FURTHER THAN APOPTOSIS

CELLULAR DEATH AND ITS RELATION WITH CARCINOGENIC PROCESSES

Xènia Oliver[1]

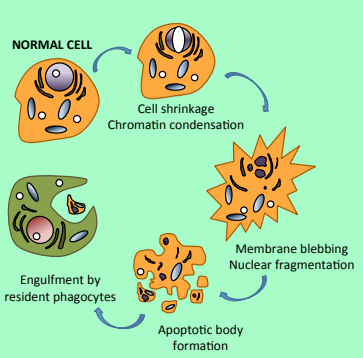
[1] Facultat de Biociències, Universitat Autònoma de Barcelona. 08193 Bellaterra, Catalunya, Spain.

INTRODUCTION

Cellular death is essential for embryonic development, tissue homeostasis, cellular stress and immunitary system regulation of multicellular organisms. Defects on these cellular death pathways lead to different pathologies, amongst which we shall highlight immortalization and tumorigenesis. In recent years, cellular death research has been basically focused on apoptosis, in which one cell takes the decision to die in response to certain signals and using the intrinsic cellular machinery. However, the elucidation of additional non-apoptotic, programmed cell death pathways is gradually opening new ways to explain many physiologic processes which were unknown.

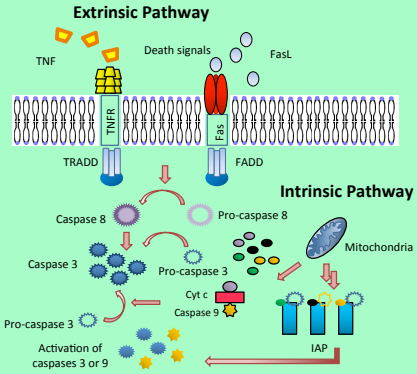
In this project six different programmed cellular deaths have been studied in a molecular and morphologic basis. The understanding of death programs, may open new ways in treating carcinogenic processes.

APOPTOSIS



Morphological features concerning apoptotic processes

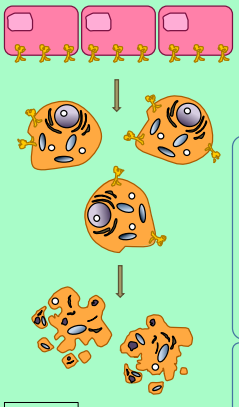
The decision to perform apoptosis comes from the cell itself, from the surrounding tissue, or from cells derived from the immune system.



Apoptotic pathways

Extrinsic pathway: Induced by pro-apoptotic cytokines which activate the initiator caspases with the subsequent activation of effector caspases.
Intrinsic pathway: Certain stimuli evoke the mitochondrial membrane permeabilization, through which the intermembrane space proteins (such as cit c) are released to the cytosol and initiate the caspase cascade.

ANOIKIS



Loss of integrin adhesion and attachement

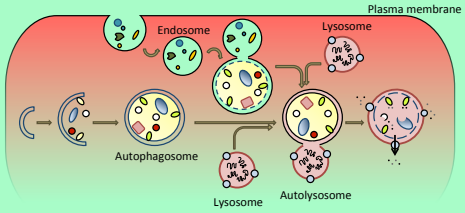
THE IMPORTANCE OF CELL TO CELL ATTACHEMENT

Cells only grow and differentiate in the correct context and eliminate themselves when they are not.

Apoptosis induced by loss of adhesion and attachment of cells to the matrix is named anoikis.

Anoikis has been proposed to be regulated both by intrinsic and extrinsic apoptosis pathways

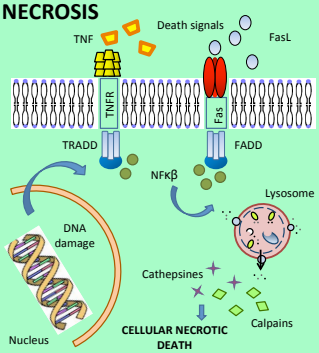
AUTOPHAGY



Autophagy as an evolutionarily conserved intracellular catabolic mechanism

Autophagy mediates the degradation of cytoplasmic components, thus allowing the turnover of the different cellular components.
Under normal conditions, autophagy plays an important role in maintaining intracellular homeostasis. Under nutrient deprivation, cell survival is promoted by degrading disposable intracellular contents, thereby generating energy .

NECROSIS

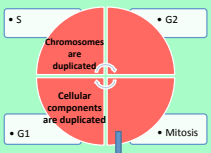


Two protein families play a main role in the process. These are calpains and cathepsines, which become activated in lysosomic acid medium, and are released to the cytosol when lysosomes lose their integrity.

Cellular processes involved in necrosis

Mitochondrial uncoupling, nuclear changes, production of reactive oxygen species, lipid degradation, permeabilization of lysosomal membrane and increases in the cytosolic concentration of calcium

MITOTIC DEATH



Mitotic Arrest may be undergone by two main mechanisms

MULTIPOLAR MITOSIS
Aberrant duplication of chromosomes which have not been uniformly distributed within nuclei of new cells.
formation of micronuclei.

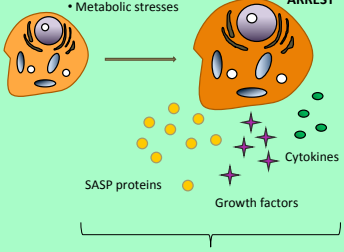
POLYNUCLEATED MITOSIS
DNA damage, incorrect chromatin compaction or incorrect chromosome alignment.
Premature mitosis.
Presence of two or more nuclei of heterogeneous or similar size.

MITOTIC CELLULAR DEATH
(depending on the stimuli)

APOPTOSIS NECROSIS SENESCENCE

SENESCENCE

Senescence stimuli
- Telomere erosion
- Lack of telomerase enzyme
- Persistent DNA damage
- Strong mitogenic signals
- Metabolic stresses



In addition to suppressing tumorigenesis, cellular senescence might also promote tissue repair and fuel inflammation associated with aging and cancer progression. Depending on which molecule (or cytokines, proteases, SASP proteins…) act, senescence may participate in different biological processes (tumor suppression, tumor promotion, aging, and tissue repair).

CONCLUSION

When we talk about cellular death we must not only think about apoptosis, since many processes imply other types of death. The changing perception of regulated cell death as an array of diverse responses is crucial for the understanding of many physiological and pathological conditions and provides novel opportunities for cytoprotective therapies. Thus, studying the molecular networks underlying tumorigenesis and cellular escape from programmed cell death (spontaneous or induced) is prerequisite to develop new approaches to effective cancer treatment.

Most relevant references

1. Blank M, Shiloh Y. Programs for Cell Death. Landes Bioscience: Cell Cycle. 2007 March 15;6(6):686-695. **2.** Degterev A, Yuan J. Expansion and evolution of cell death programmes. Nature Publishing Group. 2008 May;9: 378-390. **3.** Martinou JC, Youle R. Mitochondria in Apoptosis: Bcl-2 family Members and Mitochondrial Dynamics. NIH Author Manuscript. 2011 July 19; 21(1):92-101. **4.** Johnson D. Cell Death Signalling in Cancer Biology and Treatment. 2013 edition. London. USA; November 2012. **5.** Gordy C, Wen He Y. The crosstalk between autophagy and apoptosis: where does this lead?. Protein & Cell. 2012;3(1):17-27.