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The impact of new technologies in our understanding of testis formation and function

The testis has two main roles, production of gametes for reproduction and synthesis of hormones for masculinization and spermatogenesis. Testis organogenesis is a complex developmental process. Bipotential progenitors undergo coordinated differentiation leading to the development of a testis rather than an ovary, which includes the formation of testis cords and interstitial cells providing a unique microenvironment known as the germ stem cell niche (Svingen and Koopman, 2013). Failure of normal testicular development and function is associated with a variety of male reproductive disorders including disorders of sex development (DSD) and infertility. Although considerable progress has been made in identifying the molecular mechanisms of human testis development and function, many DSD and male infertility cases remain idiopathic (Punab, Poolamets, Paju et al., 2017).

This situation is likely to change, as more powerful tools become available for detailed analyses of testis development and function and their relevant pathologies. This issue synthesizes recent advances in the male reproductive field taking advantage of the emergence of new technologies such as next-generation sequencing, single cell transcriptomic, exome sequencing, epigenetics, the CRISPR/Cas9 system, novel experimental models utilizing human testicular tissues and gene therapy delivery systems. We expect that these new tools will have a major impact on our understanding of the genetic causes of DSD and male infertility. To set the scene, the first article by Stévant et al. provides a historical perspective on sex determination and how societies and technical improvement influenced our understanding of sex determination (Stevant, Papaioannou and Nef, 2018). From the *Renaissance*, former theories of the involvement of heat, laterality, or food in sex determination have been challenged by systematic scientific research and the emergence of new tools such as the microscope, histological techniques and, more recently, with the advances in genetics, genomics, and epigenetics. The first half of the following reviews, then, discuss in more detail how the latest technological advances improved our knowledge of vertebrate sex determination and testis development; while the second part of this issue examines how these new technologies can potentially be used for the diagnosis and treatment of human reproductive pathologies.

Our understanding of early molecular and cellular events during gonad development expanded greatly due to the emergence of single-cell RNA sequencing (scRNA-seq) as a new powerful tool to obtain unique insights into gene expression at the level of the most fundamental unit of an organism: the single cell. The application, as well as strengths and limitations of this technique to sex determination, is discussed (Stevant and Nef, 2018). It allows the identification and classification of cell populations that are present in the developing gonads in a comprehensive and unbiased manner. In particular, scRNA-seq enables the tracing of cells along developmental trajectories and characterization of the transcriptional dynamics controlling cell differentiation. In addition to these cellular and transcriptional mechanisms, epigenetic regulation is important for vertebrate sex determination and is discussed in detail in two reviews. Epigenetic regulation not only contributes to the bipotential state of the fetal gonad but also to cell fate commitment through the fine-tuning of the timing and expression levels of sex-determining genes. While the review of Garcia-Moreno et al. provides a comprehensive overview of epigenetic control of sex determination in several vertebrate species (Garcia-Moreno, Plebanek and Capel, 2018), the review by Makoto et al. more specifically covers epigenetic regulation of the male-determining gene *Sry* and the role of the H3K9 demethylase JMJD1A in this process (Kuroki and Tachibana, 2017). The next article focusses on one of the important cell types within the testis, Leydig cells, which are responsible for the production of androgens. The authors provide a summary of the most recent advances in the understanding of the differentiation of not only fetal but also adult Leydig cells in mammals, their developmental and functional relationship, as well as their specific characteristics (Shima and Morohashi, 2017). This first half of the issue finishes with a comprehensive overview of the current literature as well as datasets and resources that are available concerning the transcriptional analysis of testis development and germ cell function (Lecluze, Jegou, Rolland et al., 2018).

The next set of reviews expands the discussion from enhancing our knowledge through new technologies to applying these technologies to human reproductive disorders including DSDs and male infertility. DSDs are defined as congenital conditions in which the development of chromosomal, gonadal, or phenotypical sex is atypical. One of the biggest challenges regarding DSDs is to identify the underlying genes causing these disorders. The review by Barseghyan *et al.* describes the advantages and limitations of genetic methods currently available for DSD diagnosis (Barseghyan, Delot and Vilain, 2018). It includes classical techniques such as Sanger sequencing, karyotyping, exome sequencing and chromosomal microarrays as well as newer approaches, for example whole genome sequencing and mapping, along with gene expression studies that should improve the capacity to identify causative variants for DSD. To follow on from this, the review by Kherraf and colleagues demonstrates a nice example of how the combined use of whole exome sequencing of human patients and CRISPR/Cas9 genome

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modification in mice can be used as an efficient strategy to identify new genetic variants and genes involved in male infertility and create animal models to validate in a timely fashion, mutations responsible for infertility phenotypes in human (Kherraf, Conne, Amiri-Yekta et al., 2018). However, since there are significant species differences in testicular development and function between human and rodents, it highlights the need for suitable experimental models utilizing human testicular tissues or cells. This is addressed in the next review by Tharmalingam and colleagues, which outlines established and novel approaches used to culture cells and tissue from human testis as well as discuss relevant experimental endpoints such as survival, proliferation, and differentiation of cell lineages within the testis as well as paracrine and endocrine function (Tharmalingam, Jorgensen and Mitchell, 2018). The authors also highlight the possibility to use these experimental approaches to assess the effects of environmental exposures on testicular development. A different aspect of cell biology techniques, namely the delivery of RNA or DNA into cells and tissues along with the potential use of these gene delivery systems for the diagnosis or treatment of common male reproductive disorders is discussed in the following article by Darbey et al (Darbey and Smith, 2017). It details the advantages and limitations of each gene delivery system, including relevant histories and examples of successful and unsuccessful studies and clinical trials. This review will be a useful repository of fundamental gene therapy information that likely will be a first source of information for years to come. Finally, the last two reviews focus on the development and physiology of sperm, an important matter in the development of treatments for subfertile men and designing of male contraceptives. The review by Balbach and colleagues summarizes the current knowledge about the molecular makeup and functional role of cAMP-signaling pathways in controlling sperm functions (Balbach, Beckert, Hansen et al., 2017), while the last article by describes the mechanisms involved in epigenetic programming in the male as well as female germlines and relates these processes to the emergence and clinical use of epigenomic drugs (Western, 2018). This review highlights an important clinical need to develop an informed position that underpins the use of epigenetic modifier drugs in patients of reproductive age.

Taken together, this volume was written by experts in the fields of sex determination and testicular functions. It is intended to inform the reader about the emergence of new tools and technologies for detailed analyses of testis development and function and their relevant pathologies. We hope that you will enjoy the reading.

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