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PREFACE

Gene Regulatory Networks in the Genomics Era

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The precise regulation of gene expression is critical to the normal development and biological function of all organisms. Dysregulation of gene expression during early development can result in a spectrum of failures ranging from minor defects to the termination of development. In adult life, dysregulation can lead to the uncontrolled cell proliferation of cancer or programmed cell death leading to neurodegenerative diseases. The regulation of gene expression is controlled by multiple systems with more being discovered. The immediate regulators are transcription factors which bind to specific sequences in the promoter or enhancer regions of individual genes. The activity of transcription factors can be regulated by the presence of other transcription factors and cofactors, methylation status of the promoter or enhancer region, accessibility of the DNA due to the local compactness of the chromatin and various modifications of the histone tails. Transcribed mRNAs are then subject to degradation before being translated into protein products, during which microRNAs play a major role [1]. In this special issue, we present recent advances in the elucidation of gene regulatory networks (GRNs).

After the completion of the human genome project, people realized that even excluding the repetitive sequences, protein coding regions are only a small portion of the whole genome. To explore the functional roles of the "junk" regions, the National Institutes of Health (NIH) started the encyclopedia of DNA elements (ENCODE) project in 2003, which has generated vast amounts of functional data for non-protein coding regions over the past 10 years. In this issue, Qu and Fang provide a short review of the history and current status of the ENCODE project [2].

Enhancers are DNA elements directly involved in the regulation of gene expression. Enhancers can be located near coding regions or far away. The activity of enhancers with respect to gene expression depends on the specific tissues and/or developmental stages, as a consequence of the presence or absence of transcription factors and the epigenetic modifications of the enhancers themselves. In this issue, Wang et al. review computational efforts to identify spatially and temporally active enhancers using the recently available ENCODE data [3].

The activity of enhancers requires the presence of mediator complexes. Mediator complexes are large protein complexes which bind to transcription factors, RNA polymerase II and various transcription regulators such as non-coding RNAs. Mediator complexes are essential for transcription, and defects in mediator complexes have been associated with severe diseases. In this issue, Grueter presents a review of the role of mediator complexes in cardiac development and disease [4].

We have also included two original research articles in this special issue. Bickhart and Liu use a bioinformatics approach to identify approximately 380,000 putative transcription factor binding sites in the cattle genome, validating a subset of them and demonstrating their specificity [5]. This work paves the way for comparison of GRNs between cattle and other mammalian model systems. In order to construct complex interaction and regulatory networks, Sun et al. incorporate information from multiple sources, including protein-protein interaction databases, pathway databases, transcription factor target gene predictions and microRNA target gene predictions to generate regulatory networks from an input gene set [6].

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The resources from both works are available online. In addition, Li et al. present a summary of the discovery of biomarkers for lupus nephritis from serum and urine employing genomic approaches [7].

The elucidation and study of GRNs is a fast evolving field. Recently, RNA methylation has emerged as yet another layer of regulation [8]. With the rapid development and application of genomic technologies, we anticipate that many new layers of regulatory complexity will emerge. In the meantime, it becomes increasingly important to understand the complex relationships between genes and how changes in GRNs can result in phenotypic change.

Acknowledgements

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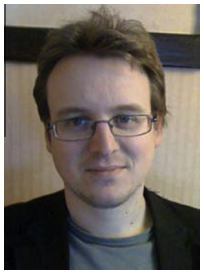
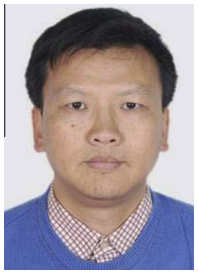


Matthew Loose, PhD, Lecturer in School of Biology at the University of Nottingham, UK. He has been working in the field of developmental gene regulatory networks (GRNs). Ongoing research projects in his lab include defining the GRNs specifying mesoderm in amphibians, blood in frogs and mice, and heart in various organisms. He developed tools to collate and explore networks (http://www.mygrn.org) and developed mathematical models describing these networks. He has recently been investigating the conservation of regulatory networks in organisms with induced and pre-determined germ lines, the interplay of mesoderm specification and germ cells, and exploring how gain and loss of genes can dramatically alter network behavior.

Roger Patient, PhD, Professor of Developmental Genetics at Oxford University and Deputy Director of the MRC Molecular Haematology Unit in the Weatherall Institute of Molecular Medicine on the John Radcliffe Hospital site, UK. Ongoing research projects in his lab include defining the transcriptional networks that programme hematopoietic stem cells during embryonic development, and the embryonic signalling pathways that lay these programmes down. A similar approach to development of the myocardium is being taken. He has served as Deputy Chair of the MRC Molecular and Cellular Medicine Board and a member of the British Heart Foundation Chairs and Programme Grants Committee. He has been elected to EMBO.

Xiangdong Fang, MD, PhD, Professor of CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, China. Dr. Fang received his Doctor degree from Nanfang Medical University in Guangzhou, China and postdoctoral training from the Medical School at University of Washington in Seattle, USA. Dr. Fang's current research interest is focused on the epigenetic regulation of eukaryotic genes, especially the delineation of the molecular mechanism of genetic diseases and carcinomas using various omics techniques based on different high-throughput sequencing platforms.



Hongxing Lei, PhD, Professor of CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, China. Dr. Lei received his PhD degree from the Department of Biochemistry at Kansas State University and postdoctoral training from the Genome Center at UC Davis, USA. Dr. Lei has been working in the field of computational biology. Current research in his lab is mainly focused on the understanding of the complex interaction and regulatory networks in neurological disorders such as Alzheimer's disease.