Apoptosis is a form of programmed cell death that occurs throughout life in essentially all tissues as part of normal development, as well as in disease settings including chronic inflammation and infection.[1-3] It is a fundamental biological process that plays a key role in eliminating unwanted and potentially harmful cells.[1-3] Apoptosis is most notably recognised by the morphological features that occur during its progression.[1][4] An apoptotic cell can undergo a series of well-defined morphological steps (as described in detail below) to facilitate the fragmentation of the cell, leading to the formation of membrane-bound vesicles called apoptotic bodies[1][4][5] (Figure 1). The process of generating apoptotic bodies during apoptosis is known as apoptotic cell disassembly.[4][5] The functional significance of this process is still not well understood. Nevertheless, the formation of apoptotic bodies has been hypothesised to mediate intercellular communication and promote efficient clearance of apoptotic cells.[2][4][6]

Upon extrinsic (receptor-activated) or intrinsic (mitochondrial-mediated) induction of apoptosis,[7] the dying cell can generate circular bulges or blebs on the cell surface, a process known as apoptotic membrane blebbing.[7] Apoptotic membrane blebbing is considered the first step (Step 1) of apoptotic cell disassembly, which may appear as small surface membrane blebs at the early stages of apoptosis, or as large dynamic membrane blebs at later stages.[4][5] The formation of large dynamic membrane blebs could facilitate the fragmentation of organelles such as the nucleus during the progression of apoptosis.[4][8] Apoptotic membrane blebbing is regulated by a number of molecular factors, in particular caspase-activated ROCK1 (rho associated coiled-coil-containing protein kinase 1).[9][10]

After apoptotic membrane blebbing, cell can undergo further morphological changes to generate a variety of thin apoptotic membrane protrusions, including microtubule spikes, apoptopodia and beaded apoptopodia.[11][12][13] The formation of these apoptotic membrane protrusions are often cell type dependent and represents the second step (Step 2) of apoptotic cell disassembly[4][5] (Figure 1). For example, microtubule spikes have been observed on apoptotic squamous epithelial cells.[11] Mechanistically, the formation of microtubule spikes is dependent on microtubule polymerisation and establishment of the microtubule network.[11] Microtubule spike formation has been proposed to facilitate the separation of membrane blebs, as well as the distribution of nuclear contents into membrane blebs.[11] More recently, another type of less rigid and string-like apoptotic membrane protrusion, known as apoptopodia (‘*feet of death*’), was identified on apoptotic T cells, thymocytes and fibroblasts.[12] Like microtubule spikes, the formation of apoptopodia can mediate the separation of membrane blebs.[12] Furthermore, apoptotic monocytes can generate another type of apoptotic membrane protrusion termed beaded apoptopodia that resembles ‘beads-on-a-string’.[13] Beaded apoptopodia formation begins with the generation and elongation of an apoptopodia-like protrusion, which then becomes segmented and appears as a sting of beads.[13] Currently, the only known molecular regulator of apoptopodia and beaded apoptopodia formation is caspase-activated PANX1 (pannexin 1) membrane channels.[12,13]

Lastly, the release of individual membrane-bound apoptotic bodies (approximately 1 to 5 microns in diameter) represents the final step (Step 3) of apoptotic cell disassembly.[4,5] Although the mechanism underpinning the final fragmentation process is not well defined, the disassociation of apoptotic bodies from different types of apoptotic membrane protrusion may require shear stress or perhaps even interaction with neighbouring cells.[4] The release of apoptotic bodies from the dying cell have been proposed to facilitate communication between cells through proteins, microRNA and DNA present on/in apoptotic bodies.[2][4][14][15] Apoptotic cell disassembly have also been proposed to aid cell clearance, as it could prove

more efficient for a phagocytic cell to engulf smaller cell fragments (i.e. apoptotic bodies) rather than an apoptotic cell as a whole.[4][6]

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