Introduction to mammalian genome special issue: metabolism

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I would like to thank my fellow guest editors Professor Stephen O’Rahilly (FRS), Professor Frances Ashcroft (FRS), Professor Jeffrey Friedman, Professor Alan Attie, and Professor Je Kyung Seong for their many suggestions for contributors. Metabolism is a huge field and is intimately involved in many diseases, although for this issue we have focused on diabetes, obesity, and energy metabolism.

Three of our reviews deal directly with aspects of the genetics of obesity, diabetes, and the complications of diabetes. The review by Sadaf Farooqi deals with genetic studies in humans and how these impact on differences in susceptibility to environmental factors and how highly penetrant genetic variants have informed us about central pathways controlling energy expenditure. A consequence of chronic hyperglycemia is the development of micro- and macrovascular complications that are the cause of much of the morbidity and mortality in diabetes and this again has a genetic component interacting with environmental factors. The review of Sami Alkayyali and Valeriya Lyssenko addresses this in the genetics of diabetic complications and the role of epigenetic factors in their pathogenesis. Finally, Hans-George Joost and Annette Schürmann discuss the use of mouse models to investigate the complex genetic basis of obesity and diabetes.

Extending the theme of body weight regulation is a review by Myrte Merkestein et al. who give an evolutionary perspective on adipose tissue function and in utero programming of brown adipose tissue development. Critical to any understanding of whole body energy metabolism is the mitochondria, the main site of cellular energy

production. The contribution from Adrienne Mottis et al. examines the maintenance of mitochondrial proteostasis and of cell and organism health. It reviews the protein quality control network and the role of the relatively newly discovered mitochondrial unfolded protein response and considers how fine-tuning of these processes could be used in treatment of metabolic diseases.

Metabolic homeostasis requires signaling between many organs, tissues, and cells. Mary LaPierre et al. report on how the hypothalamus responds to hormones and nutrients to regulate hepatic glucose output and glucose homeostasis. This includes the exciting recent work from the Lam laboratory on glucagon signaling in the hypothalamus. The review from James Cantley returns to the theme of adipose tissue in detailing the influence of adipose tissue-secreted ‘adipokines’ in insulin secretion. Plasma sulfur amino acids in humans are correlated with body composition and Amany Elshorbagy reviews these relationships and how knockout mouse models have been useful in beginning to understand how sulfur amino acid metabolism is linked to body composition. Finally, within this theme of metabolic regulation, Abram Katz and Häken Westerblad review the effects of exercise on skeletal muscle function and adaption.

Two reviews deal with modeling of disease in the laboratory mouse. Jesse Riordan and Joe Nadeau describe non-alcoholic fatty liver disease (NAFLD) modeling in the mouse and how well-defined model systems can be used to understand the transition in some individuals from this relatively mild state to the more serious pathologies of non-alcoholic steatohepatitis (NASH) and further to liver cancer. Michelle Goldsworthy and Paul Potter discuss the use of the mouse in modeling aging-related diseases, describing the Harwell aging mutagenesis screens.

In the last section, we have four articles on metabolic phenotyping in the mouse. The mouse remains an important

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model in metabolism and is being used to understand the function of individual genes, for example, in the study of candidate genes identified from human genome wide association studies (GWAS) and in more systematic programs to link phenotypes to genes by the international mouse phenotyping consortium (IMPC). Metabolic phenotyping requires the application of techniques on mice that are well defined in terms of genetics and environment and that use standardized operating procedures—if the results are to be robust and reproducible. The rigorous application of the ARRIVE guidelines (Kilkenny et al. (2010)), for example, should help in the generation of accurate preclinical data that can be used to further our understanding of metabolic disease and develop new therapeutic opportunities. Robust animal studies are essential (for further discussion see, for example, Perrin (2014)) and these reviews address some of these issues. The reviews by Jan Rozman et al. and Hui-Young Lee et al. cover many of the standardized metabolic phenotyping procedures used in the mouse. Curtis Hughey et al. discuss sophisticated approaches to assessing glucose

homeostasis in the conscious mouse and explore some of the issues around study design, test selection, and interpretation of data. Finally, Steven Ciciotte et al. describe techniques for imaging the whole mouse pancreas, which are important in understanding the role of the islet in diabetes progression.

I hope that you enjoy the reviews that we have collected for this special issue of Mammalian Genome and that they provide a sense of the potential for a greater understanding of metabolism that can be obtained through a proper consideration of the genetics and physiology of mammalian organisms.

References

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