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Divide and die another day

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Regulated cell growth and proliferation, as well as the execution of carefully controlled cell death, form the basis for the continuation of all life on our planet. Recent decades have seen an explosion of a wealth of genetic information on the molecular components that make up cells and their regulatory circuits. At first sight, it may seem that we understand the principles of cell growth and death. On closer inspection, however, it becomes quickly obvious that our knowledge has just merely begun to scratch the surface of what goes on inside the cell and between cells. Classic genetics in model organism has been extended by high throughput proteomic and phenotypic screens to include human cells. Yet the parts lists provided are just the starting point to begin asking questions. How do the identified molecules work, how do they orchestrate the multitude of reactions that together make cells grow, divide and die, each at the right place and time. Ideas and concepts have emerged from intelligent observations, yet the cell is not the product of intelligent design. As we move forward, our approach must take into account the complex evolved nature of cellular networks that connect cell growth and cell death. Breathtaking advances in many molecular and imaging techniques allow an unprecedented view of important aspects of cell growth and death. Together with a systems level analysis of these observations we hope to increase our understanding of cellular reactions, information processing and decision making.

This issue brings together reviews on recent advances on topics of central importance to the processes and regulation of cell growth and death. In preparation for cell division, the cellular content needs to be duplicated. This poses a particularly formidable challenge for the accurate information stored in the genomic DNA. The fluctuating levels of cyclin-dependent kinase (Cdk) activity provide universal control over the cell division cycle, yet how Cdk activity regulates the initiation of chromosomal DNA replication has only recently been revealed. The emerging ideas and their implications are considered by Hiroyuki Araki, 'Control of initiation of eukaryotic DNA replication'. Following on from there, Kaitlin Stimpson and Beth Sullivan, 'Epigenomics of Centromere Assembly and Function', discuss how a single region on each chromosome is singled out to become the attachment site for the mitotic spindle apparatus that segregates the replicated copies of each chromosome during cell division. This process is made possible by pairwise cohesion between sister chromatids after their synthesis. The ring-shaped cohesin complex is thought to embrace pairs of sister chromatids and María Carretero, Silvia Remeseiro and Ana Losada, 'Cohesin

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ties up the genome', describe how these cohesin rings have emerged as versatile organisers of DNA interactions within the chromosome.

The body of any metazoan species consists of organs of the right size, containing the correct number of cells. This is an observation that is as obvious as it is puzzling, as Barry Thompson, 'Developmental control of cell growth and division in *Drosophila*', illustrates. Not only will the rate of cell growth impact on cell division, it turns out that the cell cycle status feeds back on the rate and pattern of cell growth, as reported by Alexi Goranov and Angelika Amon, '*Growth and Division - not a one-way road*'. A multitude of intrinsic and extrinsic parameters are likely to influence cellular behaviour. How information can be processed and robust decisions reached is discussed in examples by Bela Novak, Orsolya Kapuy, Maria Rosa Domingo-Sananes and John Tyson, 'Regulated Protein Kinases and Phosphatases in Cell Cycle Decisions'.

An important part of biological systems is their continuous optimization and adaptation to changing environments by evolution. Among various drivers of variation that forms the basis of evolution, Norman Pavelka, Giulia Rancati and Rong Li, 'Dr. Jekyll and Mr. Hyde: Role of Aneuploidy in Cellular Adaptation and Cancer', set the spotlight on the distinct contribution of whole chromosome number changes. Such changes may not only have contributed to phylogenetic changes in our ancestry, they may also contribute significantly to the evolution of devastating human neoplastic disease. It is in such a disease setting that cell cycle regulators are put into unprecedented context, and the complex but important implications of this are dissected by Vassilis Gorgoulis and Thanos Halazonetis, 'Oncogene Induced Senescence: The bright and dark side of the response'.

Apoptosis is not the only mechanism of programmed cell death, but it is the best known and most widely investigated. Peter D. Mace and Stefan J. Riedl, '*Molecular Cell Death Platforms and Assemblies*' describe how scientific interrogation of fundamental apoptotic mechanisms has recently led to the atomic level elucidation of how cellular signals engage different arms of this death response, revealing distinct upstream mechanisms to engage conserved downstream events. Taking advantage of the latent apoptotic potential of cancer cells has led to the development of innovative anti-tumor therapies, as described by Annie Yang, Nicholas S. Wilson and Avi Ashkenazi, 'Proapoptotic DR4 and DR5 signaling in cancer cells: toward clinical translation'. Although the role of BCL2 family members in regulating apoptosis has been appreciated for at least 15 years, only recently have scientists been able to define the mechanisms, and Christian Bogner, Brian Leber and David W. Andrews, '*Apoptosis: Embedded in membranes*' illuminate the interaction of these pro- and anti-apoptotic proteins with each other and with the mitochondrion, a theme that is continued by Stephane G. Rolland and Barbara Conradt, 'New role of the BCL2 family of proteins in the regulation of mitochondrial dynamics'. Ultimately, apoptotic death is executed through specific limited proteolysis by caspases, and Francis Impens, Joël Vandekerckhove and Kris Gevaert, '*Who gets cut during cell death?*' explain how state-of-the-art focused proteomics has revealed the protein victims of proteolytic reprogramming of cells fated to die.

In keeping with the theme of this issue, Jeniffer B. Hernandez, Ryan H. Newton and Craig M. Walsh, 'Life and death in the thymus – cell death signaling during T cell development' explore the emerging cross-talk between cell proliferation and cell death in education of the adaptive immune system, a mechanism that is also explored by Juanita Lopez and Pascal Meier, 'To fight or die - Inhibitor of Apoptosis Proteins at the crossroad of innate immunity and death' in terms of innate immunity.

Finally, Kim McCall, 'Genetic control of necrosis - another type of programmed cell death' and Hyung Don Ryoo and Eric H. Baehrecke, 'Distinct death mechanisms in *Drosophila* development' reveal how blossoming investigations into non-apoptotic cell death mechanisms, utilizing model organisms, are forcing revisions of how specific organs and tissues deal with their requirements for cell ablation.

As we move into the second decade of a new century we face the challenge of understanding how cell growth, proliferation, and death are coordinated. The chapters in this issue are in the hands of individual experts on these forms of cell behavior. But the wave of upcoming scientists is going to have to grapple with the fact that these forms are interconnected, and should probably be considered together, before the next surge of scientific advances can be made to understand how the complex machine that we know as a cell makes its decision to divide or to die.

Biographies

Frank Uhlmann studied biochemistry at the University of Tübingen before receiving a PhD degree for work at Memorial Sloan-Kettering Cancer Centre, New York, in 1997. He performed postdoctoral work at the I.M.P. in Vienna and since 2000 is a research group leader at the ICRF, now Cancer Research UK, in London.

Guy Salvesen received his Ph.D. in biochemistry from Cambridge University in 1980. In 1996 he was recruited to Sanford-Burnham Medical Research Institute where he is Director of the Program in Apoptosis and Cell Death. He holds an Adjunct Professorship in Molecular Pathology at the University of California, San Diego