

Preface

Programmed cell death is a fascinating process common to all multicellular organisms. Programmed cell death results in the elimination of cells via a complex but a highly defined programme. Defects in the regulation of programmed cell death are associated with serious diseases such as cancer, autoimmunity, AIDS, and neurodegeneration.

Apoptosis has been the best studied type of programmed cell death so far. Cells that undergo apoptosis are characterized by chromatin condensation, nuclear fragmentation, membrane blebbing, cell shrinkage, and formation of apoptotic bodies.

The central role in apoptosis execution belongs to cysteine-specific aspartate proteases (caspases). Caspases are enzymes that orchestrate apoptosis via cleavage of cellular substrates.

There are two major pathways of apoptosis: intrinsic and extrinsic. The intrinsic pathway is triggered via chemotherapeutic drugs, irradiation, and growth factor withdrawal. These stimuli lead to mitochondrial outer membrane permeabilization (MOMP), which results in cytochrome *C* release and caspase activation. In the extrinsic apoptotic pathway, the caspase cascade is triggered by signals emanating from the cell-surface death receptors (DR) triggered by death ligands (DL) (TNF, CD95L/FasL, TRAIL). The DR stimulation results in the formation of the death-inducing signaling complex (DISC) and subsequent caspase activation.

Despite the fact that signaling pathways of apoptosis have been described with an impressive level of detail, the understanding of apoptosis regulation in quantitative terms has been missing until recently. There were many unclear points: when does a cell decide that it has to die, what are the rate-limiting steps in apoptosis, is there a point of no return, how can cell death be accelerated or blocked, and many others. From another side the years of apoptosis research resulted in a profound understanding of how signaling in apoptosis occurs. All major apoptotic complexes have been identified from the DISC to the apoptosome, including the death receptors and adaptors and the most important enzymes and their inhibitors. Therefore, apoptosis was an ideal system to go into quantitative studies using the emerging field of systems biology.

Systems biology combines mathematical modeling with experimental approaches in a closed loop cycle (Fig. 1). On the modeling side there are a number of mathematical formalisms, e.g., Ordinary Differential Equations (ODEs), Boolean models, etc., that allow to address different biological questions. Experimental work for systems biology of apoptosis involves the generation of quantitative data using different apoptotic assays.

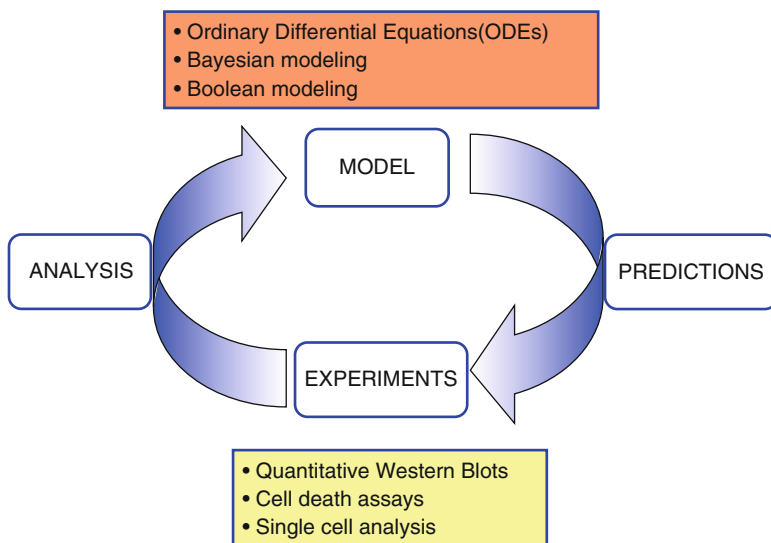


Fig. 1 Systems biology of apoptosis. Schematic view of systems biology of apoptosis

The development of this field in the recent years is fascinating. Studies of apoptosis using systems biology have provided novel insights into the quantitative regulation of cell death. In this book we describe contemporary systems biology studies devoted to cell death signaling both from experimental and modeling sides and focus on the question how systems biology helps to understand life/death decisions made in the cell and how to develop new approaches to rational treatment strategies.

Chapter 1 starts with an overview of the major types of mathematical modeling used in apoptosis and cell death. A simple minimalistic model of CD95/Fas-induced apoptosis is designed to introduce the most commonly used mathematical formalism, ordinary differential equations (ODEs). Besides ODEs, other modeling approaches are discussed in depth as well.

In Chap. 2 we focus on the biology of the extrinsic apoptotic pathway and its modeling by Ordinary Differential Equations (ODEs). We discuss new insights in the extrinsic death signaling which have been obtained using modeling.

Chapter 3 is devoted to model reduction approaches and uses the extrinsic apoptotic signaling as an example. This chapter provides a beautiful example of

how complex biological signaling can be simplified using mathematical modeling and how a simplified model can provide new insights in complex biological questions. The first three chapters provide a major insight into the modeling of extrinsic pathways.

Chapter 4 covers the molecular mechanisms of the mitochondrial apoptotic pathway and the major models describing this pathway. An emerging question in the field how bioenergetics influence the cell death pathway is also addressed in detail.

Chapter 5 further addresses the molecular mechanisms of extrinsic and intrinsic apoptosis in the context of modeling hepatocytes. Notably, an enormous progress has been recently made in modeling the signaling pathways in the liver and, in particular, cell death in the liver. This work is essential to define new therapeutic strategies for liver regeneration and liver disease.

Chapter 6 explores other forms of cell death, e.g., necrosis, autophagy, their cross talk with apoptosis, as well as the way to model cross talk between different cell types using Boolean modeling.

Chapter 7 describes a single cell analysis. Single cell analysis is compared to bulk approaches and the importance to follow a single cell rather than a cell population is discussed.

Chapter 8 discusses a systems-level understanding of cytokine–cytokine cross talk, namely how the cross talk between different cytokine pathways could be modeled on intracellular and extracellular levels. The importance of this cross talk for development and disease is also highlighted.

Chapter 9 deals with an important question in the field: the importance of searching for new components of cell death networks using different screening techniques. The unraveling of new components versus the investigation of dynamic models, which include all known components of the network, is a highly discussed question.

Taken together, the different chapters of the book describe in detail the remarkable progress which was made in recent years in systems biology of apoptosis and show new challenges in this field that can provide even more exciting insights into cell death regulation.



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