In focus in HCB

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This last 2018 issue of HCB includes 12 review articles commemorating the 60th anniversary of *Histochemistry and Cell Biology*. To conclude volume 150, we will highlight each of the reviews contained herein.

The cell nucleus: insights into the blank spots

Misteli, together with several of his team members (Adriaens et al. 2018) present a review that is structured around key open questions on genome architecture, nuclear organization and nuclear lamins. As the authors point out, the set of questions they address is not comprehensive, nor is the choice fully objective. In regard to genome architecture, they consider the regulatory function of genome organization, the molecular mechanisms underlying 3-D genome organization and the mechanisms that underlie the dynamic nature of genome organization. Furthermore, they ask specific questions regarding the nature of the structure of chromatin in intact cells, whether post-translational modifications regulate genome organization, how heritable the nuclear organization is, and whether spatial genome reorganization can be helpful for diagnostic and prognostic purposes in the clinical setting. In regard to the nuclear organization in subcompartments not defined by membranes that may arise spontaneously from liquid phase condensation, it is discussed whether the nucleus and consequently the genome is an emulsion of phase separated droplets composed of nucleic acids and proteins, what determines the sites and timing of droplet assembly and disassembly, how these condensates may affect gene expression, and if so whether anomalies

in phase separation of the genome contribute to disease development. Numerous functions of the nuclear lamina are known, that are as diverse as providing physical stability to the nucleus or serving as a platform for nuclear signaling. However, emerging observations point to the involvement of the nuclear lamina in protein homeostasis and suggest a role in defining genome organization patterns associated with differentiation. This aspect and the relationship between the disruption of the nuclear lamina architecture and the development of aging-associated diseases are examined and discussed.

The nuclear pore proteins: not only for transport

Jühlen and Fahrenkrog (2018) focus on nucleoporins (NP), the building blocks of the nuclear pore complex, and highlight their moonlighting tasks, which are way beyond their classical function in nucleocytoplasmic transport. The authors also emphasize the fact that many nucleoporins are expressed in a tissue- and cell type-specific manner, a fact that needs to be considered in research on nucleoporins and which becomes manifest in tissue-specific human disorders caused by mutations in nucleoporin genes. For instance, mutations in the gene coding for the scaffold NP ALADIN cause the triple A syndrome, while those in the cytoplasmic filament component NUP358 play a role in acute necrotizing encephalopathy. On the other hand, mutations in various scaffold NP's have been shown to be involved in cardiac disorders, and mutations in other NP's such as *GLE1* and *NUP88* may lead to different developmental disorders. Mutations in *NUP93* and *NUP205* are not only linked to cardiac disorders but also cause nephrotic syndrome which is also observed for mutant exportin 5 and NUP107. To summarize many studies, abnormal composition of the nuclear pore complexes, abnormal nucleoporin distribution, and defects in nucleocytoplasmic transport are important aspects not only of neurological and neurodegenerative disorders but also of cardiac and renal disorders. Thus, the authors

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conclude that disorders in humans associated with nonfunctional NP's might be linked to moonlighting functions of distinct NP's.

Cancer: nucleoli and obstacles for treatment

Three reviews discuss aspects of cancer biology. Following the above-discussed reviews concerning nuclear structure and function, Stepiński (2018) discusses many aspects of the relationship between nucleolar and ribosomal proteins, as well as different RNAs and cancer biology with a focus on cell growth and proliferation. In addition to their canonical function as a ribosome factory, nucleoli have additional tasks in signaling pathways important during carcinogenesis, all of which are related to the regulation of ribosome biosynthesis. The importance of oncogenes such as c-Myc in cooperation with AKT, of nucleophosmin, nucleolin, nucleostemin, GRWD1, RRP12, NIKF and others in directly regulating cell proliferation, and therefore, carcinogenesis is considered. On the other hand, the role of nucleoli as opponents of cancer cells without involvement of p53 or involving p53-dependent pathways is detailed, and the multifaceted anticancer strategies targeting nucleolar functions are discussed.

Nandigama and colleagues (2018) review the effect that the tumor microenvironment (TME) has on restricting access of therapeutic agents to the tumor cells themselves, thereby diminishing the potential efficacy of these anti-cancer drugs. The review begins with a section highlighting the disturbing fact that most anti-cancer drugs accumulate to a high degree in non-target organs such as liver, heart, kidney, and gastrointestinal tract, while being found only to a very small extent in the targeted tumor. Next, the authors discuss in detail the seemingly incongruous effects of anti-angiogenic agents, or agents to support a more functional vascular network within the tumor, either alone or in combination with anti-tumor drugs on tumor suppression. The review then focuses on the TME itself, with sections detailing the contributions of tumor-associated fibroblasts and cells of the innate and adaptive immune system (particularly macrophages and neutrophils) to effects on drug delivery to the tumor cells themselves. The authors have provided a most useful glimpse into the current world of cancer therapeutics, deftly illustrating how the complex cell biological characteristics of the TME and the vascularization of the tumor present unique challenges for the development of effective anti-tumor agents and treatment regimens.

Kuwahara and colleagues (2018) review another aspect of the lack of effectiveness of cancer treatment to that just described above; namely, the existence of cells resistant to radiotherapy (RT). They have developed multiple clinically relevant radioresistant cells lines, and in this review, they focus their attention on defining the mode(s) of regulated

cell death triggered in these cell lines upon exposure to X-ray irradiation. They present time-course images acquired over several days from cultured cells exposed to X-ray irradiation, to identify morphological characteristics accepted as hallmarks for the various modes of programmed cell death. Based upon their careful observations, the authors determined that radiation-induced cell death could be subclassified into (1) apoptosis, (2) autophagy-dependent cell death, and (3) necroptosis (cells display morphological features of necrosis, but a unique signaling pathway is involved). Thus, although apoptosis has been considered the primary mode of regulated cell death in irradiated cancer cells, the authors conclude that autophagy-dependent cell death and necroptosis also represent significant regulated death pathways under these circumstances.

Breathe, breathe in the air...

Two reviews focus on aspects of pulmonary structure and function. Knudsen and Ochs (2018) provide a very informative and comprehensive discussion of the linkage between form and function in the alveolar (parenchyma) gas exchange region of the lung. They begin by describing in very great detail the morphological characteristics of the parenchyma: a thin layer of epithelium consisting of alveolar type I and type II cells, separated from a continuous endothelial layer by a connective tissue interstitial space. The remainder of the review focuses on the maintenance of alveolar mechanical stability during the process of respiration. They describe two main tissue components responsible for this stability: (1) the connective tissue matrix found in the interstitial space; and (2) a layer of surfactant synthesized and secreted by alveolar type II cells to cover the thin epithelial layer. A long and detailed description of the mechanisms underpinning alveolar micromechanics is provided, allowing an integration of the “form and function” concept of pulmonary mechanics. The review then describes pathological conditions resulting from alterations in the structural maintenance of alveolar mechanical stability, and the resulting impact on the physiology of respiration. An “Outlook” section finishes the review with a discussion of the use of additional experimental methodologies, including *in vivo* microscopy and computational models to further our understanding of alveolar micromechanics.

The second lung-related review highlights the recent contributions of high-resolution 3-D imaging techniques, including synchrotron radiation based X-ray tomographic microscopy (SRXTM) and ³Helium Magnetic Resonance Imaging (HMRI) in conjunction with design-based stereology to investigate postnatal lung development (Schittny 2018). Following a brief description of classical lung development, the review details the need to use innovative high-resolution 3-D

imaging techniques to follow the development of alveoli and tiny pulmonary acini which cannot be resolved in classic 2-D imaging of lung sections. Crucially, unbiased, design-based stereological analyses were then performed on the improved high-resolution images, allowing new details to emerge concerning the development process of alveolarization and the pulmonary acini. The review is beautifully illustrated, and provides a most informative table describing the stages and time scales of lung development in multiple mammalian species.

Enteroendocrine cells and enteric neurons

Fothergill and Furness (2018) present an up to date and authoritative review on hormone-producing cells of the gastrointestinal tract, the enteroendocrine cells (EEC). After presenting a very informative historical account, the authors survey the importance of gastrointestinal hormones in ingestion, digestion and metabolism. They go on to discuss species and regional differences in EEC populations, recent results on the subcellular storage sites of the different hormones as obtained by super-resolution microscopy and electron microscopy, and critically evaluate the threshold problem of hormone detection by immunostaining and gene expression analysis. A most important outcome of all these investigations is that the “one-cell one-hormone” concept is untenable since a majority of EEC contain several hormones which are often stored in different secretory vesicles. In addition, the observed colocalization patterns differ between species and regions which must be taken into account. Thus, the need for a new classification scheme is obvious and the authors propose that the new nomenclature for EEC should be based on cluster analysis to identify cells with common attributes.

Neuhuber and Wörl (2018) review a related aspect, the role monoamines play in the physiology and pathophysiology of the gastrointestinal tract. Monoamines, such as catecholamines are synthesized by enteric neurons, whereas serotonin is produced by both enterochromaffin cells and enteric neurons, and histamine, by contrast, is mainly derived from mucosal mast cells. The review contains a comprehensive treatment on the cellular localization of the catecholamines noradrenaline and dopamine, of serotonin and of histamine and their various roles related to gut motility, secretory reflexes, control of arterial perfusion, immune functions, enteric neuron development, as transmitters, and finally their importance in the modulation of gastrointestinal inflammation and nociception.

Just say “No” to dietary phosphate...

Erem and Razzaque (2018) present a most enlightening review on the pathological systemic effects of dietary phosphate toxicity. Since phosphate levels in purchased

foods are not revealed via product labeling, consumers may be unwittingly ingesting high levels with potentially serious health effects resulting. The review details the plethora of foods containing phosphates, either naturally or as additives, and describes the physiological pathways responsible for the uptake of phosphate into the body. Next, the authors elucidate the potential systemic effects of phosphate overload, including cardiovascular disorders, such as arterial calcification, renal diseases, and type II diabetes. Moreover, the effects of phosphate overload on human health were corroborated by animal studies as outlined by the authors. The review concludes with a discussion of the potential long-term implications of phosphate overload on the health of low-income populations, since lower-cost, processed foods tend to contain higher levels of phosphate as an additive. Since disclosure of the amount of phosphate contained in foods is not required by regulatory agencies, the authors propose global educational initiatives to alert consumers to the potential long-term adverse health effects of dietary phosphate toxicity.

Autophagy at the root of stem cell maintenance

Offei and colleagues (2018) offer a comprehensive summary on the role of cellular autophagy in organism morphogenesis and the maintenance of stem cells. The review begins with a definition and description of the three types of autophagy to date identified (chaperone-mediated autophagy, microautophagy, and macroautophagy), and a summarization of the multiple steps involved in the process of autophagosome formation and the autophagy regulatory mechanism. The authors then discuss a potential role for autophagy during organism morphogenesis, including assisting in epithelial-to-mesenchymal and mesenchymal-to-epithelial transitions by degrading obsolete protein complexes. The role of autophagy in cell fate decisions is also presented in detail, including its association with cellular primary cilia, influencing early cell decisions to form neuroectoderm or mesendoderm layers. The remainder of the review focuses on autophagy and stem cell maintenance. The authors present examples for the requirement of basal levels of autophagy for the maintenance of “stemness” in a variety of cell types, and for cell reprogramming (formation of induced pluripotent stem cells from mature, terminally differentiated cells). In the final section of the review, a discordant role for autophagy in cancer is discussed, whereby in the initial stages of carcinogenesis autophagy appears to serve as a tumor suppressor, whereas in later stages it may serve as a tumor promoter.

Nano-dwarfs for imaging

Thurner and Debbage (2018) revisit the ever-growing field of molecular imaging with nanoparticles and focus on quantum nanoparticles prepared from allotropes of carbon. This most comprehensive review starts with a section on energies and materials, since for simplicity the authors consider nanoparticles composed of light-emitting material and bearing a single targeting group and continue with a section on quantum aspects of matter, the principle behind strong tunable photoluminescence. After a highly detailed discussion about quantum nanoparticles made from allotropes of carbon, which highlights important properties such as their low intrinsic toxicity and the easy availability of raw materials for synthesis by “green” synthetic pathways, nonquantum nanoparticles and their physicochemistry are considered. The following sections represent the core of the review: imaging of glowing nanoparticles in a human body, targeting in nanomedicine, and translation to the clinical market with a highly informative discussion of the various adversities and benefits encountered during this process.

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