

# Trends in Endocrinology & Metabolism



## Forum

### Organ-ovary crosstalk as a vital determinant of women's health

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**The ovary is more than just a reproductive organ. Recent evidence in mammalian and invertebrate models consistently highlights novel mechanistic insights into organ-ovary crosstalk via classical hormones and emerging secretomes, such as extracellular vesicles. Thus, the ovary functions as an integral organ to maintain organismal health through crosstalk with various organs.**

#### The ovary is more than just a reproductive organ

Across the female reproductive lifespan, women experience a period of healthy reproductive years, which is followed by a rapid decline in fertility and ultimately culminates in menopause. Menopause is associated with accelerated aging of bodily functions and an altered risk profile for cardiovascular–kidney–metabolic syndrome and cancer [1–5]. Simultaneously, young women with poor metabolic health or a suboptimal fat-to-lean body mass ratio are often associated with reproductive dysfunctions. These reciprocal associations highlight that the ovary functions not only in reproduction but also as an integral organ that maintains whole-body homeostasis through organ-ovary crosstalk.

Despite its importance, the underlying mechanisms of organ-ovary crosstalk in sustaining systemic health remain poorly understood. Addressing this knowledge gap allows for the development of targeted

therapeutic strategies to improve both reproductive functions and healthspan via the sustenance of ovarian health as a proxy. In this forum article, we discuss recent evidence in mammalian and invertebrate models that highlight novel mechanistic insights into organ-ovary crosstalk via classical hormones and emerging secretomes, such as extracellular vesicles (EVs).

#### Expanding views on hormonal regulation of organ-ovary crosstalk

Organ-ovary crosstalk refers to the inter-organ exchange of biomolecules going in and out of the ovary, where they activate molecular signalling to support homeostatic physiological interactions. In mammals, the widely known organ-ovary crosstalk is the hypothalamus–pituitary–ovarian (HPO) axis, where the hypothalamus and pituitary gland secrete follicle-stimulating hormone (FSH) and luteinizing hormone that regulate follicular development and ovulation. In turn, the ovary produces oestrogen which maintains secondary sexual characteristics and regulates reproductive functions. Recent studies have discovered additional organs that participate in the organ-ovary crosstalk.

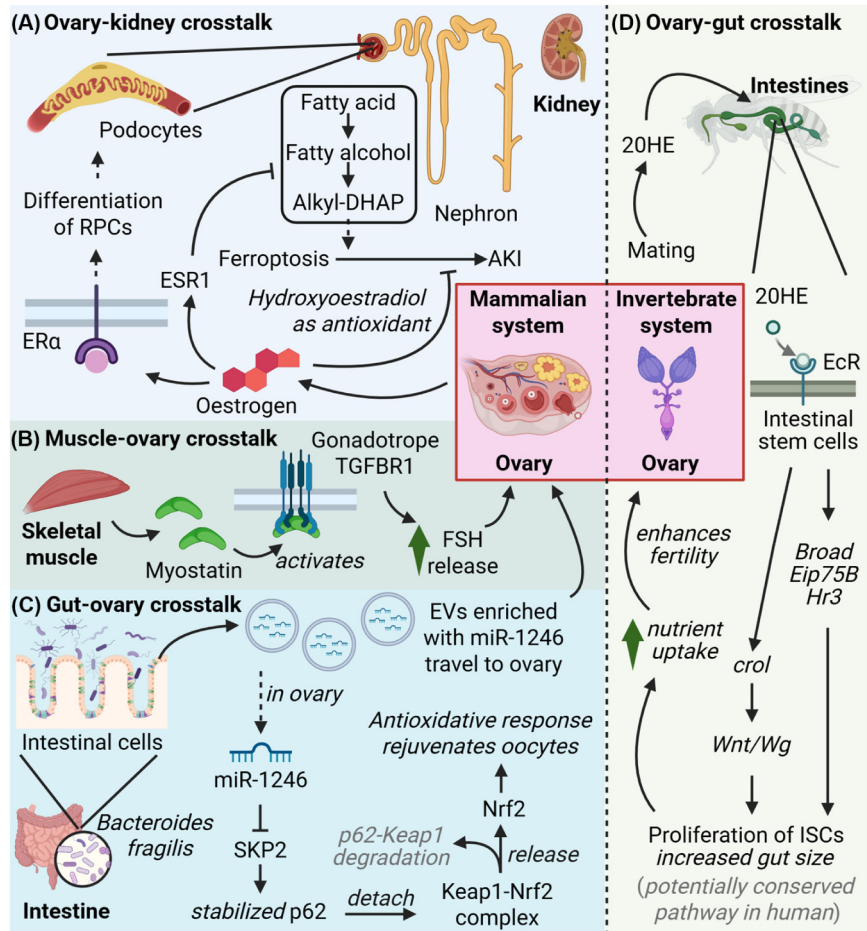
Apart from its roles in reproduction, the ovary confers protective effects on renal physiology, particularly in the context of acute kidney injury (AKI) [2] and chronic kidney disease (CKD) [3], through ovary-kidney crosstalk. As highlighted in recent mouse studies (Figure 1A), ovarian-derived oestrogen acts as a radical-trapping antioxidant and suppresses ferroptosis in the renal tubules. Ferroptosis is an iron-dependent form of regulated cell death that drives renal cell damage and can secondarily promote inflammatory responses leading to AKI. Besides being an antioxidant, oestradiol also binds oestrogen receptor 1 to activate the cellular hypopersulfide system and repress the pro-ferroptotic proteins involved in the ether

lipid pathway. Oestrogen signalling in kidney tubules also supports the regeneration and differentiation of renal progenitor cells (RPCs) into podocytes. Disruption of this pathway and the resulting dysfunctional RPCs are linked to a higher risk of CKD, pre-eclampsia, postnatal hypertension, and an intergenerational effect in limiting nephron formation in offspring. Collectively, oestrogen plays indispensable roles in maintaining renal health and may explain why there is a higher prevalence of AKI and CKD in men and postmenopausal or ovariectomised women.

A recent study highlighted an unexpected role for skeletal muscle in regulating ovarian function [6]. Skeletal muscle-derived myostatin was identified as a key regulator of pituitary FSH production in mouse (Figure 1B) and rat models. This discovery suggests a potential skeletal muscle-ovary crosstalk and muscle fitness as a modulator of ovarian function. Mice injected with myostatin neutralising antibodies had reduced circulating serum FSH levels, resulting in lower follicle formation. Stronger phenotypic changes were also observed in *myostatin* knockout mice, including delayed puberty onset, smaller litter size, and reduced ovarian weight. Mechanistically, myostatin stimulates FSH production by binding to the TGFB (Transforming growth factor beta) type 1 receptor (TGFB1) at the pituitary gonadotroph. This raises several clinical implications as to whether therapies targeting myostatin need to be carefully evaluated in view of the potential side effects on fertility.

#### An emerging 'language' in organ-ovary crosstalk

Recent literature suggests the involvement of the secretome, such as EVs, as an emerging 'language' in organ-ovary crosstalk beyond hormones. EVs contain diverse regulatory noncoding RNAs, including microRNAs (miRNAs), that can modulate biological processes in their target recipient organs. For instance, a recent



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**Figure 1. Organ-ovary crosstalk in mammalian and invertebrate systems.** (A) In ovary-kidney crosstalk, oestrogen exerts protective effects on ferroptosis and AKI by acting as an antioxidant and repressing pro-ferroptotic proteins in the ether lipid pathway. Oestrogen signalling in renal tubules also supports regeneration and differentiation of RPCs into podocytes, playing crucial roles in renal health and homeostasis. (B) In skeletal muscle-ovary crosstalk, studies in murine models suggest that myostatin acts as an important and additional regulator of FSH secretion in maintaining ovarian function, along with the traditional HPO axis. Skeletal muscle-derived myostatin stimulates FSH secretion by binding to the TGFBR1 receptors on gonadotrope. (C) Beyond hormones, the gut is involved in a crosstalk with the ovary by releasing circulating EVs enriched with microRNAs. The gut microbiome, *B. fragilis*, induces EV secretion from intestinal cells and these functionally active microRNAs that are delivered to the ovary to modulate ovarian functions. (D) In *Drosophila melanogaster*, organ-ovary crosstalk is coordinated through hormones as well. Mating triggers 20HE secretion from the ovary where it subsequently promotes proliferation of ISCs, increased gut size and improved food intake. Notably, the *crol*/Wnt/Wg pathway is also observed in human, suggesting that insights from *Drosophila* may reveal conserved regulatory mechanisms relevant to human biology. This image was created with Biorender ([www.biorender.com](http://www.biorender.com)). AKI: acute kidney injury; *crol*: crooked legs; EcR: ecdysone receptor; ERα: oestrogen receptor alpha; EVs: extracellular vesicles; FSH: follicle-stimulating hormone; HPO: hypothalamus-pituitary-ovarian; ISCs: intestinal stem cells; RPC: renal progenitor cells; TGFBR1: TGFβ type 1 receptor; 20HE: 20-hydroxy-ecdysone; DHAP: dihydroxyacetone phosphate; SKP2: S-phase kinase-associated protein 2; Nrf2: Nuclear factor erythroid-2-related factor 2; Eip75B: Ecdysone-induced protein 75B; Hr3: Hormone receptor 3; TGFβ: Transforming growth factor beta; Wnt/Wg: Wnt/Wingless.

exhibited different miRNA profiles, and administration of FF-EVs from young mice rejuvenated ovaries in aged mice.

Two recent publications highlighted that the gut and adipose tissues secrete EVs containing miRNAs that act as modulators of ovarian health [4,8]. In the mouse study (Figure 1C), gut microbiome *Bacteroides fragilis* (BF)-treated intestinal cells secreted EVs enriched with miR-1246 that were transported to the ovary [8]. Uptake of EVs by the ovary led to lower oxidative stress and rejuvenated ovarian function. Inhibition of these EVs using a neutral sphingomyelinase inhibitor (GW4869) ablated the benefits observed in BF-treated mice, reinforcing their functional importance. Mechanistically, miR-1246 stabilises p62 protein by reducing levels of SKP2 (S-phase kinase-associated protein 2), promoting dissociation of the Keap1-Nrf2 (Kelch-like ECH-associated protein 1-Nuclear factor erythroid-2-related factor 2) complex and activating antioxidant pathways in aging oocytes. Together, these studies provide promising examples of EVs enriched with miRNAs as potential mediators of organ-ovary crosstalk, encouraging more in-depth studies.

### Learning from organ-ovary crosstalk in invertebrate models

*Drosophila* is a powerful alternative model to dissect organ-ovary crosstalk and human diseases [9]. Two recent studies in *Drosophila* have highlighted an ovary-gut crosstalk with high relevance to human physiology [5,10]. These studies demonstrated that the steroid hormone 20-hydroxy-ecdysone (20HE), secreted from the ovary of mated females, enhances fertility by promoting intestinal stem cell (ISC) proliferation (Figure 1D). Mechanistically, 20HE activates ecdysone signalling and upregulates downstream targets, including the transcription factor broad and nuclear receptors Eip75B (Ecdysone-induced protein 75B) and Hr3

mouse study demonstrated that when follicular fluid-derived EVs (FF-EVs) were injected into one side of the ovary pair, these FF-EVs

traveled to the other ovary and even to distal organs such as the liver and kidney [7]. Interestingly, FF-EVs from young and aged mice

(Hormone receptor 3) [10]. Mated females exhibited more ISC division compared with virgin flies, and hormone-dependent intestinal remodelling enhanced reproductive output. Knockdown of the ecdysone receptor in midgut ISCs reduced egg production, underscoring the physiological significance of the ovary–intestine axis.

Continual ISC proliferation and gut resizing may increase the susceptibility to age-dependent dysplasia and tumorigenesis, suggesting a potential trade-off. Knockdown of *Notch*, the ISC-specific receptor involved in enterocyte (EC) differentiation, induced tumour formation in mated females but not in virgin females or males. A complementary study demonstrated that 20HE activates *crooked legs (crol)* in ISCs and ECs, promoting ISC proliferation via *string* and *cyclin B* [5]. Mating induced upregulation of 20HE, which also activated the Wnt/Wg (Wnt/Wingless) pathways through *crol*. Notably, hyperactivation of Wnt/Wg by *hZNF267*, a human homolog of *crol*, is linked to the growth of colorectal cancer. Taken together, these studies emphasise the importance of ovary–gut crosstalk and prompt further investigations on the roles of oestrogen in affecting human intestinal health.

### Concluding remarks

Accumulating evidence has underscored the importance of organ–ovary crosstalk in coordinating systemic physiology not only via hormones but also through EVs. Future

directions may explore other bioactive components packaged in EVs such as neuropeptides, adipokines, proteins, and regulatory ncRNAs (noncoding RNAs). Integrating insights from physiologically relevant models such as *Drosophila*, human organoids, and microfluidic organ-on-a-chip platforms [11] will accelerate mechanistic discoveries. In support of the notion that ovarian health reflects systemic healthspan, key markers of ovarian reserve, such as anti-Müllerian hormone, may therefore hold promise as integrative indicators of lifestyle-associated risks for cardiovascular–kidney–metabolic syndrome and cancer. Further studies are required to validate this potential, and more biomarkers may be needed to further enhance our assessment of ovarian health. Ultimately, while the ovary is not essential for immediate survival, it holds pivotal roles in maintaining women’s healthspan by acting as a regulatory hub that extends well beyond reproduction.

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### Declaration of interests

The authors declare that there are no conflicts of interest.

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