

1 Introduction

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Tissue homeostasis in complex, multicellular organisms is dependent upon a dynamic equilibrium between cell proliferation, differentiation and death. These three vital processes ultimately determine cell number, tissue architecture and function. To preserve balance, cells are required to communicate constantly with one another, either directly or indirectly. Direct communications are mediated by cell-cell contact or by changes in the surrounding extracellular matrix. Indirect communications involve the secretion of growth factors, cytokines and hormones. To maintain tissue homeostasis, each cell within a tissue must decode the incoming signals and translate them into the correct cellular response.^{1,2}

Binding of growth factor to its specific receptor, which is usually located on the cell surface, triggers a network of intracellular signals that eventually result in altered gene expression. This cascade of intracellular events upon activation of a receptor is called ‘signal transduction’. Signal transduction is commonly mediated through a chain reaction that involves phosphorylation and dephosphorylation of relay proteins by kinases and phosphatases as well as by the release of second messengers such as inositol, calcium ions and diacylglycerol (DAG). Different signal transduction pathways interact with one another and it is this cross-talk that triggers the formation of larger, combinatorial signalling networks. For example, upon activation of their receptors, growth factors can activate a number of distinct, but intertwined, signalling cascades such as the JAK/STAT (Janus kinase/signal transducer and activator of transcription) the PI3K (phosphatidylinositol 3-kinase) and the MAPK (mitogen-activated protein kinase) pathways.³⁻⁹

Cells are therefore capable of responding differently to a stimulus, depending on which combinatorial signal transduction network is used to relay the signal to the nucleus.

The critical interplay between cell proliferation, death and differentiation is best exemplified by the haematopoietic system.^{10,11} An adult human turns over 10^{11} blood cells daily by a process called programmed cell death. To compensate for this high rate of cell loss, the haematopoietic system must produce an equally high level of new blood cells every day. Moreover, increased production is required in times of physiological or pathological stress. For example, red blood cell numbers increase under conditions of hypoxia while granulocyte, macrophage and lymphocyte populations expand during infections. Perturbation of this equilibrium between cell production and elimination can lead to haematopoietic disorders, including autoimmune diseases, leukaemias and other myeloproliferative and lymphoproliferative disorders.

Cell proliferation requires activation of the cell cycle, a tightly regulated process that ensures that the cell is ready to divide.^{11–13} The replicating DNA has to be free from damage to avoid mutation. Cellular events include duplication of DNA, condensation and segregation of the chromosomes and their symmetrical distribution into two daughter cells. The mammalian cell cycle can be divided into four phases: an S (DNA synthesis) phase and M (mitosis) separated by two intervals, G1 (gap 1 — between M and S) and G2 (gap 2 — between S and M) phases. The cell cycle is under stringent control during cell development and by restricting entry into the cell cycle stem cell and progenitor populations are protected from exhaustion. Conversely, unrestricted cell proliferation causes hyperplastic disorders and cancer.

Programmed cell death or apoptosis is a physiological process whereby superfluous cells commit suicide.^{10,14} Apoptosis is an active, energy consuming process, characterised by a number of unique physiological features including loss of mitochondrial membrane potential, activation of the caspase protease cascades, membrane blebbing, condensation of the nucleus and the cytoplasm, and cleavage of proteins and DNA. *In vivo* these apoptotic cells will then be removed by macrophages or adjacent cells through a process termed autophagy. Depletion of growth factors and loss of appropriate cell-cell contact are common triggers for programmed cell death.

In addition, specific signals that activate death receptors, such as the Fas and TNF-receptors, can also induce apoptosis in target cells. A third way of inducing apoptosis is through cellular stress, including DNA damage, oxidative stress, viral infection and hypoxia.

The phosphoinositide 3-kinase (PI3K) signal transduction pathway has emerged as a critical regulator of cell fate decisions such as proliferation, differentiation and apoptosis.^{3,5,6,8,9,14,15} Inhibition of this pathway invariably leads to cell cycle arrest and/or apoptosis. PI3Ks are a family of lipid kinases that serve as a nexus for signals generated by many different activated receptors and adhesion molecules. Once activated, PI3Ks generate phosphatidylinositols (PtdIns) (3,4,5) P₃ which lead to the recruitment and activation of PDK (3'-phosphoinositide-dependent kinase), Akt/PKB serine/threonine kinase, and G-proteins (e.g. Rac-GTPases). These intermediate molecules in turn regulate the activity of an ever-growing list of target proteins involved proliferation, survival and apoptosis. Downstream targets of the PI3K/Akt pathway include glycogen synthase kinase-3beta (GSK-3beta), mammalian target of rapamycin (mTOR), p70S6 kinase, endothelial nitric oxide synthase (eNOS) and several pro-apoptotic proteins, such as Bad, Bim and Caspase-9.

Perturbation in PI3K signalling underpins many diseases including heart disease, autoimmune/inflammatory disorders, cancer and resistance to chemotherapy.^{3,6,8,9,15} Constitutive activation of the PI3K pathway is a consequence of enhanced expression of genes that encode class I PI3K subunits or Akt (PKB) genes or caused by genetic mutations in components of the pathway. For example, somatic deletions or mutations of *PTEN* (phosphatase and tensin homologue deleted on chromosome 10), an inhibitor of the PI3K/Akt pathway, have been identified in a large fraction (12%–60%) of human tumours of different histological origin. Consequently, considerable efforts are being made to develop new drugs that selectively target components of the PI3K signalling pathway for the treatment of cancers and other diseases.

This book provides a detailed overview of the recent advances in our understanding of PI3K signalling and its role in regulating cell proliferation, survival and apoptosis. Chapter 2 introduces the mechanisms and molecules that control cell proliferation and apoptosis. Chapter 3 provides an overview of the structural components of the PI3K signalling pathway

while Chapter 4 discusses how this pathway functionally regulates cellular proliferation and apoptosis. The focus in Chapter 5 is on FOXO sub-family of forkhead transcription factors, the most recently uncovered downstream components of the PI3K signalling cascade. FOXO proteins are involved in the transcriptional regulation of many genes important for cell proliferation, cell death and differentiation.^{3,6,8,9,15}

This book is intended for all those that are interested in cellular proliferation and apoptosis, whether a student or scientist. All authors responded enthusiastically when invited to contribute to this book and all have produced authoritative chapters which made editing an easy task.

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