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Balancing cell growth and death

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Life within a cell, a tissue, or an organism requires a delicate balance between the promotion and inhibition of growth. Subcellular structures expand and contract in concert with cell cycle progression and environmental conditions, while tissue homeostasis requires the coordination of these processes in populations of cells along with the ability to promote the proliferation of some cells while expunging others. De-regulation of these processes can have drastic effects on organismal health and lifespan. This issue of *Current Opinion in Cell Biology* explores the intricacies of cell growth and death at a number of levels, from the epigenetic mechanisms underlying the tight maintenance of gene expression, to the control of the membranes that compartmentalize cellular processes and delimit cell size, to the signaling processes that allow cells to communicate with and modulate growth in distant regions of a multicellular organism.

The duplication and segregation of chromosomes are the fundamental processes during cell cycle transitions that support the ability of cells to survive and produce healthy daughter cells. The fidelity of these basic chromosomal processes can become compromised in aged organisms, triggering signaling pathways that can impart cell death. Henriques and Ferreira provide a fresh perspective on the often-touted relationship between telomere length and aging. They highlight the pros and cons of the various eukaryotic models used to study this relationship and propose a model for how declining telomere length in highly proliferative tissues might affect tissue homeostasis throughout the organism in a non cell-autonomous manner.

Genome instability wreaks havoc with the orderly control mechanisms that promote and restrain cell growth. While problems incurred during DNA replication are prime destabilizers of chromosomes, Vitre and Cleveland highlight the prominent causative role played by centrosome amplification in the genesis of cancers exhibiting chromosomal instability; they also propose mechanisms by which centrosomes are overproduced, and how such amplified centrosomes in turn engender aneuploidy.

The spindles that emanate from centrosomes are not only crucial for proper genome segregation, but also dictate the plane of cell cleavage when cells divide and in turn the organization of tissue geometry. These issues are explored by Stevermann and Liakopoulos, who provide an eye-opening discussion of how external signals are detected within cells and

interpreted by force generators, in turn controlling spindle positioning and tissue architecture.

The movements and positions of chromosomes are functions not only of spindle forces but also of the activities of myriad chromatin binding factors and transactions that occur during DNA replication and transcription as well as DNA damage repair. Mammalian X-chromosome inactivation is not only a fascinating process allowing the coexistence of two genders but also a microcosm for understanding genome-wide principles of nuclear organization and epigenetic regulation. Pollex and Heard develop the idea that not only the association of non-coding RNAs and proteins with the chromosome but also the large-scale organization of domains within the nucleus is required to confer expression of only one of the two X chromosomes.

Cell growth and division involves not only mechanisms to ensure perfect duplication and segregation of chromosomes, but also mechanisms to ensure that cells divide when and only when they have accumulated sufficient levels of cellular components to ensure that daughter cells will be self-sufficient. Navarro *et al.* discuss recent progress on how cell division is coordinated with the stockpiling of cellular components, illuminating the key moments at which cell growth rates are altered, the subcellular gradients that translate cell growth into cell cycle transitions, and the influence of environmental factors on these parameters. Davie and Petersen discuss the TOR pathway, a key signaling module that transmits information on nutrient availability to the cell growth machinery, and put forward a plausible rationale for why cells bother to control cell size with such exquisite precision. McCusker and Kellogg explore recent ideas for how membrane growth is achieved, illuminating multiple types of vesicles and secretory pathways that respond to changing cell cycle regulatory parameters as well as external cues.

Appropriate scaling of cell size to function is one of the reasons cell growth is so carefully regulated. The growth of Schwann cells, which wrap around and insulate axons to accelerate neurotransmission, is tightly scaled to axon size. Roberts and Lloyd explain how some mitogens exclusively induce Schwann cell proliferation whereas certain growth factors exclusively regulate cell size; they argue, at least in this cell type, for non-autonomous size control of cells, which may facilitate size matching between different cell types and to environmental stimuli more accurately than intrinsic cell size control.

A detailed molecular understanding of cellular morphogenesis is emerging from studies of rod-shaped fission yeast. Hachet *et al.* review how this organism’s elongated shape is controlled by kinase gradients and the polar localization and dynamic activation of a Rho-family GTPase. The rod shape is also used to position the mitotic machinery in the middle, and to coordinate cell length and cell division.

Tissue homeostasis often balances cell division with cell death. However, in the epithelium, overcrowding can cause viable cells to be actively extruded to restore tissue size and shape. Gu and Rosenblatt cover the importance of maintaining the fidelity of the epithelium during cell extrusion and explain how the surrounding cells conspire to extrude excess cells while

sticking together to retain barrier function. Interestingly, pathogens have evolved ways to circumvent this mechanism of barrier maintenance to mediate their invasion of tissues.

Classic studies have shown that cell death is mediated by caspases that are restrained by IAP (inhibitor of apoptosis) ubiquitin ligases. More recent findings explored by Kenneth and Duckett reveal that IAPs also regulate other processes, including animal development and cell migration, probably through the ubiquitin proteosome system.

Nutrient availability and metabolism are central to cell growth control and also impact cell life, fate and death decisions. Sirtuin deacetylases translate metabolic status denoted by acetyl-CoA and NAD+ levels to protein signaling pathways through control of protein acetylation. Johnson and Kornbluth consider how protein acetylation can interfere with phosphorylation to promote caspase activation, thereby linking cellular metabolic state with apoptosis sensitivity.

Following apoptosis, cells are engulfed and degraded by neighbors to prevent inflammatory reactions to cellular debris. Pinto and Hengartner review the mechanism of cell corpse removal in *C. elegans*, where powerful genetic screening has unraveled an intricate pathway. Exposure of phosphatidylserine on corpses initiates their recognition by surface receptors on neighboring cells, which selectively ingest them into phagosomes for fusion with lysosomes and final elimination. Corpse clearance utilizes certain gene products involved in autophagy and many of these steps appear to be well conserved between worms and mammals.

Tremendous progress has been made in understanding the array of strategies organisms use to maintain cell and tissue homeostasis. These reviews not only reveal our current knowledge of these topics, but also offer clear insights into what major unresolved issues remain to be further explored, underscoring future pathways for unraveling the imbalances in cell life and death decisions that impair human health.

Biographies

Julia Promisel Cooper received her PhD from the University of Colorado (with Paul Hagerman) and did postdoctoral work at the NIH (with Robert Simpson), University of Colorado (with Thomas Cech) and Imperial Cancer Research Fund (with Paul Nurse). Her team studies telomere function throughout mitotic and meiotic cell cycles at the Cancer Research UK London.

Dr. Youle received his Ph.D. degree from the University of South Carolina. He joined the lab of David Neville at the NIH for postdoctoral work on the engineering of new cell-type-specific protein toxins. He joined the Surgical Neurology Branch of NINDS in 1985 as a PI where he has developed new treatment strategies for brain tumors. His lab is now exploring the molecular mechanisms of programmed cell death and engineering therapeutic proteins to regulate cell survival.