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EDITORIAL

In focus in HCB

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This issue of HCB is packed with eight review articles as part of the 60th anniversary of *Histochemistry and Cell Biology*, along with three original articles. We will briefly mention all of the review articles in this issue, and then highlight four of them in more detail.

Two reviews focus on **aspects of peroxisomes**, from their biological functions and their role in various disease processes (Islinger et al. 2018), to how cells maintain peroxisome homeostasis via selective autophagy, and the physiological consequences of misregulation of this process (Eberhart and Kovacs 2018); Mattes and Scholpp (2018) describe the function of the **signaling protrusions termed cytonemes and tunneling nanotubes in cell–cell communication**; Saraste and Marie (2018) provide an update on aspects of the **autonomous cellular intermediate compartment**; Groeneweg and colleagues (2018) present a timely review on aspects of **gephyrin regulation of synapses**; Rand and Taatjes (2018) review the use of **various microscopy-based imaging techniques to investigate the antiphospholipid syndrome**, a human thrombotic disorder; and the last two reviews cover instrument/technique applications for cell biology: Pirozzi and colleagues (2018) describe **"ColorEM", analytical nanoscale techniques** encompassing energy-dispersive X-ray analysis, electron energy loss spectroscopy, and cathodoluminescence combined with electron microsocopy for investigating elements and molecules from the tissue to the cellular to the organelle level (see cover image); and Segura-Valdez and colleagues (2018) describe the use of **atomic force microscopy** for the imaging of internal cellular structures.

Peroxisomes: the Swiss army knife of organelles?

Islinger and colleagues (2018) provide an extensive and thorough update on recent discoveries in peroxisome cell biology and pathology-related disorders. This contribution is a continuation of the authors' "Mystery Series" (Schrader and Fahimi 2008; Islinger et al. 2012), timely reviews providing updates on peroxisome research. In this latest contribution, the most up-to-date literature is presented detailing aspects of peroxisome cell biology, including metabolism, heterogeneity, functions of the peroxisomal membrane, peroxisome formation and division, and peroxisome motility. A fascinating section details peroxisome–organelle contact sites via tethers, highlighting the multifaceted associations and interactions between peroxisomes and mitochondria, endoplasmic reticulum, and lysosomes. The review also describes the activity of peroxisomes in anti-viral and -bacterial defenses, as well as potential roles in diseases of the central nervous system (including Alzheimer's and Parkinson's diseases), hearing loss, diabetes, obesity, and various cancers. Clearly, research has demonstrated that peroxisomes are not solitary organelles, but rather are mutifunctional ubiquitous cellular organelles, actively moving throughout the cell and interacting with other cytoplasmic organelles, involved in various physiological functions in both healthy and diseased cells.

In the second review article in this issue concerning peroxisomes, Eberhart and Kovacs (2018) focus on peroxisome homeostasis, the balance between biogenesis and degradation, produced via a specific autophagic process referred to as "pexophagy". The review begins with a detailed molecular and cell biological description of autophagosome formation, and then proceeds to detail the complex and selective molecular events precipitating the differing pexophagy processes occuring in various yeast strains and mammalian cells. In yeasts, two main modes of pexophagy are found, termed macropexophagy and micropexophagy, occuring via different mechanisms, and different yeast strains present varying complexities on this theme. In mammalian cells,

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complex molecular interactions resulting in pexophagy occur continuously as the half-life of a mammalian peroxisome is between 1.5 and 2 days. The authors describe in great detail these peroxisomal protein associations, and then describe pexophagy regulation via protein ubiquitination during changes in local cellular environmental conditions including amino acid starvation, oxidative stress, and defects in the peroxisomal matrix protein machinery. The review ends with a perspectives section positing many questions remaining to be answered concerning the maintenance of peroxisome numbers via the complex processes of pexophagy in healthy and diseased cells.

Biologic cell phones for cell–cell communication

The review by Mattes and Scholpp (2018) addresses the fascinating area of cell–cell communication and signaling mediated via plasma membrane protrusions. They focus on and compare two distinct cellular protrusions capable of transmitting information between cells over large distances: (1) cytonemes, which are membrane-associated filopodia; and (2) tunneling nanotubes (TNTs), which are essentially thin membranous tubes connecting the cytoplasm of two cells, and allowing the sharing of soluble and membrane-tethered biochemical signals. Cytonemes, originally defined in Drosophila, are specialized filopodia involved in signal transduction and containing ligands or receptors. More recently, cytonemes have also been identified in vertebrate cells and tissues, and like their Drosophila counterparts are involved in a myriad of singaling events, often associated with tissue development and stem cells (the most thoroughly characterized cytonemal processes in vertebrates are involved with the Wnt signaling family of proteins). TNTs, like cytonemes, are considered to be contact-dependent cell–cell communication effectors. Unlike cytonemes, TNTs can transport even large organelles, such as mitochondria, between cells, along with pathogens, and even electrical signals. TNTs can form stable bridges between cells, linking the cytoplasmic interior of the cells and transporting material bidirectionally. Two subcategories of TNTs have been identified based upon diameter of the tubules: (1) short and thin displaying diameters of up to hundreds of nanometers and lengths below 50 μm, which are similar to gap junctions allowing transport of small molecules; and (2) longer and thicker with diameters more than several hundreds of nanometers and lengths over hundreds of microns. TNTs have been speculated to play a role in various diseases and pathologies, including prion-based conditions, HIV, and cancers via their ability to allow cells to share cytoplasmic components. The authors conclude their excellent review by discussing the similarities and differences between cytonemes and TNTs, proposing that further characterization of these intriguing cell communication structures will be required to ascertain what extra functions they may be performing in cells and tissues.

The intermediate compartment (IC) takes center (and peripheral) stage

Saraste and Marie (2018) provide a concise, yet highly detailed summary of the characterization and properties of the somewhat enigmatic intermediate compartment (IC) in mammalian cells. The IC is a complex membrane system involved in protein sorting and trafficking between the endoplasmic reticulum (ER) and Golgi apparatus in mammalian cells. Contemporary views continue to question whether the IC represents a stable cytoplasmic compartment, or is of a more transient nature. The review contains a thorough and most informative historical review of the IC concept, from its identification in the 1980s by antibodies against Golgi apparatus subfractions (Saraste et al. 1987; Schweizer et al. 1988). More recently, live cell imaging using fluorescent proteins has led to the development of three different models to define the IC: (1) *transient* transport carriers; (2) *stationary* ER exit site (ERES)-associated membrane clusters; and (3) *permanent* network of dynamic vacuoles and tubules (this model combines aspects of the first two models). The authors compare these models in great detail, backstopping their discussion with references to experimental results supporting the various models. They then describe a number of potential novel functions of the IC, including direct contact between IC components and the endocytic recycling system (bypassing the Golgi apparatus), as a membrane source for autophagosome formation, as a post-ER quality control checkpoint for protein maturation, in protein kinase signaling cascades, and finally in the biogenesis of Golgi stacks. They conclude their most informative, well-illustrated, and comprehensive review with a take home message, positing that rather than corresponding to a collection of transient transport carriers shuttling cargo between the ER and *cis*-Golgi, the IC represents a permanent membrane system extending throughout the cytoplasm to the cell periphery.

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