PREFACE

Our concept of the cell's nucleus has undergone significant reevaluation. Primarily, it had been regarded a largely amorphous porous sphere, containing the cell's genome. Macromolecules (protein–RNA) would enter and exit the nucleus, as part of the gene regulation–translation process, via the nuclear pores that traverse the nuclear membranes.

This view has changed over the past decade. One aspect in this altered perspective has been (unsurprisingly) that there is an extensive network of subnuclear structures/organelles, such as gems, speckles, and Cajal bodies, among others, that appear to largely function in regulating the synthesis of different types of RNA. Firstly, chromosomes are confined to specific locations or territories, with the spatial location of genes on these chromosomes changing as these genes are transcribed/suppressed, so implicating the position of genes being important for their regulation. Secondly, the nuclear periphery, comprised of the nuclear envelope (NE) and underlying nuclear lamina, contains a range of proteins whose expression varies according to cell type and that also show dynamic changes during embryonic development. Among the NE proteins are those of the LINC complex which functions to tether nuclei to the various components of the cytoskeleton—again in a cell-specific manner. This connection between the interphase nucleus and the cytoskeleton is particularly intriguing since it may function as a direct physical link between the cell membrane/extracellular matrix and nuclear interior, that is, nucleoplasm/chromatin. Such a link implicates nuclear structure being a key component in the mechanosignaling/transduction process. Whether such a link has a role in regulating gene expression/chromatin organization in response to mechanical stimuli is a tantalizing prospect.

However, the greatest stimulus to initiating interest in nuclear structure (its functional architecture) has been the finding that some 30 different inherited diseases are caused by mutations in genes encoding many of the NE proteins and above all the lamins. Paramount in generating this interest has been the lamin A gene of which more than 450 mutations have been mapped that result in some 6–8 diseases, the so-called laminopathies. Within the field of human genetics, no other gene is known that when mutated in different ways results in so many different, seemingly tissue-specific diseases.

Linking so many diseases to the proteins of the lamina and NE has stimulated a major reassessment of how the structural organization of the nucleus

is important to its function. At the clinical level, despite these diseases being relatively rare, they may potentially provide novel insights into their more common variants, some of which include some of the more pressing issues in twenty-first century "developed world" health issues. These include obesity/diabetes, cardiovascular disease, neurological decline, and aging; the latter being the major catalyst for the other diseases, hence this rather eclectic collection of review articles which cover nuclear structure, the LINC complex, and some of the diseases associated with lamin/NE protein mutations and how they may shed light on their more prevalent equivalents.

In Chapter 1, Burke and Stewart provide an up-to-date summary of the different mouse lines that have been derived with mutations in the three lamin genes and a selection of some of the better-studied NE proteins. The extent to which the various pathologies resulting from these mutations in mice can vary between the mouse and human patient is discussed; however, some of these mice have provided valuable insights into the (continuing) development of therapeutics that may treat the human disease. Some of these mutants have also exemplified how genetics can reveal unexpected interactions between the various NE proteins and lamins, indicating that the different NE proteins function as an integrated network.

In Chapter 2, lipodystrophy, a group of rare diseases resulting from the loss or redistribution of white fat, is covered. Paradoxically, a loss of white fat results in many of the same pathologies associated with obesity, including diabetes, altered triglyceride/cholesterol levels, and steatotic liver. In this chapter, Rochford reviews what insights, together with their strengths and weaknesses, mouse models of the so far 10 generalized and partial congenital lipodystrophies have provided. Many of these diseases arise from mutations in proteins associated with forming or maintaining the intracellular lipid droplets, where others arise from, including the lamins, nuclear proteins.

In Chapter 3, Dauer and colleagues cover mouse models of diseases arising from neurological defects in the basal ganglia and associated circuits in the subcortical region of the brain. These structures are involved in coordinating movement and learning-related motor functions. Congenital diseases that affect these neural circuits include Tourette syndrome and obsessive compulsive disorder, Rett's syndrome, and primary dystonia, with the last arising due to disruption of the NE protein Torsin.

Fiedler and colleagues in Chapter 4 cover the extensive literature relating to the contribution of cell death to heart failure and the extent to which defects in signaling pathways are responsible. They review a wide range

of mouse models of heart failure and how some of these models have been used in developing potential therapeutics with varying degrees of success.

Overshadowing all of these congenital diseases is the influence that the aging process has on their development, since aging is the greatest risk factor to developing cancer, cardiovascular disease, and many neurodegenerative diseases. Since the discovery that life-span can be genetically regulated, this has stimulated an enormous interest into what factors/genes influence longevity, either in prolonging or shortening (progeria) life-span. This is now an enormously diverse area of research and Kennedy and Chen in Chapter 5 have accomplished the not insignificant task in reviewing current studies on mouse longevity and how they related to other animal models, as well as suggesting possible avenues that would promote *healthy* human aging, rather than increasing longevity.

The last chapter (Chapter 6) by Horn provides the first comprehensive review of the LINC complex of proteins in many different organisms and their importance in various different tissue functions in mice, fertility, skeletal–cardiac muscle function, and hearing, among others.

From these chapters, it is apparent that the mouse genetics and models of some of the various diseases have had and still make an important contribution to understanding the complexity of the molecular pathology underlying the diseases covered in this issue. At present, existing mouse models are coming under increasingly critical focus as having been often unsatisfactory in developing therapeutics for the equivalent human disease. This situation is echoed in the chapters by Schneider, Kennedy, and Stewart, where it is clear that if mice are to be useful models then greater care has to be used in both developing and maintaining the model in question (Perrin, S. 2014. *Nature* 507, 423–425). Given the enormous level of knowledge gained and the extent of mouse genetic resources developed over the past quarter of a century, it would a shame to squander such a resource. On top of these issues, new techniques of gene manipulation (Talens, Crispr) will help in surpassing some of these concerns (e.g., the genetic heterogeneity of current ES lines to used to manipulate mice). These techniques are also making it easier and economically feasible to develop alternative animal models (rats, pigs, even primates) to model these diseases. Mouse genetics is still an important tool in biomedical research. However, with the advent of new techniques of gene manipulation, these other species will become increasingly important in both modeling various human diseases and in searching for novel therapeutics and may well eclipse mice.

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