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Review

Lysosomal involvement in cell death and cancer

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ABSTRACT

Lysosomes, with their arsenal of degradative enzymes are increasingly becoming an area of interest in the field of oncology. The changes induced in this compartment upon transformation are numerous and whereas most are viewed as pro-oncogenic the same processes also render cancer cells susceptible to lysosomal death pathways. This review will provide an overview of the pro- and anti-oncogenic potential of this compartment and how these might be exploited for cancer therapy, with special focus on lysosomal death pathways.

1. Introduction

Since the discovery of lysosomes by de Duve in 1955[1] this organelle has been mainly viewed as a final destination for endocytic cargo and macromolecules destined for breakdown. This view of the lysosomes as, at best, a garbage disposal unit, and at worst, an unspecific "suicide bag" has changed dramatically due to recent discoveries that provide evidence for numerous more specific tasks for lysosomes and their contents.

As the main compartment for intracellular degradation and subsequent recycling of cellular constituents, the lysosomes receive both hetero- and autophagic cargo, which in the degradative lumen of this organelle find their final destination. The degradation is carried out by a number of acid hydrolases (phosphatases, nucleases, glycosidases, proteases, peptidases, sulfatases, lipases, etc) capable of digesting all major cellular macromolecules [2]. The best-studied lysosomal hydrolases are the cathepsin proteases which can be divided into three sub-groups according to their active site amino acid, i.e. cysteine (B, C, H, F, K, L, O, S, V, W and X/Z), aspartate (D and E) and serine (G) cathepsins [3].

Until recently the function of lysosomes and their cathepsins was thought to be limited to intralysosomal protein-turnover, and the degradation of the extracellular matrix once secreted. However, during the past few years many of the cathepsins have been accredited with more specific functions including roles in bone remodeling, antigen presentation, epidermal homeostasis, prohormone processing, maintenance of the central nervous system in mice, angiogenesis, cell death and cancer cell invasion [4–8]. Importantly, cancer cells show transformation-induced changes of the lysosomal compartment which have pro-oncogenic effects when lysosomal hydrolases participate in tumor growth, migration, invasion and angiogenesis [9] (Fig. 1). Simultaneously, however, the very same changes in the lysosomal compartment may sensitize cells to the lysosomal death pathway, hereby allowing cell death to occur even in cancer cells with multiple defects in the classical apoptosis signaling pathways [10].

This review will seek to offer a detailed view of how the pro- and anti-oncogenic potential of this degradative compartment can be exploited to the benefit of the cancer patient, with emphasis on lysosomal induced cell death.

2. Lysosomes and cancer cell death

Regulation of overall cell number as well as the amount of cells constituting the different tissues along with the need for a mechanism of eliminating unwanted cells is of fundamental importance in multicellular organisms [11]. Apoptosis is the primary means to this end, endowing the multicellular organism with the potential to rid itself of unwanted cells without the leakage of cellular constituents, thus avoiding the inflammation associated with necrosis, the conceptual counterpart to programmed cell death. A recurrent theme in the development of cancers is the development of defects in the complex pathways controlling programmed cell death [10]. Cancer cells often harbor mutations in pro-apoptotic proteins (e.g. Bax, Apaf-1 and p53) and can also rely on the overexpression of anti-apoptotic proteins (e.g. Bcl-2, Bcl-xL, Akt/PKB and inhibitors of apoptotic proteins) as a means to protect them from cell death. As such, cancer cells have a number of opportunities to block classical apoptotic pathways and interfere with efficient caspase activation [10]. Fortunately several lines of evidence suggest that although

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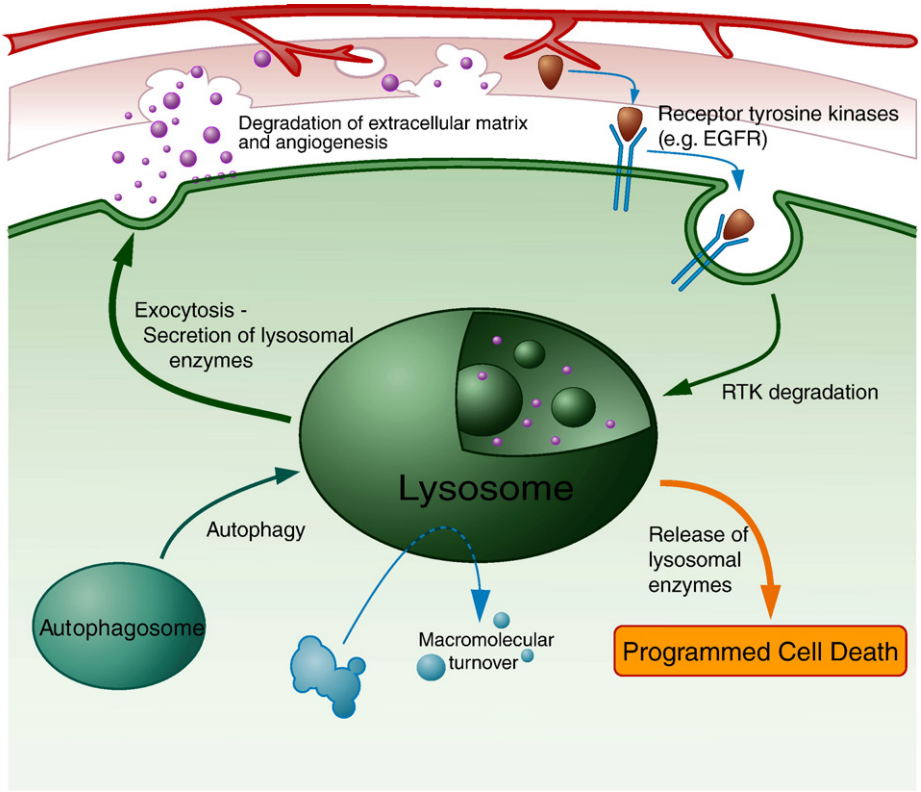

Fig. 1. Lysosomal involvement in cancer. Lysosomes and their enzymes serve multiple roles in cancer depending on the context. An example is the case of release of cysteine cathepsins; if released intracellularly they can contribute to the demise of the cancer cell; if released extracellularly they can act pro-oncogenic in breaking down the extracellular matrix, stimulating angiogenesis and migration. Other roles for lysosomes in cancer include their role as a degradative compartment in the turnover of macromolecules; downregulation of signaling from receptor tyrosine kinases as e.g. the EGFR as well as being the final station in the autophagic pathway. RTK: Receptor tyrosine kinase, EGFR: Epidermal growth factor receptor.

cancer cells may have a block in their normal apoptotic programs, cell death can still occur through the release of lysosomal enzymes. Importantly, the lysosomal cell death pathway can be efficiently triggered by many conventional chemotherapeutic regimens (Table 1 and references herein).

The appreciation of a regulated lysosomal involvement in cell death began within the past decade where the exclusive role of caspases as the executioners of cell death was challenged [12–15].

As newly developed caspase-specific pharmacological inhibitors as well as inactivation of caspase-pathways by different factors [10,16,17] did not always stop the progression towards death, they revealed, or even enhanced, a subset of underlying caspase-independent death programs. These programs include death-receptor initiated pathways [10,18,19] as well as pathways elicited by cancer drugs, growth-factor deprivation, staurosporine, Bax-related proteins and the depletion of Hsp70[16,20–22]. The morphological features of these caspase-independent death programs are often reminiscent of the ones observed for classical apoptosis, and experimental support for a role for other proteases such as cathepsins, calpains and serine proteases as essential cofactors either upstream or downstream of caspases is rapidly growing [14,23–28]. The argument is strengthened by the findings that many non-caspase proteases are able to cleave at least some of the classic caspase substrates, which might explain some of the similarities observed between the caspase-dependent and -independent death programs [14,27,29,30].

The discovery of lysosomal cell death pathways may have been additionally delayed, because the lysosomal ultrastructure appears intact in apoptotic cells analyzed by electron microscopy [31]. Thus, the lysosomal rupture has until recently been considered as an all-or-nothing switch during late stages of uncontrolled necrotic cell death and tissue autolysis [32]. However, newer studies have revealed that lysosomes with normal ultrastructure may have leaked part of their enzymes, and that partial lysosomal membrane permeabilization (LMP) not only occurs early in many death paradigms, but can in fact trigger apoptosis and apoptosis-like cell death [8,27].

Although one can argue the relevance of such lysosomal death programs, as they are masked by the efficacy of the caspases, evidence is gathering for an evolutionarily conserved role for lysosomal cathepsin proteases in cell death programs initiated as a response to various stimuli such as death receptors of the tumor necrosis factor receptor family, hypoxia, oxidative stress, osmotic stress, heat and anti-cancer drugs [15,31,33–35].

2.1. Evidence for lysosomes as cell death initiators

Evidence for the potential of lysosomes as programmed cell death initiators come from studies with various compounds that directly target the integrity of the lysosomal membranes. These have convincingly proven that moderate lysosomal permeabilization can result in programmed cell death [8,36–40]. A quantitative relationship between the amount of lysosomal rupture and the mode of cell death has been suggested to explain the widely different morphological outcomes following LMP [41]. According to this model, low stress intensities trigger a limited release of lysosomal contents to the cytoplasm followed by apoptosis or apoptosis-like cell death, while high intensity stresses lead to a generalized lysosomal rupture and rapid cellular necrosis. Accordingly, low concentrations of sphingosine, an acid ceramidase-generated metabolite of ceramide with detergent-like properties at low pH, induces partial LMP and caspase-mediated apoptosis, whereas higher concentrations result in massive LMP and caspase-independent necrotic cell death. In this model, the death triggered by partial LMP can be inhibited by pharmacological