Trends in Cell Biology

CellPress

Review

Disassembly of the Dying: Mechanisms and Functions

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The disassembly of an apoptotic cell into subcellular fragments, termed apoptotic bodies (ApoBDs), is a hallmark of apoptosis. Although the generation of ApoBDs is generally understood as being stochastic, it is becoming increasingly clear that ApoBD formation is a highly regulated process involving distinct morphological steps and molecular factors. Functionally, ApoBDs could facilitate the efficient clearance of apoptotic material by surrounding phagocytes as well as mediate the transfer of biomolecules including microRNAs and proteins between cells to aid in intercellular communications. Therefore, the formation of ApoBDs is an important process downstream from apoptotic cell death. We discuss here the mechanisms and functions of apoptotic cell disassembly.

Trends

Apoptotic cell disassembly is a highly complex process regulated by a series of well-coordinated morphological steps including apoptotic membrane blebbing, apoptotic protrusion formation, and fragmentation.

Plasma-membrane blebbing is not the sole process required for apoptotic body (ApoBD) formation, but membrane protrusions including microtubule spikes, apoptopodia, and beaded apoptopodia may act in concert to aid the generation of ApoBDs.

The mechanism of how apoptotic cells disassembly can determine the quantity and quality (size and contents) of ApoBDs.

ApoBDs can aid intercellular communication by transporting DNA, microRNAs, proteins, and infectious agents between cells.

Several clinically approved drugs can target the apoptotic cell disassembly process and may represent novel therapeutics to treat diseases associated with cell death.

Cell Disassembly as a Key Downstream Process of Apoptotic Cell Death

Billions of cells undergo apoptosis (a form of programmed cell death) daily as part of physiological homeostasis [1]. At later stages of apoptosis, some cell types can generate subcellular (1–5 μm) membrane-bound extracellular vesicles termed **apoptotic bodies** (ApoBDs, see Glossary) [1–3]. ApoBDs are the largest type of extracellular vesicle compared to microparticles (50–1000 nm) and exosomes (30–100 nm) [2,4–6] (Box 1). The formation of ApoBDs involves a series of morphological changes through a process termed apoptotic cell disassembly [1] (Figure 1). It has been well documented that a key mediator of apoptotic cell disassembly is plasma-membrane **blebbing**, a process controlled by **actomyosin contraction** [7]. The subsequent separation of plasma-membrane blebs to generate discrete ApoBDs is dependent on the formation of thin membrane protrusions [1,8,9]. Although the importance of apoptosis and the prompt removal of **apoptotic cells** in normal physiological and disease settings have been extensively studied [10,11], the function of apoptotic cell disassembly (i.e., the intermediate step between apoptosis and cell removal) is not fully defined. Nevertheless, the disassembly of apoptotic cells can facilitate efficient cell clearance [12] and mediate the transport of biomolecules between cells to aid in intercellular communication [13,14].

Because most investigators focus on the level of cell death rather than on the cell disassembly process, and because the clearance of apoptotic material by phagocytes is extremely rapid, *in vivo* evidence of ApoBD formation is limited. Nonetheless, several studies have observed the ability of apoptotic cells to disassemble into ApoBDs under *in vivo* settings, including the generation of thymocyte-derived ApoBDs [9,15] and the formation and subsequent removal of epithelial cell-derived ApoBDs in the basal epithelium [16] (Table 1). These studies support the concept that ApoBD formation can occur *in vivo* under physiological conditions and is not simply an *in vitro* phenomenon when neighbouring phagocytes and tissue architecture are absent. We review here the current mechanistic insights into the complex steps of apoptotic cell disassembly, and the significance of this process in physiological and pathological settings.

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Box 1. Comparison of the Three Major Classes of Membrane-Bound Extracellular Vesicles

Apoptotic Bodies (ApoBDs)

ApoBDs (1–5 μm) are the largest type of vesicle in the extracellular vesicle family. Their formation is regulated by the morphological steps of apoptotic cell disassembly, controlled by protein kinases such as ROCK1 [20] and MLCK [7], the membrane channel PANX1, and vesicular transport [1]. The formation of ApoBDs can promote efficient removal of cell debris by surrounding phagocytes. In addition, ApoBDs can harbour biomolecules including microRNA [13] and DNA [14] to regulate intercellular communication. Currently, the only known surface marker of ApoBDs is PtdSer [1].

Microparticles (MPs)

MPs (50–1000 nm) are generated through budding or shedding from the plasma membrane under healthy and apoptotic conditions. The release of MPs is facilitated by spectrin, calpain, and Ca^{2+} stimulation [4], and can regulate processes including coagulation, inflammation, and cell activation [5]. Therefore, MPs are often implicated in the pathogenesis of particular disease settings including thrombosis and arthritis, and are often considered to be a biomarker for diseases such as atherosclerosis [5]. Characteristic markers of MPs include PtdSer exposure, integrins, VCAMP3, and CD40 [2].

Exosomes

These are the smallest (30–100 nm) and the best-characterised vesicle in the extracellular vesicle family. Exosome biogenesis is mediated by ESCRT, Rab, and SNARE proteins [2]. When observed by electron microscopy, exosomes have a distinct cup-shaped morphology. In addition, exosomes can be characterised based on enriched protein content including ALIX, TSG101, and CD9. Owing to their density, exosomes can be purified by various centrifugation techniques. Exosomes are involved in an array of biological processes including protein secretion, antigen presentation, and viral pathogenesis [6].

Molecular Mechanisms of Apoptotic Cell Disassembly

The dismantling of an apoptotic cell into ApoBDs has been thought to be a stochastic process. However, recent studies suggest that the generation of ApoBDs is controlled by several well-coordinated morphological steps. The apoptotic cell disassembly process can be divided into three sequential steps governed by distinct morphological changes [1] (Figure 1). Step 1 describes the formation of plasma-membrane blebs on the cell surface. Particular cell types can then generate thin membrane protrusions (Step 2) including **microtubule spikes** (Step 2a), **apoptopodia** (Step 2b), and **beaded apoptopodia** (Step 2c). Lastly, the fragmentation process (Step 3) leads to the generation of individual ApoBDs.

Step 1. Apoptotic Membrane Blebbing

In healthy cells, plasma-membrane blebbing plays a key role in directed cell migration [17]. Plasma-membrane blebbing is also a morphological hallmark of apoptosis *in vitro* and *in vivo* [7,15,18]. Apoptotic membrane blebbing (Step 1) constitutes the dynamic formation and retraction of plasma-membrane blebs at the cell surface during the early stages of apoptosis and is regulated by a series of processes (Figure 2). Hydrostatic pressure within the dying cell can facilitate the movement of intracellular fluids into membrane blebs and enable bleb inflation [19]. Simultaneously, actomyosin contraction and microtubule assembly regulate cytoskeletal dynamics to aid in the cyclic extension of blebs at the cell surface [8,20]. Notably, apoptotic blebs are distinct from necrotic blebs, which are generally larger, independent of actomyosin contraction, and are generated after membrane permeabilisation [21].

Apoptotic membrane blebbing is regulated by several protein kinases, in particular the Rho-associated protein kinase 1 (ROCK1) [22]. During apoptosis, active caspase 3 proteolytically cleaves ROCK1 and triggers kinase activation by releasing its autoinhibitory C-terminal domain [20,22]. In turn, caspase-activated ROCK1 phosphorylates myosin light chain (MLC) of myosin II and promotes actomyosin contraction to facilitate membrane blebbing [20]. The importance of ROCK1 activation in apoptotic membrane blebbing has been demonstrated in a variety of cell types including fibroblasts [12,23], epithelial cells [24], and T cells [20]. In addition to ROCK1,

Glossary

Actomyosin contraction: a cellular process that describes the generation of contractile force though the interaction between filamentous actin and myosin II.

Apoptotic body (ApoBD): a subcellular (1–5 μm diameter) extracellular vesicle generated from an apoptotic cell at the final stages of apoptotic cell disassembly.

Apoptotic cell: a cell that has begun apoptosis but has not undergone apoptotic cell disassembly.

Apoptopodia: string-like membrane protrusions found on apoptotic cells.

Beaded apoptopodia: beads-on-a-string-like membrane protrusions found on apoptotic cells.

Blebbing: a cellular process that describes the formation and retraction of plasma-membrane bulges at the cell periphery.

Cell body: the largest membrane-bound portion of an apoptotic cell generated at the final stages of apoptotic cell disassembly; often contains the majority of the nuclear and cytoplasmic contents.

Early-stage membrane blebbing: the formation of small membrane blebs at the cell periphery.

'Eat-me' signals: molecular factors exposed on the surface of dying cells that could trigger their uptake by phagocytes.

'Find-me' signals: molecular factors released from dying cells that could recruit phagocytes towards the site of cell death.

Late-stage apoptotic membrane blebbing: the formation of dynamic and large membrane blebs after early-stage blebbing. Blebs at this stage often contain nuclear materials.

Microtubule spikes: rigid and microtubule-rich membrane protrusions found on apoptotic cells.

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