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Apoptosis and Cell Signalling: Overview

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Introduction

Apoptosis is one of the modes of Programmed Cell Death, a physiological process that eliminates unwanted cells from the body. Programmed Cell death can be classified as: apoptosis, necroptosis, pyroptosis, etc. The term Programmed Cell Death was given by Lockshin in 1965 while observing intersegmental muscle degeneration in the abdomen of a silkworm during metamorphosis. However, apoptosis was first observed by John Kerr while studying hepatocytes; he observed that, apart from necrotic cells, other cells were undergoing shrinkage and phagocytosed without any inflammatory response. Later on, John Kerr, Willie and Curie gave the term Apoptosis, a Greek word where "apo" means "separation" and ptosis means "falling off"; it generally refers to "falling off leaves from trees". During apoptosis, cells undergo peculiar morphological changes; prominent morphological changes seen are: decrease in cell volume due to loss of water and electrolytes, membrane blebbing due to breakdown of the cytoskeleton causing the plasma membrane to bulge, pyknosis and karyorrhexis. These changes are brought out by various proteins involved in the apoptosis signalling pathway, most of which are present in the cytosol and mitochondria. The two most important families are Caspases and Bcl-2 family member proteins (Table1). Caspases are cysteine proteases that cleave after aspartate amino acids and can further be classified as initiator and executioner caspases. CED-3 gene in C. *elegans* and CASP in mammals are responsible for the expression of these proteins.

Proteins	Function
Caspases (protease)	
Initiator caspases (caspase 8,9)	Cleave and activate Effector caspases (caspase 3, 6)
Bcl2 family members	
Antiapoptotic	Regulate the release of Cytochrome c
Proapoptotic	Cytochrome c release

Table1: Major proteins involved in apoptosis

Most executioner caspases exist as zymogen procaspases; upon cleavage, they are converted into active heterotetramers $(p20)_2(p10)_2$ and release the prodomain. Two heterodimers fit together, forming beta sheets sandwiched by alpha helices; during maturation, the intersubunit linker is cleaved, resulting in cross-protomer interaction in active site loops. Whereas most initiator caspases dimerise to form active caspases. Caspases target nuclear lamins, resulting in fragmentation of the nucleus; cytoskeletal proteins (tubulin, myosin, actin), resulting in cytoskeletal disruption, cell fragmentation, and membrane blebbing; inhibit Inhibitor of caspase-activated DNAase (ICAD), resulting in DNA fragmentation; transfer phosphatidylserine to the cell membrane outer leaflet via scramblase, which acts as a signal for apoptosis.

Bcl-2 proteins are characterised by regions of specific sequence homology termed Bcl-2 homology domains, critical for their function. These apoptotic proteins are involved in different apoptotic pathways.

Major apoptotic pathways:

Intrinsic pathway: Internal stressor (DNA damage) activates the Bcl-2 homology domain sensor protein, which activates the genes PUMA and NOXA to inhibit antiapoptotic Bcl-2 proteins, resulting in oligomerisation and activation of BAX and BAK proteins, which form the Mitochondrial Outer Membrane Permeabilisation (MOMP) complex. MOMP causes release of cytochrome c and Second Mitochondrial Activator of Caspases (SMAC); cytochrome c forms a complex with Apoptotic Protease Activating Factor (APAF-1) and Procaspase 9 (gets activated on dimerisation), triggering activation of the caspase cascade: active caspase 9 heterodimer cleaves and activates caspase3 and caspase7, whereas SMAC inhibits X-linked Inhibitor of Apoptosis Protein (XIAP) to further activate caspase 3 and caspase7 and hence cell apoptosis.

Extrinsic pathway: Ligand get attached to trimeric death receptor (eg., TRAIL with TRAIL-R); Fas-Associated Death Domain (FADD) is recruited to the death receptor via homotypic death domain interaction; FADD recruits procaspase 8 through interaction of their respective death effector domains, forming DISC; procaspase dimerises and is activated to release active caspase 8. Caspase 8 in type I cells activates caspase 3 and 7 by cleavage, whereas in type II cells caspase 8 mediates cleavage of BID, activating tBID, which translocates to mitochondria to induce BAX and BAK-mediated mitochondrial outer membrane permeability transition pore complex. MOMP effectively represents the point of no return and is highly regulated by Bcl-2 member proteins.

Major research interventions: Different studies focus on expression profiles of apoptotic proteins, the effects of antioxidants and other chemical substances on cell apoptosis, determining the anti-apoptotic effects of substances, and understanding the pathogenic pathways of different causative agents. Imbalance between cell survival mechanisms and programmed cell death, due to pathogens and environmental factors, may lead to systemic diseases. Mapping target pathways unlocks therapeutic intervention using bioactive/ antioxidant compounds.

Thermal stress due to rising global temperatures acts as a catalyst for cell death. Prolonged exposure of Indian Gir Cattle to high temperatures leads to thermal apoptosis and hence reduced peripheral blood mononuclear cells (Onasanya *et al*., 2025). Similarly, thermal stress in bovine oocytes alters the expression profile of pro- apoptotic and anti-apoptotic genes, suppressing growth competence (Ahmed *et al*., 2019). Further, it has been seen that genetic equilibrium between pro- apoptotic genes BAX and anti-apoptotic genes BCL-2 remains strictly coupled to the lactation cycle of high-producing animals like Deoni and Holstein Friesian (Raj *et al*., 2023).

Besides climate change, chemicals and toxins also affect the apoptotic pathway and hence animal health. Aflatoxin B1 in goats generate free radicals, which act through the intrinsic pathway of apoptosis, resulting in non-hepatic neuroaflatoxicosis (Sahoo *et al*., 2024). Chemicals like phthalates and organophosphate pesticides, such as triazophos, induce testicular toxicity in rodents by acting on the apoptotic pathway (Suhas *et al*., 2024; Baker *et al*., 2025).

Pathogens can hijack cell death pathways: Rous sarcoma virus alters the expression profile of apoptotic genes and chemokines within the tumour and thus promotes cell survival (Khare *et al*., 2022). *Pasteurella multocida* in mammals hijacks the FAK-AKT-FOXO1 signalling axis, resulting in cytokine storm, bacteremia, and activation of host cell apoptosis (Zhao *et al*., 2014). *Ehrlichia canis* similarly triggers immune system activation coupled with ER stress-mediated apoptosis (Yanar et al., 2026).

Apoptotic machinery can also be used against a disease: the oncolytic capability of canine distemper virus induces apoptosis in cervical tumour-derived cell lines (Det Puerto *et al*., 2011). Curcumin-induced stress in Theileria *annulata-transformed* bovine leukocytes triggers apoptosis and autophagy,

reversing the parasite-induced malignancy (Araveti & Srivastava, 1867).

Summary and Future Perspective: Whether defending livestock from heat stress or toxic chemicals, generating compounds to destroy tumours, mastering the language of apoptosis remains a cornerstone of modern veterinary science. Apoptosis provides a critical point for cell survival and turnover. The future lies in the development of specific molecular therapies and circulating biomarker identification for precision targeting of diseases like cancer and viral infection in domestic animals.

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