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Regulation of ovarian function

The ovary today and tomorrow

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COMER editorial

Regulation of Ovarian Function: the ovary today and tomorrow

General introduction: (NOTE: also Introductory Text for Science Direct)
We are both very excited to have this opportunity to gather together a collection of papers that reflect recent advances in ovarian physiology, and highlight new technological methodologies that increase our understanding of this wonderfully complex and dynamic organ. This compilation covers the latest techniques, up-to-date molecular findings, new understandings of the importance of cell-cell interactions and also places current research into its clinical context. Since we are focussing on the ovary, the importance of transgenerational effects becomes paramount. The authors of these reviews have been carefully chosen in light of their expertise in the field, and we thank them for their contributions.

Section 1: Formation of a finite pool of follicles
The volume begins with two reviews covering the early steps of ovary development. Whilst ovarian anatomy has been well understood for many years, there are still surprising gaps in our understanding of the molecular and genetic regulation controlling how the early, indifferent gonad can develop to form an ovary. **Greenfield's** review details how new transcriptomic and epigenomic approaches have furthered our understanding of the pathways required for granulosa cell determination, highlighting the plasticity of the system which can continue to be perturbed through adulthood. This area is also a fabulous illustration of how mouse models and clinical studies can together improve our understanding of disorders or differences of sex development. **O'Connell and Pepling** then examine how the granulosa cells and oocytes form ovarian follicles, showing the importance of cell adhesion as germ cell cysts break down and primordial follicles form. This review also discusses the surprising role that autophagy can play throughout the process of follicle formation: there is discrepancy between different studies here, but increasing evidence showing that autophagy can at some stages counterbalance the apoptotic pathway, promoting the formation of primordial follicles.

Section 2: Regulation of follicle development
Follicle development is regulated by steroids, gonadotrophins and local growth factors. The signalling pathways that are initiated by these factors are transmitted between different cell types in the ovary. Two key cell types that have to communicate with each other are the oocyte and the granulosa cells; failure to do so disrupts follicle and oocyte development. Signals between these two cell types have to traverse an intervening layer of extracellular matrix, the zona pellucida. **Clarke** has focused on the essential two-way dialogue between the oocyte and the surrounding granulosa cells via physical interactions, namely transzonal processes crossing the zona pellucida, allowing direct passage of a variety of small molecules. Moving on from physical contacts between different cell types leads us to an exploration of the key signalling molecules themselves. **Franks** provides an in-depth overview of the action of an important steroid, androgen. Androgen is the essential substrate for oestrogen production, and also plays a role in the demise of subordinate follicles just before ovulation of the dominant follicle. However, elevated androgen levels in women can be associated with a variety of health issues, including infertility, hirsutism, acne, metabolic syndrome, obesity and Type 2 diabetes, which collectively lead to a diagnosis of polycystic ovary syndrome, a common disorder in women. Moving on to the role of growth factors in the ovary, **Patton, Madadi and Pangas** provide a comprehensive overview of an essential family of growth factors in reproduction, the TGFβ superfamily. This family comprises a variety of ligands produced by different cell types in the ovary which bind to various receptor combinations, interacting with an equally extensive array of binding proteins: this results in a tightly regulated system that controls many aspects of follicle development.

Section 3: Perturbations of ovarian function.

The next set of reviews moves on to examining how different endogenous factors can affect the ovary. The first two of these examine the consequences of the finite supply of follicles in the ovary, decreasing over time, with women then entering the menopause once that supply is too low to allow the ovary to support full follicle development and ovulation. **Sutherland and McLaughlin** discuss the consequences of ovarian ageing, leading amongst other things to an increase in aneuploidy, mitochondrial dysfunction and DNA damage. There is a particular focus on the increase in chronic inflammation that is associated with ageing, inflammaging. The review highlights the extent to which new technologies can help us work out the interplay between the different factors changing during the ageing process. Early loss of the ovarian follicle pool is discussed in **Rosario and Anderson's** review on premature ovarian insufficiency (POI), which examines how the candidate gene approach and that of genome wide analyses have helped us uncover the genetic aetiology of POI. Particular attention is paid to examination of non-coding RNAs, and the variability in the effect of gene variants across different genetic backgrounds. The final review in this section, by **Andreas, Winstanley and Robker**, turns to obesity, a factor that has been shown to affect female reproduction in general, and ovarian function in particular, in a myriad of ways. The authors discuss the diverse nature of effects, pointing to the likely early timepoint at which these can be laid down, with transgenerational consequences also clear. With worryingly high and still accelerating rates of world-wide obesity, this is an increasingly important factor to understand.

Section 4: Effects of the environment on ovarian function.

We move from there on to examination of exogenous effects on the ovary. One clear consequence of modern living is constant and growing exposure to pollutants, an issue of increasing international concern, and the first two papers here examine different aspects of this. First, **Lecante, Lelandais, Mazaud-Guittot and Fowler** focus on effects on the developing fetal ovary. The long-term and widespread consequences of disruptions to fetal development has been clear for decades, and this review looks at a range of environmental toxicants, their outcomes, chemistry, and windows of vulnerability for the fetus. Studies here are notable for the range of model species used to complement human investigations. **Neff and Flaws** then focus specifically on the effects that plasticizers can have on ovarian development and function. With continual and pervasive exposure to plasticizers resulting in increasing accumulation through an individual's lifetime, it is not surprising that effects range from those on fetal ovary development through to reproductive outcome, with clear transgenerational effects. In addition to consequences of pollution exposure, detrimental effects on the ovary can arise from deliberate, planned exposure to clinical treatments. The third article in this section is one example of that, examining how cancer treatment can impact on the ovary. Chemotherapeutics have revolutionised cancer treatment over the last few decades, making a notable contribution to improved survival rates; one result of this has been the need to determine the extent of chemotherapy drug-induced damage to reproductive health, as well as consequential effects on general health. As well as outlining the main detrimental effect of these drugs, **Alesi, Winship and Hutt's** review focusses on potential protectants from that damage, as well as the future treatments that will hopefully be more specific in their effects, thus mitigating against this kind of collateral damage.

Section 5: Future technologies

This issue was put together as the Covid-19 pandemic took hold, a time when the importance of mathematical modelling came to the attention of the public as it became a key tool to inform management of the spread of this terrible virus. This is not a new approach, having been a cornerstone for gaining insight and testing hypotheses in a wide variety of fields for decades. One field that has benefited from this approach is that of modelling ovarian physiology and follicle

development, elegantly described in the chapter by **Clément and Monniaux**. They discuss the use of modelling to gain a greater understanding of follicle dynamics in a number of contexts, including aging, follicle development and selection. Following on from this, one key regulator of reproductive lifespan is the rate of follicle activation. Activation of follicle growth is the first step in follicle development - a transition that shifts the primordial follicle from quiescence to growth, with only two possible outcomes, ovulation or follicle death. The entry of follicles into the growing pool must be tightly regulated to allow a steady supply of mature oocytes throughout the reproductive lifespan. Sadly, for some younger women the follicle pool is depleted prematurely, resulting in POI (a topic that has been covered in an earlier review in this volume by **Rosario and Anderson**). A key area that requires further research is that of the signalling pathways involved in regulating follicle activation. **Wu, Liu and Zhang** have been exploring the manipulation of signalling pathways such as PTEN/PI3K, Hippo and M-Tor, by fragmenting pieces of excised ovary and stimulating activation of the few remaining primordial follicles in women with POI, with the aim of generating mature oocytes to achieve pregnancy. We then move on to two reviews that explore different approaches to generating mature oocytes. **Nagaoka, Saitou and Kurimoto** consider the development of techniques enabling the differentiation of mouse oocytes from pluripotent stem cells, while also examining approaches to achieve this in other species, including human. **Dolmans** then discusses the technology of developing artificial ovaries, placing this work in context of a potential fertility preservation treatment, thus linking this topic to **Alesi, Winship and Hutt's** earlier review on the effect of cancer treatment on the ovary. Finally, **Fan and Chuva de Sousa Lopes** have drawn together an extensive array of data from single cell sequencing obtained from different cell types in the ovary. They have provided an incredible resource, highlighting the gene signatures in the different cellular compartments of the ovary at different stages of development.

Editing this volume of COEMR has provided us with an opportunity to bring together a range of viewpoints from experts working on diverse aspects of this fascinating organ, the ovary. We believe that the result will prove to be a superb information resource for those studying female reproductive biology.