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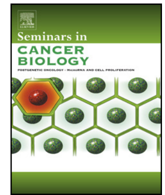

Review

Autophagy proteins regulate cell engulfment mechanisms that participate in cancer

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ABSTRACT

Recent evidence has uncovered cross-regulation of mechanisms of cell engulfment by proteins of the autophagy pathway, in what is called LC3-Associated Phagocytosis, or LAP. By LAP, lysosome fusion to phagosomes and the degradation of engulfed extracellular cargo are facilitated by autophagy proteins that lipidate LC3 onto phagosome membranes. Here we discuss the contexts where LAP is known to occur by focusing on potential roles in tumorigenesis, including predicted consequences of LAP inhibition.

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1. Introduction

To maintain cellular homeostasis, the continual turnover of macromolecules that are aged, damaged, or no longer needed, must be balanced by new macromolecular synthesis. Eukaryotic cells have adapted a variety of strategies to maintain homeostasis, including protein- and vesicle-based degradation and quality control systems [1]. One important homeostatic pathway is ‘macroautophagy’ (or commonly ‘autophagy’), that targets aged or damaged organelles, protein aggregates, or long-lived proteins for degradation and recycling [2,3]. Through autophagy, intracellular substrates are sequestered into ‘autophagosome’ vesicles that fuse with lysosomes, which harbor digestive enzymes that degrade internalized cargo. By this mechanism, the autophagy pathway allows eukaryotic cells to harness the degradative power of lysosomes to turnover bulk and long-lived intracellular substrates and recycle their building blocks for use in macromolecular synthesis. For cells experiencing nutrient starvation, autophagy also represents an important mechanism of nutrient recovery that can support cell survival by allowing for self-digestion [3].

Like intracellular substrates, extracellular substrates are also constantly turned over by eukaryotic cells through endocytic mechanisms that maintain cell signaling and metabolism, and regulate cell adhesion and plasma membrane homeostasis [4]. Bulk extracellular substrates, like dying cells and pathogenic organisms, must also be cleared and degraded in order to support metazoan development, tissue homeostasis, and immunity [5]. The turnover of these various extracellular substrates, like intracellular substrates targeted by autophagy, is controlled by lysosomes that fuse with endocytic vesicles or vacuoles to degrade and recycle internalized cargo [6,7].

While endocytosis and autophagy were once considered largely separate pathways, recent evidence has shown extensive collaboration between them in mammalian cells, including the identification of an endocytic origin for vesicles utilized for autophagosome biogenesis [8], fusion between autophagosomes and endosomes [9], and co-regulation of endocytic trafficking and autophagy by Beclin1–Vps34 protein complexes [10,11]. It was also recently discovered that autophagy proteins control the degradation of engulfed dying cells or pathogenic organisms, in an autophagosome-independent manner, by facilitating lysosome fusion to phagosomes, in what is called LC3-Associated Phagocytosis, or LAP [12]. As links between autophagy gene dysfunction and a variety of human diseases are emerging (for example Crohn’s disease is linked to mutations in Atg16L [13], neurodegeneration is associated with dysfunctional autophagy [14], and various cancers are associated with loss of function of autophagy genes [15]), it is important to consider that loss of the non-autophagy functions of autophagy proteins, including endocytic functions such as LAP, may also contribute to disease onset or progression. Here we consider several potential roles of autophagy proteins in cancer that are based on the recent discovery of the mechanism of LAP and the contexts where this process has been identified (see Fig. 1).

2. LC3-Associated Phagocytosis (LAP)

LAP was first identified by the recruitment of the autophagy protein microtubule-associated protein 1 light chain 3 (LC3) to

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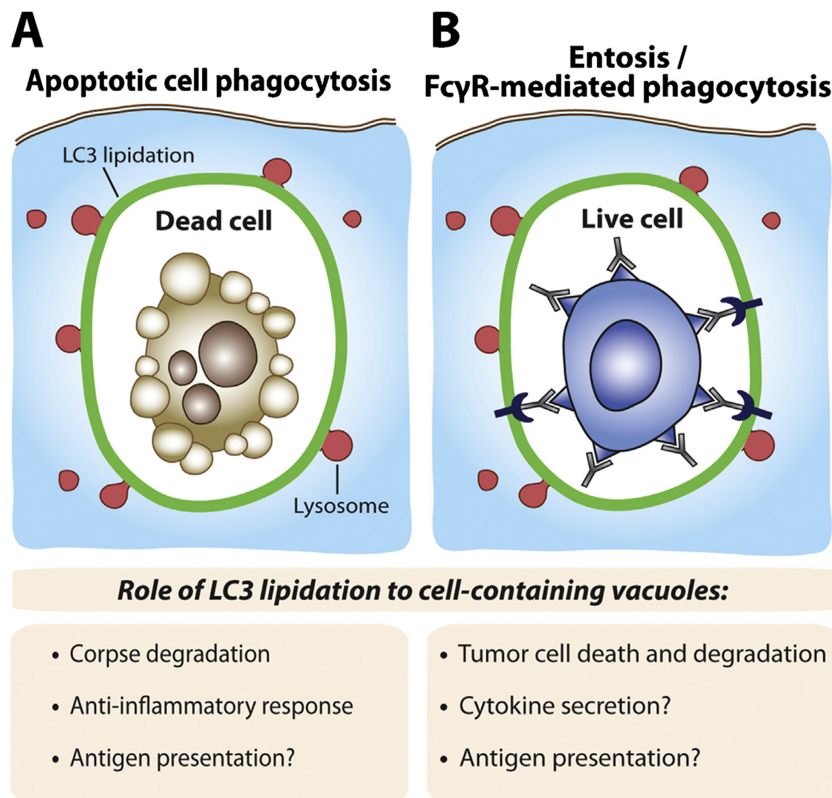

Fig. 1. Predicted consequences of LC3 lipidation to different cell containing vacuoles. (A) The lipidation of LC3 (green) to phagosomes (referred to as 'LAP') facilitates lysosome fusion (red). For phagosomes harboring dead or dying cells, LC3 lipidation allows for efficient corpses degradation, and is required for an antiinflammatory response mediated by secreted cytokines. For immunogenic forms of cell death, LC3 lipidation may also facilitate antigen presentation. (B) Vacuoles harboring viable cells engulfed by the cell cannibalism mechanism entosis also exhibit LC3 lipidation that facilitates lysosome fusion and the death of engulfed cells. FcγR-mediated phagocytosis of live tumor cells could also induce LC3 lipidation, which could facilitate tumor cell killing, modulate cytokine secretion or influence antigen presentation. A viable engulfed tumor cell with antibodies bound to its surface is depicted.

phagosomes harboring engulfed microorganisms in macrophages [12]. LC3 and its homologs are ubiquitin-like molecules that are lipidated to phosphatidylethanolamine (PE) at sites of autophagosome formation, where they control elongation of autophagosome precursor membranes, or phagophores, as well as autophagosome closure, potentially by mediating vesicle–vesicle fusion events [16,17]. LC3 proteins are conjugated to PE following a series of reactions mimicking a ubiquitination cascade, where Atg7 and Atg3 act as E1 and E2 enzymes, respectively, and the E3-like enzyme, Atg5-12:16L, is a multimeric complex involving a second ubiquitin-like molecule, Atg12. Atg12 is conjugated to Atg5 by the E1 and E2-like activities of Atg7 and Atg3, respectively, and the Atg5-12 conjugate forms a complex with Atg16L that functions as the E3 for the LC3-PE conjugation [18]. Acting upstream of these in the canonical autophagy pathway are several additional protein complexes, including two kinase complexes, one involving Beclin1 and the lipid kinase Vps34, that produces phosphatidylinositol-3-phosphate (PI(3)P) at sites of autophagosome formation, and another complex involving the Ulk1/2 kinase that is required for most forms of autophagy, potentially by facilitating the recruitment of Vps34 [18,19].

As autophagosomes form by elongation of phagophore membrane vesicles, upon closure they have a characteristic double-membrane structure that is identifiable by transmission electron microscopy [18]. While some internalized pathogenic organisms have been found enwrapped inside of double-membrane autophagosomes [20], the engulfment by macrophages of yeast, beads coated with lipopolysaccharide (LPS) or Toll-like receptor (TLR) ligands, or *Escherichia coli*, was associated with the acquisition of lipidated LC3 at phagosomes in a manner independent of the appearance of double-membranes structures, suggesting that LC3 was lipidated directly onto phagosome membranes [12]. The autophagy proteins Atg5 and Atg7 were required for LC3 lipidation onto phagosomes, phagosome acidification, and killing of live engulfed yeast, demonstrating a role for autophagy proteins in phagosome maturation and lysosome fusion that is distinct from the formation of double-membrane autophagosomes that mediate autophagy [12]. This autophagy-independent function of autophagy proteins was termed LC3-Associated Phagocytosis, or LAP [21].

Since the initial discovery of LAP occurring with agonists of TLR signaling [12], this non-canonical function of autophagy proteins has been shown to occur in a variety of contexts including the phagocytosis of apoptotic and necrotic cells [22,23], FcγR-mediated engulfment of IgG-opsonized substrates [24], macropinocytic uptake of fluid-filled vacuoles [23], and the ingestion and killing of live epithelial cells by the engulfment program 'entosis' [23]. The variety of vacuole types that are targeted by LAP-like activity suggests that this non-canonical function of autophagy lipidation machinery may be a more general mechanism to facilitate lysosome fusion in cells than originally thought [25]. Consistent with this idea, even the fusion of lysosomes to specialized plasma membrane domains in osteoclasts that are actively engaging in resorbing bone, called ruffled borders, involves LAP-like activity of autophagy proteins that appears to facilitate secretory lysosome fusion [26]. Lipidated LC3 at these membranes may promote lysosome fusion by facilitating membrane-membrane fusion directly or by recruiting other interacting proteins, such as Rab GAPs (GTPase-Activating Proteins), to the membrane [16,25,27–29]. One common feature that links these LAP-associated cell systems is their occurrence in

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