

# Extranuclear Apoptosis: The Role of the Cytoplasm in the Execution Phase

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**T**HE execution phase is the “active” phase of apoptosis occurring immediately after a cell commits to the death program. It lasts about an hour and is characterized by the hallmark morphologic features of apoptosis (e.g., membrane blebbing, chromatin condensation, and DNA fragmentation) culminating with disassembly and packaging of the cell for phagocytosis. Most studies of the execution phase have focused on elucidating nuclear events with the identification of important mechanisms responsible for nuclear execution such as the link between release of cytochrome c, activation of caspase 9/3, and DNA fragmentation (Li et al., 1997; Liu et al., 1997; Enari et al., 1998). Study of cytoplasmic or extranuclear events, on the other hand, has lagged. However, within the past two years, insights into underlying mechanisms and biochemical regulation have led to greatly increased interest in execution phase events occurring outside the nucleus.

Despite the recent interest in the extranuclear execution phase, there has been no previous review of the literature, and, at first glance, the various studies appear relatively disparate. However, by subdividing the execution phase into three sequential phases, almost all the data obtained on extranuclear execution phase events can be organized into a relatively coherent paradigm (Fig. 1). In the model we propose, the first stage is release. As most cells enter the execution phase, they release extracellular matrix (ECM)<sup>1</sup> attachments and reorganize focal adhesions (FA), adopting a more “rounded” morphology. This outward change correlates with loss of stress fibers (if present) and a reorganization of actin into a peripheral (cortical), membrane-associated ring. Microtubule disassembly also occurs in this stage. The blebbing stage begins with myosin II-dependent contraction of the actin ring followed by a period of sustained, dynamic plasma membrane protrusion and retraction. It continues until finally the cell enters the condensation stage, which is characterized by con-

densation into small apoptotic bodies or into a single, shrunken ball, correlating with dissolution of polymerized actin. This article will review advances in extranuclear execution phase events within the context of these stages. The goal of the proposed organizational scheme is not to be all-inclusive but, rather, to offer a temporal and structural framework within which nonnuclear execution phase events can be classified.

### Release (Actin Reorganization)

The first step in most cells undergoing apoptosis is to partially detach from the ECM and “round up.” The process is most dramatic in cells that are spread out, with firm matrix attachments and stress fibers, such as fibroblasts, epithelial, and endothelial cells (Brancolini et al., 1997; Levkau et al., 1998; Huot et al., 1998). The process is least pronounced in cells with weak ECM attachments, such as lymphocytes. The release stage has been partially elucidated in endothelial cells, wherein strong peripheral-lateral FA complexes disassemble with reconcentration of focal adhesion complexes ventrally underneath the newly rounded cell body (Bannerman et al., 1998; Huot et al., 1998; Levkau et al., 1998). Concomitantly, actin rearranges into a peripheral ring in preparation for blebbing. Inhibiting actin polymerization with low concentrations of cytochalasin D maintains the spread state in the face of an apoptotic stimulus, suggesting that actin rearrangement is critical (Huot et al., 1998). Anoikis (apoptosis due to ECM detachment) represents direct entry into the Release stage. In anoikic cells, FA kinase (FAK) signaling is disrupted (Frisch et al., 1996), leading to changes in a variety of key signal transduction pathways (e.g., Ilic et al., 1998).

### Key Cytoskeletal Proteins

**FA Proteins.** Intracellularly, FAK is cleaved, as are three other FA structural proteins ( $\alpha$ -actinin, talin, and p130-CAS) that link actin to focal adhesions (Wen et al., 1997; Bannerman et al., 1998; Levkau et al., 1998; van de Water et al., 1999). Paxillin, another structural FA protein, is dephosphorylated and dissociates from the FA (Bannerman et al., 1998).

**Actin Regulators.** hsp27, which mediates actin reorganization, is critical for actin rearrangement in apoptosis of endothelial cells (Huot et al., 1998). Gelsolin is also implicated in this phase based on studies with gelsolin  $-/-$  cells

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1. *Abbreviations used in this paper:* BDM, butanedione monoxime; ECM, extracellular matrix; FAK, focal adhesion kinase; MLCK, myosin light chain kinase; MT, microtubule; PAK-p21-activated kinase.

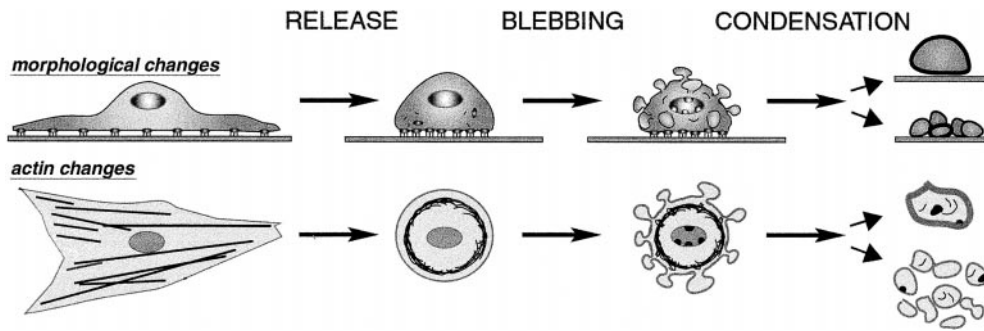


Figure 1. Scheme for temporal and mechanistic organization of the cytoplasmic execution phase. (Top) Morphological view. (Bottom) Corresponding actin rearrangements.

showing significant delay in onset of blebbing, though blebbing eventually occurs (Kothakota et al., 1997).

**Microtubules.** Microtubule (MT) disassembly occurs early in the execution phase and may be necessary for cells to round up (Mills et al., 1998a). Besides crippling intracellular transport, disassembly of MTs alters cellular compartments and releases a number of regulatory proteins that are normally bound to MTs (e.g., Reszka et al., 1997; Mills et al., 1998a; Nagata et al., 1998).

### Effectors

**Proteases.** Caspases are implicated in this phase, as many cell types do not begin morphological manifestations of the execution phase if caspases are inhibited (however, this may occur predominately in systems where signal transduction of the apoptotic stimuli requires upstream caspases). Caspases cleave FA proteins including FAK and p130CAS (Bannerman et al., 1998; Levkau et al., 1998). However, many cell types retract and/or begin blebbing despite caspase inhibition (McCarthy et al., 1997; Mills et al., 1998b; Huot et al., 1998). Calpains, which cleave  $\alpha$ -actinin, fodrin, and talin (structural proteins linking actin and the plasma membrane) are also implicated in release (Knepper-Nicolai et al., 1998; Wang et al., 1998).

**Kinases.** p38MAP kinase signaling activates hsp27 and actin reorganization (Huot et al., 1998). In anoikis, MEKK-1, an upstream regulator of p38MAP kinase, is activated by caspases and may in turn play a role in caspase-7 activation (Cardone et al., 1997); this potential positive feedback loop may explain why entry into the execution phase is apparently irreversible. The p21-activated kinase 2 (Pak2), which is activated by the small GTPases, Rac and Cdc42, and is known to reorganize the actin cytoskeleton, is cleaved into an active form by caspases (Lee et al., 1997; Rudel and Bokoch, 1997). In nondying cells, a different family member, Pak1, causes stress fiber disassembly and retraction by phosphorylating myosin light chain kinase (MLCK), and decreasing myosin activation (Sanders et al., 1999). Thus, Pak1 could be important for stress fiber disassembly and, indirectly, actin reorganization (see also below).

### Blebbing (Actin-Myosin II Contraction)

After the cell rounding up that occurs during release, the model we propose involves myosin II activation centripe-

tally contracting the cortical actin ring. At the same time, membrane-actin linkages weaken focally, resulting in bleb extrusion in areas of weakness (Fig. 2). A counterforce (perhaps myosin I or VI) retracts the blebs and the cycle repeats. Actin and myosin may concentrate at the base of blebs, and a thin rim of membrane-associated actin lines the blebs. Blebbing does not occur in some cells lacking caspase 3 (Janicke et al., 1998; Zheng et al., 1998); cells appear to release but do not bleb (Pittman, R., unpublished observations), suggesting a cellular checkpoint exists between release and blebbing.

### Key Cytoskeletal Proteins

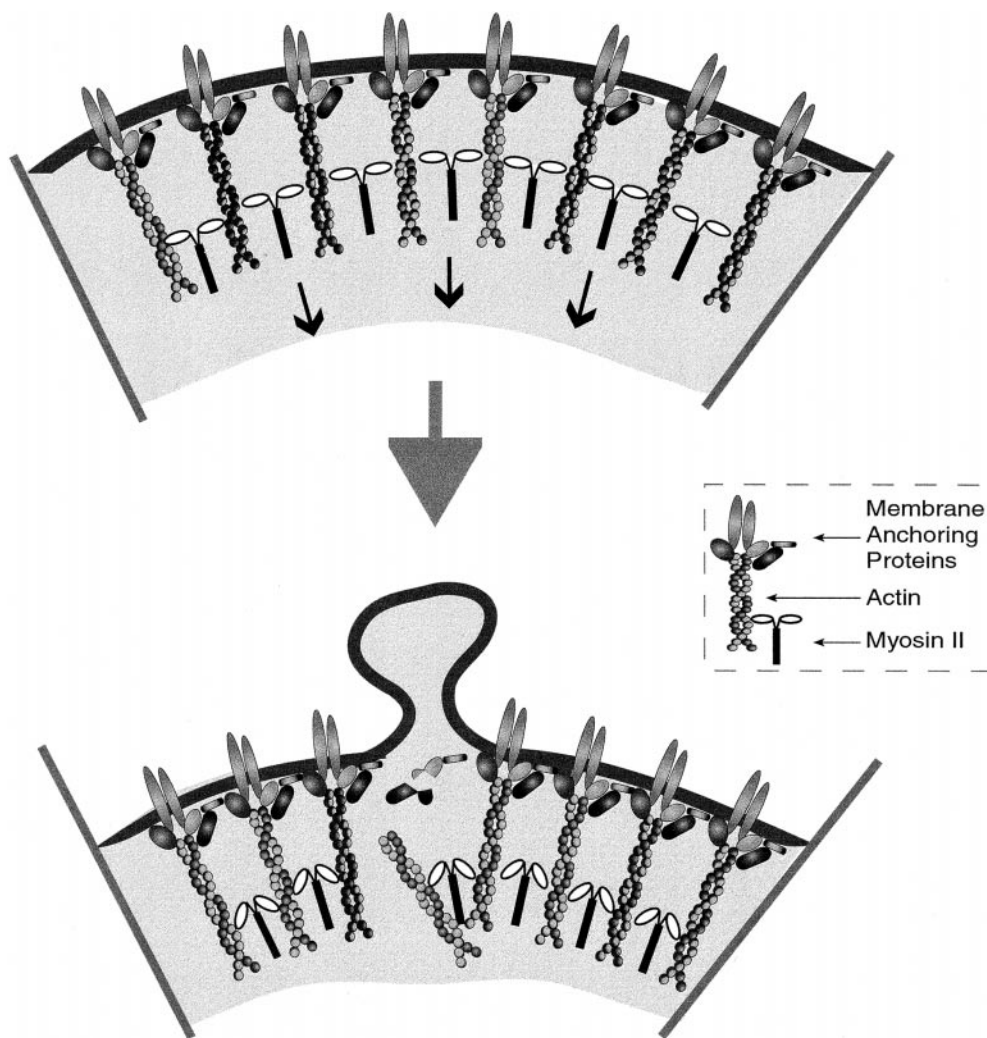
**Myosins.** Myosin II, or conventional myosin, seems to provide the force for dynamic membrane blebbing in both apoptotic and nonapoptotic systems (Mills et al., 1998b; Torgerson and McNiven, 1998). Inhibition of myosin motor activity or the myosin activators MLCK or RhoA stops bleb formation in apoptotic cells (Mills et al., 1998b). A role for nonconventional myosins is based on the fact that the general myosin motor inhibitor butanedione monoxime (BDM) inhibits bleb retraction (Mills et al., 1998b) and based on the role nonconventional myosins like myosin I and VI have in regulating protrusive membrane structures in general (for example see Mitchison and Cramer, 1996).

**Actin.** Disruption of the actin cytoskeleton with cytochalasin D decreases membrane blebbing (Mills et al., 1998b), implying that actin polymerization and/or polymerized actin are needed for force generation.

**Actin-membrane Linking Proteins.** The links these proteins provide between the actin cytoskeleton and the plasma membrane may be broken focally, allowing blebs to protrude at foci where the plasma membrane is no longer anchored to the cytoskeleton. Fodrin (nonerythrocyte spectrin) has been implicated in blebbing numerous times, as it is readily cleaved in multiple places by caspases and calpains (Martin et al., 1995; Cryns et al., 1996; Nath et al., 1996; Wang et al., 1998). The ezrin, moesin, radixin family of actin membrane-linking proteins is also dephosphorylated and dissociates from the membrane during the execution phase (Kondo et al., 1997), and ezrin can be cleaved by calpains (Knepper-Nicolai et al., 1998).

### Effectors

**Proteases.** Although caspases cleave cytoskeletal compo-



*Figure 2.* Model for bleb extrusion. Contraction of cortical actin filaments by myosin II causes contraction of plasma membrane, except in focal regions of weakness in actin links to the membrane. Such regions of weakness can be caused by cleavage of membrane-anchoring proteins (e.g., fodrin). The combination of contraction and focal loss of membrane support leads to bleb formation.

nents like fodrin and, therefore, have been implicated in this stage, many cells bleb for days with caspases apparently inhibited (McCarthy et al., 1997; Mills et al., 1998b).

**Myosin Activators.** MLCK, which activates nonmuscle myosin II by phosphorylating the regulatory light chain, is necessary for initiation and propagation of blebbing (Mills et al., 1998b; Torgerson and McNiven, 1998). RhoA has also been shown to be important for blebbing (Mills et al., 1998b), probably by activating Rho kinase, which phosphorylates and inhibits myosin phosphatase (Noda et al., 1995; Kimura et al., 1996).

**Miscellaneous.** Large amounts of ATP are required for blebbing (to maintain myosin contractility), so cellular energy generation most likely is not compromised (Nicotera and Leist, 1997; Tsujimoto, 1997).

### **Condensation (Actin Dissolution)**

All cells eventually stop blebbing. Under normal conditions, this usually happens with striking regularity after about an hour. Cessation of blebbing is followed by fragmentation into small apoptotic bodies or condensation into a small ball with actin and MTs largely disassembled

or degraded (Mills et al., 1998a). The Condensation Stage may simply represent the end result of blebbing, when contraction occurs strongly enough to pinch off apoptotic bodies. However, caspase inhibition can stop apoptotic body formation without stopping blebbing (McCarthy et al., 1997; Hirata et al., 1998). Hence, apoptotic body formation, although a direct offshoot of blebbing, must represent a distinct stage of the execution phase, immediately downstream of blebbing. There may be a cellular checkpoint between blebbing and condensation, or perhaps cells can condense only after enough cytoskeleton has been dismantled/reorganized to allow cytoplasmic dissolution.

### **Key Cytoskeletal Players**

Little is known about specific, regulatable aspects of this final active stage of apoptosis; however, F-actin seems to be required for apoptotic body formation (Cotter et al., 1992).

### **Effectors**

**Proteases.** Caspases almost certainly play a role, as inhibition of caspases leads to either no morphologic changes

during apoptosis or leads to cells trapped in a blebbing state, unable to condense (McCarthy et al., 1997; Hirata et al., 1998; Huot et al., 1998; Mills et al., 1998b). Perhaps the role of caspases in cell shrinkage events is merely to limit blebbing and induce condensation. This might happen by caspases slowly degrading proteins necessary for blebbing (e.g., actin). Other proteases might also be important (e.g., serine proteases and proteasomal proteases).

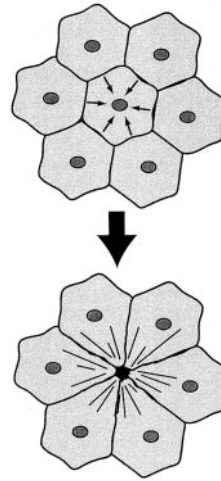
**Paks.** The p21-activated kinase Pak1 appears critical for apoptotic body formation (Rudel and Bokoch, 1997).

**Transglutaminase.** In some cells, activation of the protein cross-linking enzyme, transglutaminase, has been implicated in cytoplasmic packaging during condensation (Fesus, 1993).

### ***Roles of the Extranuclear Execution Phase***

Apoptosis is known to be a broadly conserved means of eliminating cells without damaging neighboring cells, without spreading pathogenic DNA, and without inciting an immune response. It is during the execution phase that these evolutionary directives are carried out. However, it is not yet understood exactly which events in the execution phase correlate with the evolutionarily driven functions of apoptosis. For example, although blebbing is an almost universal feature of apoptosis, it is not clear why cells bleb. Perhaps, cytoplasmic blebs represent a mechanostuctural communication to neighboring cells to begin the process of phagocytosis, or maybe membrane blebbing functions within the dying cell to deplete ATP, to mix compartments as part of cellular packaging, or as a prerequisite for apoptotic body formation. In any case, the release, retraction, and condensation stages culminate with the creation of a smaller cell or cell fragments for facilitated phagocytic clearance. For cells that maintain strong cell-cell contacts (such as epithelial or endothelial cells), the cytoplasmic execution phase machinery may be very important for another reason. The contraction of an apoptotic cell may be an altruistic means of preserving an intact monolayer, as the dying cell expends its energy contracting neighboring cells to cover the potential gap that would be created by the dying cell (Fig. 3). In epithelial monolayers the execution phase of a cell results in stretching of neighboring cells toward the dying cell (Nagai and Kalnins, 1996; Soler et al., 1996). Stress fibers form in the neighbors, suggesting that they are being pulled rather than locomoting themselves. The dying cell likely generates force by the same mechanism underlying membrane blebbing (actin-myosin contractions); therefore, inhibiting blebbing and/or condensation phases should decrease barrier function in epithelia.

In conclusion, from the standpoint of the organism, the most important aspect of apoptosis is that death occurs without the release of potentially pathogenic or harmful macromolecules and without inflammation or injury to neighboring cells. A primary role of the execution phase is to insure that the dying cell is packaged to avoid these potentially devastating sequelae. The past two years have been marked by considerable increase in basic information on mechanisms underlying the extranuclear execution phase. While it is still too early to generate a precise model or scheme of this critical aspect of apoptosis, it is possible



**Figure 3.** Possible altruistic role of apoptosis in epithelial cells. The same actomyosin contractile forces that cause blebbing can pull neighboring cells to cover potential gaps in the monolayer and maintain barrier function.

to organize most of the results as they pertain to three distinct stages: release, blebbing, and condensation. It is becoming clear that these stages represent specific, inhibitable underlying processes with evolutionarily important roles. Given the recent flurry of information, it appears that research on the extranuclear execution phase is now primed to advance our fundamental understanding of apoptosis into uncharted areas. Besides the obvious impact of this area of work for understanding the apoptotic process, an additional benefit of investigation into cytoplasmic execution should be a better understanding of the cytoskeleton in general with potential novel roles for microtubules, actin, and myosin.

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