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Editorial

Does cytoskeleton 'Akt' in apoptosis?

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This issue of *Cell Death and Differentiation* contains three reviews dedicated to the role of the cytoskeleton in cell death. Since the beginning it has been obvious that the dramatic alteration in cell shape observed in apoptotic cells was dictated by the deep remodelling of the protein filaments system, but only recently accumulating evidence has shed some light on the molecular mechanisms of this event.

Cells deprived of attachment to their extracellular matrix (ECM) substrate undergo apoptosis *in vitro*.[1,2] This process, known as anoikis, can be attributed to the lack of ECM binding, resulting in the inhibition of integrin survival signalling.[3] Apoptosis can also be induced by promoting cell retraction and rounding in epithelial cells that remain adherent to ECM.[4] In the last few years many studies trying to unravel the molecular mechanisms involved in adhesion-dependent survival have been carried out, but still little is known about the molecular pathway(s) that transduces a structural signal, such as that associated with cell rounding or retraction, into an apoptotic response. Cell shape is governed by the cytoskeleton, which acts as the mechanical supporting framework[5,6] providing the basis for most of the cell's signal transduction machinery.[7] Alteration of mechanical coupling between microtubules and actin microfilaments has been shown to play a key role in cell shape stability as well as control of proliferation in adherent cells. However, it is not yet clear whether cytoskeletal components contribute to shape-dependent apoptotic control and how they couple to relevant biochemical transduction pathways.

The 'active' phase of apoptosis, occurring immediately after the cell commits to death, is characterized by major morphological changes such as contraction, dynamic membrane blebbing and chromatin condensation, and culminates with the disassembling and packaging of the cell for phagocytosis. On the basis of these mechanics, the execution of apoptosis can be divided into three sequential sub-phases: release, blebbing and condensation. The release phase is characterized by cell rounding and contraction, dependent upon focal adhesion protein cleavage and rearrangement of actin into a peripheral ring. Key regulators of these processes have been identified in caspases, calpains and kinases. During blebbing, contractile forces are generated by myosin activation, operated by the Rho GTPase pathway (reviewed by Coleman this issue), while dissociation of actin from its membrane linking proteins takes place as a consequence of caspase/calpain activation. The last condensation step of the execution phase leads to the formation of apoptotic bodies, in which the cell is packed in smaller units in order to facilitate phagocytic clearance. The action of caspases, Paks kinases and transglutaminase-dependent protein cross-linking seems to play a role in the process.

Although the profound alterations to the cytoskeletal network suggest an important role for the reorganization/disorganization processes, it is not yet clear if these changes are primarily a result of the activation of various enzymes and signalling molecules or whether the reorganization is an essential step for the accomplishment of the death program. One potential candidate signal-transducing molecule that may be involved in this form of apoptotic control is the serine threonine kinase, Akt/PKB, which is known to regulate adhesion-dependent survival in epithelial cells.[8,9] Akt has been implicated in several cytoskeleton-mediated processes, including regulation of actin reorganization[10] and signalling by the cytoskeleton-plasma membrane linker PTEN, a protein with homology to the cytoskeletal protein tensin which is also able to promote apoptosis.[11] Phosphorylated Akt can down-regulate apoptotic factors and up-regulate various survival factors.[12,13] In line with this hypothesis, Bcl-2 family members can protect against apoptosis conferred by integrins[2,14,15] and the inactivation of Bcl-2 by phosphorylation appears to mediate apoptosis induced by microtubule disruption.[16] Moreover, the kinase cascade responsible for the cytoskeletal reorganization as well as the reorganization itself could also have an impact on the regulation of the pro-apoptotic activity of BH3-only proteins. Akt/PKB dependent phosphorylation is responsible for the sequestration of Bad to the cytoplasm by binding to 14-3-3 scaffold proteins, resulting in inhibition of its pro-apoptotic activity.[17,18] On the other hand, Bim and Bmf are normally expressed in healthy cells and inactivated by binding to cytoskeletal structures such as dynein and myosin V motor complexes, respectively.[19,20]

An obscure aspect of the role of the cytoskeleton in apoptosis is the way in which the different cytoskeletal components might mediate individual aspects of the cell shape changes occurring during apoptosis *in vivo*. It is also important to clarify the role of the cytoskeleton in cell death occurring in non-adherent cells such as lymphocytes and neutrophyls. Finally, an aspect that remains to be addressed is why cells bleb. It has been proposed that this could be a mechanostructural communication between neighbouring cells to initiate phagocytosis.

The three reviews contained in this issue overview these aspects of the apoptotic program with a particular focus on the role played by keratins and intermediate filaments in death receptor induced apoptosis, the regulation/activation of the signalling pathways dependent upon Rho GTPase

and both transcriptional and post-translational regulation of BH3-only protein activity. In line with the traditions of Cell Death and Differentiation we hope that these reviews will be of interest for the readership of our Journal and more important will generate further research in this interesting aspect of cell death.

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