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Cell Division, Growth and Death Editorial Overview

Decisions, decisions, decisions

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Cells must perpetually decide on three big choices in life: to grow, to divide or to die. These system-level decisions are the output of a complex and still very poorly understood molecular algorithm, which is built from many different sub-routines. Biochemical and genetic insights, sometimes coupled with good fortune, have illuminated key individual steps in the networks that dictate growth, division and death. Increasingly, the complex relationships between these discrete steps have begun to emerge from the convolved mists of evolutionary construction. A building ueber-theme is the unexpectedly deep integration of division, growth and death not only with each other, but with cellular metabolism. As covered in this *Current Opinion in Cell Biology*, this full-on system-wide view of the cell is poised to address both the how and why of big decisions in the life of a cell.

Irreversibility is a hallmark of the main transitions in the cell division cycle, whether it be commitment to division in late G1 phase (called the Restriction Point in metazoans or Start in yeast), the initiation of DNA replication or the entry into and exit from mitosis. To lead off a series of reviews on division, Remus and Diffley discuss the molecular mechanisms underlying

the initiation of DNA replication, focusing on the DNA helicases that promote DNA unwinding. In contrast to their prokaryotic counterparts, eukaryotic DNA helicases are loaded in an inert form and then activated by the cyclin-dependent kinases. This master control system not only allows DNA replication to be governed by extracellular cues, but critically ensures the once and only once per cell cycle replication of the genome, and the governance of origin activity during replication stress. In a companion review, Weinert and colleagues explain in detail the dire consequences of replication fork errors. Fork collapse is now recognized as a primary source of endogenous genome instability, and is implicated as early step in cancer progression. Not surprisingly, evolution has devised multiple means to cope with this potential catastrophe, referred to as the "fork's five degrees of freedom" by Weinert et al, who elaborate the successive means by which cells attempt to resurrect stalled forks, and how total failure leads to large-scale chromosomal rearrangements.

The most dramatically irreversible cycle event is undoubtedly the onset of chromosome segregation at the metaphase-to-anaphase transition. Initiation of anaphase requires that each kinetochore correctly attaches to the mitotic spindle in a bi-orientated manner, which ensures that each daughter cell receives a full complement of chromosomes during anaphase. A surveillance mechanism known as the spindle assembly checkpoint (SAC) ensures that all kinetochores are properly engaged with spindle microtubules. Nezi and Musacchio explain recent insights into the SAC, including how the SAC senses the absence of microtubule attachment at kinetochores, how this may relate to tension generated by microtubule forces and how the SAC halts cell cycle progression. Carmena, Ruchaud and Earnshaw build on this theme in their review of the multifaceted Aurora kinases as critical regulators of virtually all aspects of microtubule dynamics, including centrosome maturation, mitotic spindle formation, microtubule–kinetochore attachment and cytokinesis. The two isoforms of these remarkably pleiotropic and conserved protein kinases perform their diverse functions by associating with myriad interaction partners, which target Aurora activity to different subcellular locations.

The theme of targeted subcellular localization by association with different subunits is elaborated by De Wulf, Montani and Visintin, who describe the ever-expanding roles of protein phosphatases in cell cycle control. Until recently, phosphatases were regarded as the rather poorer cousins of kinases, consigned to the role of a constitutive phosphate clean-up crew necessary to reset the events so elegantly governed by the protein kinases. It is now clear, however, that the phosphatases are often as intricately regulated as protein kinases, with a

plethora of targeting subunits that direct both substrate specificity and subcellular localization of phosphatase catalytic subunits. The role of molecular recognition in cell cycle control is nowhere more manifest than in the selective degradation of critical regulatory proteins by the ubiquitin-proteasome system. Skaar and Pagano review the two pervasive E3 ubiquitin ligases in cell division, the SCF and the APC/C complexes, which collectively regulate every major decision point in the cell cycle. The multifaceted nature of these E3 enzymes continues to be unveiled through the growing lists of substrates and functions, exciting biochemical and structural insights into their catalytic mechanisms and their role in many cancers and other diseases.

The long-standing problems of cell, tissue and organism growth have begun to yield to intensive efforts to dissect this most fundamental of cellular processes. In proliferating cells, the rate of growth, i.e., the increase in cellular biomass, must be coordinated with cell division to ensure the production of cells of equal size. In terminally differentiated cells, macromolecular homeostasis must be achieved so that cells maintain a characteristic size, which can vary enormously by tissue type. Fittingly, this section topic begins with a review by Hall and colleagues on a universal conduit for growth control, the target of rapamycin (TOR) pathway. Founded on the genetic analysis of the anti-fungal compound rapamycin almost two decades ago, the burgeoning study of the conserved TOR kinases has revealed critical roles for the pathway in cancer, diabetes, aging, heart disease and even behavior. The TOR kinase responds to both nutrients and myriad signaling events, and participates in complex feedback loops that have evolved to govern metabolism, protein synthesis, membrane dynamics and the cytoskeleton. Hall et al expound on the two distinct TOR complexes, TORC1 and TORC2, their regulators and effectors, and exciting new connections to aging and other diseases.

The Hippo kinase pathway is a more recent arrival on the growth control scene. Hippo pathway mutants were first identified in *Drosophila* by virtue of an excess tissue growth phenotype, and it is now evident that the pathway is critical for the control of organ size. An overview of recent developments by Badouel, Garg and McNeill elaborates on signal transmission through the pathway, and on intriguing connections with the growth and apoptotic machineries. Notably, the Hippo pathway is now closely linked to tumorigenesis, and will likely impact many other diseases marked by defects in growth control.

The protein synthetic machinery is a primary target of growth pathways such as TOR and Hippo, both at the level of translational control and the biogenesis of new ribosomes. The

omnipotent transcription factor Myc profoundly influences the rate of growth by governing the expression of the hundreds, if not thousands, of genes necessary for protein synthesis and metabolism. Myc was discovered as one of the first and most potent oncogenes, and is limiting for the growth of many if not all cancers. Trumpp, Laurenti and Wilson cover recent findings that demonstrate a critically important role for Myc in stem cell maintenance and proliferation. This apparent dual role for Myc may reflect the stem cell origins of many cancers. Aside from its functions in transcription and chromatin structure, the control of Myc itself is now under intense scrutiny, particularly the multiple ubiquitin-dependent pathways that mediate its degradation. Ultimately, activation of growth signaling pathways leads to increased macromolecular biosynthesis, mainly in the form of ribosomes, which then further protein synthesis and cell growth. The ribosome production is a highly complex process, requiring the co-ordination of rRNA production, ribosomal protein synthesis and cellular energy state. Lempiäinen and Shore describe recent discoveries on how nutrient and energy status affect ribosome biogenesis, notably the multiple feed-forward and feedback mechanisms that couple rRNA and ribosomal protein production to nutrient signals.

While extracellular signals instruct cell growth through receptor-dependent signal transduction pathways, in multicellular organisms it is increasingly apparent that mechanical interactions between cells can play an equally important role. In an overview of this very intriguing but less familiar ground, Mammoto and Ingber describe how physical tension caused by mechanical forces influence cell growth and differentiation. This tension is transmitted across the extracellular matrix (ECM) and cell-cell adhesions through cytoskeleton-associated GTPases and cell surface-associated signaling molecules such as integrins.

Programmed cell death, or apoptosis, is critical for development, tissue homeostasis and repair. As reviewed by Benner and Mak, cell death is activated by two primary means, the extrinsic pathway and the intrinsic pathway. Extrinsic death-inducing signals play key roles in embryonic development, especially the immune system, whereas intrinsic pathways are activated by the absence of survival signals or cellular stress, and thus serve to limit inappropriate proliferation and expunge damaged cells. Benner and Mak highlight the key role of mitochondrial outer membrane perforation in the intrinsic death pathway, its regulation by the Bcl2 family of proteins, and the importance of cytotoxic factors released by the mitochondria. The release of cytochrome C from mitochondria activates a cascade of latent proteases, known as caspases that propagate and execute the intracellular degradation program. Bader and Steller review the

expanding linkages between the ubiquitin-proteasome system and the apoptotic caspase machinery. The inhibitors of apoptosis proteins (IAPs) and their antagonists are key regulators of caspases. The IAPs form a subclass of ubiquitin ligases that harbor a RING domain, which serves to recruit ubiquitin conjugating enzymes. IAP-mediated ubiquitination normally inhibits caspase activity until IAP antagonists, such as reaper, promote the self-degradation of IAPs, and thereby initiate apoptosis. This switchable negative feedback mechanism helps ensure that runaway activation of caspases does not occur in the wrong context.

The past few years have seen a resurgence of interest in the mitochondrion as not just the energy factory of the cell, but as a central arbiter of critical cellular decisions, based on metabolic status. King and Gottlieb weave together a swath of evidence that links apoptosis and glucose metabolism. Key enzymes in carbon metabolism, notably G6PDH and hexokinase, appear to directly or indirectly influence apoptosis, suggesting that there may be a gamut of mitochondrial signals that modulate apoptosis. The authors build an intriguing and potentially unifying explanation for the origins of programmed cell death, namely that single-celled organisms exploited the resource-sparing mechanisms of autophagy towards an altruistic end, whereby some cells in a colony or a multicellular aggregate might have been sacrificed for the greater good. It has also recently become apparent that mitochondrial signals impinge on far more than apoptosis, not least through oxygen sensing and consequent effects on output ranging from glycolysis to angiogenesis to ventilation rates. Hamanaka and Chandel review recent insights into how oxygen levels are sensed through reactive oxygen species (ROS) generated in the mitochondria. These ROS species influence the hypoxic response primarily at the cellular level through control of HIF-mediated transcription but also have profound higher order effects, for example on pulmonary artery constriction.

Finally, in the end game of cell death, disposal of the cellular corpse is crucial both to prevent an auto-immune response and to clear the way for tissue regeneration. As He et al describe, this purge is completed inside the phagosome of an engulfing macrophage, which is drawn to the apoptotic cell by the breakdown products that result from caspase action. Forward genetic screens in the nematode worm *C. elegans* have unveiled a suite of intricate signaling and vesicle fusion events mediated by various membrane trafficking and cytoskeletal GTPases in conjunction with phagocytic receptors. The importance of this process is underscored by its role in chronic polyarthritis and other autoimmune disorders.

The molecular details of the pathways that control cell division, growth and death are being unraveled at a breath-taking pace. Perhaps most interestingly, cross-connections between these fundamental processes, including links to cell metabolism, are driving a systems-level appreciation of how the cell coordinates its life and death decisions. Collectively, the cohort of reviews in this issue poses the next wave of major questions. Advances in our understanding of the mechanics of cell division have laid the foundation for a new assault on key issues such as the genesis and resolution of DNA replication fork stall and collapse, the molecular circuitries and spatial elements that underlie irreversible decision events, and the construction of genuinely predictive cell cycle models. The field of cell growth has hit an exponential phase of discovery, with insights on many crucial issues seemingly imminent, including the coordination of ribosome biogenesis with division, the connections between major signaling conduits such as the TOR and Hippo pathways with downstream growth effectors such as Myc, and the regulation of these processes in normal, cancer and stem cells. Footholds are now established for understanding the larger issues of tissue and organism size control, which will undoubtedly depend on intertwined relationships between signaling pathways, such as Hippo, and mechanical forces transmitted through the cytoskeleton. With regard to apoptosis, key topics under active investigation include the biophysical mechanisms that disrupt the outer mitochondrial membrane, activation of caspases by non-mitochondrial death pathways, the diverse roles of mitochondrial ROS signals, and the means whereby the end-products of apoptosis alter surrounding cells and tissue homeostasis. The view that the mitochondrion itself is proximal sensor of metabolic distress, as ineluctably crafted by evolution, may provide an overall framework that will stimulate further insights into programmed cell death. In a return to the concepts first developed by Warburg more than 50 years ago, metabolism seems set to take center stage in the coordination of division, growth and death [1, 2]. Many of these developments promise novel therapeutic concepts for intervention in cancer and other disorders.

[1] Warburg O (1956) On respiratory impairment in cancer cells. *Science* **124**:269-270

[2] Vander Heiden MG, Cantley LC and Thompson CB (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* **324**:1029-1033