagy and proteins involved in vesicular trafficking. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.09.021