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The spatiotemporal hormonal orchestration of human folliculogenesis, early embryogenesis and blastocyst implantation

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ABSTRACT

The early reproductive events starting with folliculogenesis and ending with blastocyst implantation into the uterine endometrium are regulated by a complex interplay among endocrine, paracrine and autocrine factors. This review examines the spatiotemporal integration of these maternal and embryonic signals that are required for successful reproduction. In coordination with hypothalamic-pituitary-gonadal (HPG) hormones, an intraovarian HPG-like axis regulates folliculogenesis, follicular quiescence, ovulation, follicular atresia, and corpus luteal functions. Upon conception and passage of the zygote through the fallopian tube, the contribution of maternal hormones in the form of paracrine secretions from the endosalpinx to embryonic development declines, with autocrine and paracrine signaling becoming increasingly important as instructional signals for the differentiation of the early zygote/morula into a blastocyst. These maternal and embryonic signals include activin and gonadotropin-releasing hormone 1 (GnRH1) that are crucial for the synthesis and secretion of the 'pregnancy' hormone human chorionic gonadotropin (hCG). hCG in turn signals pre-implantation embryonic cell division and sex steroid production required for stem cell differentiation, and subsequent blastulation, gastrulation, cavitation and blastocyst formation. Upon reaching the uterus, blastocyst hatching occurs under the influence of decreased activin signaling, while the attachment and invasion of the trophoblast into the endometrium appears to be driven by a decrease in activin signaling, and by increased GnRH1 and hCG signaling that allows for tissue remodeling and the controlled invasion of the blastocyst into the uterine endometrium. This review demonstrates the importance of integrative endocrine, paracrine, and autocrine signaling for successful human reproduction.

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1. Prologue

The endocrine, paracrine and autocrine factors regulating folliculogenesis and the implantation of the blastocyst into the endometrium are well described (e.g., Hillier, 2009; Pawar et al., 2014; Singh et al., 2011a). However, given its importance for human life, it is surprising that there is a relative dearth of knowledge regarding the signals that regulate reproduction between these two events, i.e. starting from the division of the human zygote through its differentiation into a blastocyst during passage along the fallopian tube and into the uterus prior to implantation. Likewise, the hormonal signals regulating blastocyst hatching also are largely unexplored. These periods of time are most crucial for the development of the embryo and importantly, signaling by the embryo to the mother, for the maintenance of the uterine lining for implantation. Indeed, upon fertilization of the ovum, the zygote typically has less than a week in which to divide and differentiate into a structure that can: 1) produce enough human chorionic gonadotropin (hCG) in order to sufficiently upregulate corpus luteum

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progesterone production, an absolute requirement for the maintenance of the endometrium, and 2) form a structure with a trophoblastic layer sufficient to attach to the endometrium. Thus, the hormonal signals regulating the growth and development of the zygote into a blastocyst complete with a trophoblastic layer and an inner cell mass containing the three germ layers are crucial to embryonic survival.

It is becoming clear that during the 5–6 day journey through the fallopian tube to the uterus, the zygote and developing embryo is continually exposed to numerous instructional and nutritional signals. Published research on the role of hormones during this 5–6 day period falls into two major eras. The first era spans from the 1950's through till the end of the century, where study endpoints typically examined hormonal production by pre-implantation embryos and the regulation of embryonic survival, morphology and attachment, fecundity, and certain biochemical parameters such as changes in DNA and RNA (Badarau et al., 1968; Buchanan, 1969; Dey and Dickmann, 1974a,b; Dickmann, 1968, 1969; Dickmann and Dey, 1974a,b; Dickmann et al., 1975; Dickmann and Sen Gupta, 1974; Flint et al., 1983; Flint et al., 1978; Gadsby et al., 1980; Gupta et al., 1977; Hafez and Sugawara, 1968; Heap et al., 1979, 1981, 1989, 1991; Huff and Eik-Nes, 1966; Johansson et al., 1968; Kaiser and Geiger, 1970a,b; Kim and Foreman, 1968; Knobil et al., 1968; Loke and Borland, 1973; Loke et al., 1972; Morisada et al., 1972; Perry et al., 1976; Prasad et al., 1968; Seamark and Lutwakmann, 1972; Skidmore et al., 1994; Sugawara and Hafez, 1967). These studies identified the necessity for hCG and certain steroids for early embryonic survival and reproductive success. During the latter half of 20th century, pioneering research from the laboratories of John Hearn and others performing basic animal, endocrinological, physiological and histological experiments identified hCG and gonadotropin-releasing hormone 1 (GnRH1) as two pregnancy-related hormones necessary for blastocyst survival and implantation for pregnancy in primates (Hearn, 2001). These important studies paved the way for Thomson and colleagues at the end of the century to develop methodologies to derive and maintain human embryonic stem cells (hESC) in culture from blastocysts (Thomson et al., 1998). These techniques provided an *in vitro* model system to examine the hormonal regulation of zygotic development into a blastocyst. The second era of research has utilized this model of pre-implantation embryogenesis to identify the paracrine and autocrine factors regulating pre-implantation cell proliferation, differentiation, migration and death (Atwood and Vadakkadath Meethal, 2011a,b). These studies have demonstrated that GnRH1 and hCG are key signals for hESC proliferation and steroidogenesis, and that progesterone is an obligatory signal for hESC differentiation into embryoid bodies (i.e. blastulation and gastrulation) and neuroectodermal rosettes (neurulation; Gallego et al., 2008, 2010; Porayette et al., 2007, 2009).

Here we review the current state of our knowledge regarding the spatiotemporal pattern of hormone signaling from the development of the follicle through fertilization, to the division of the pluripotent zygote, its differentiation into multipotent cells of the blastocyst and its subsequent hatching and implantation into the endometrium.

2. Methods

This review integrates the available evidence regarding the endocrine, paracrine and autocrine factors regulating human folliculogenesis, early embryogenesis and blastocyst implantation from a temporal and spatial perspective. A search was performed in PubMed, regarding these factors with no limits placed on time of publication, up to January 2016. In particular, the literature research was focused temporally on folliculogenesis through till blastocyst implantation, inclusive, and the hormonal factors that regulate these reproductive events in order to conceptualize the coordination of endocrine, paracrine and autocrine signals required for successful reproduction.

3. Folliculogenesis – endocrine, paracrine and autocrine regulation

Primordial follicles present in the ovary of females are comprised of a densely packed shell of somatic cells that contains an immature oocyte. During folliculogenesis, oocytes grow and acquire developmental competence in a mutually dependent relationship with their adjacent somatic cells (Demeestere et al., 2012). Each month, ovarian primordial follicles (approximately 500–1000 follicles) undergo the process of maturation (folliculogenesis) that typically results in 1, or occasionally, 2 follicles releasing an oocyte into the fallopian tubes. During life the process of follicular atresia eliminates all but 300–400 oocytes, which become available for selection, ovulation and potential fertilization. This section reviews our knowledge of the hormonal regulation of follicular maturation, ovum release from the dominant follicle(s), the subsequent atretic death of the non-dominant follicles, and the regression of the corpus luteum that allows for the activation of the next set of primordial follicles (Fig. 1).

3.1. Early folliculogenesis

In the adult ovary, oocytes exist in a quiescent state surrounded by a single layer of pregranulosa cells (primordial follicle). The development of these oocytes is arrested prenatally at the diplotene stage of prophase I of meiosis (dictyate/diplonema) – the first meiotic arrest (Nicholas et al., 2009). Shortly after stimulation by the preovulatory surge of luteinizing hormone (LH), select oocytes (typically 5-30 in women) that have been arrested at the late prophase I resume meiosis as characterized by germinal vesicle breakdown (GVBD), chromosome condensation, and extrusion of the first polar body (metaphase II) (Ye et al., 2009). LH/hCG are well-known to initiate mitosis (Atwood and Bowen, 2015a,b) and this selective resumption of folliculogenesis by LH is mediated via the regulation of Kit ligand (KL; also known as stem cell factor) expression (Ye et al., 2009) in granulosa cells and its binding to the receptor for KL (c-Kit) on the oocyte and thecal-interstitial cells.

The structure of KL and its receptor are described in (Hutt et al., 2006a). KL exists as both soluble and membrane-spanning proteins, which are synthesized from two alternatively spliced forms of the messenger RNA. KL-1 and KL-2 are comprised of an extracellular domain, hydrophobic transmembrane domain and a short cytoplasmic tail. Both forms of KL are initially anchored to the membrane. However, exon 6 of KL-2 encodes a proteolytic cleavage site that is absent in KL-1. Consequently, KL-2 tends to remain membrane bound, whereas the KL-1 is usually found in soluble form. The soluble form of KL is generated by proteolytic cleavage of transmembrane KL-1 and KL-2.

KL acts via autocrine mechanisms to not only stimulate oocyte growth in primordial and preantral follicles (Hutt et al., 2006b; Klinger and De Felici, 2002; Liu et al., 2006, 2007; Moniruzzaman and Miyano, 2007; Nilsson et al., 2002; Nilsson and Skinner, 2003; Reynaud et al., 2000; Ye et al., 2009), but to promote the recruitment, proliferation and differentiation of theca cells from the surrounding stromal tissue (Nilsson and Skinner, 2004; Parrott and Skinner, 1997) and regulate ovarian steroidogenesis (Brankin et al., 2003; Hutt et al., 2006a; Jin et al., 2005; Reynaud et al., 2000), antrum formation and meiotic maturation (Hutt et al., 2006a).

Expression of another small protein, keratinocyte growth factor (also known as fibroblast growth factor-7, FGF-7) by mesenchymal