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Contrôle hormonal de l'implantation

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Abstract

In mammals, implantation represents a key step of pregnancy and its progression conditions not only the success of pregnancy but health of the offspring. Implantation requires a complex and specific uterine tissue, the endometrium, whose biological functions are tightly regulated by numerous signals, including steroids and polypeptide hormones. Endometrial tissue is endowed with dynamic properties that associate its ability to control the developmental trajectory of the embryo (driver property) and its ability to react to embryos displaying distinct capacities to develop to term (sensor property). Since dynamical properties of the endometrium can be affected by pre- and post-conceptional environment, determining how maternal hormonal signals and their biological actions are affected by environmental factors (e.g. nutrition, stress, infections) is mandatory to reduce or even to prevent their detrimental effects on endometrial physiology in order to preserve the optimal functionality of this tissue.

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Keywords: Pregnancy; Implantation; Endometrium; Steroids

Résumé

Chez les mammifères, l'implantation est une étape clef de la gestation, dont le déroulement conditionne non seulement la réussite de ce processus vital de la reproduction sexuée mais également la santé des nouveau-nés. L'implantation se déroule au contact d'un tissu utérin spécifique et complexe, l'endomètre, dont les fonctions biologiques sont régulées par de nombreux signaux, en particulier les hormones, qu'elles soient stéroïdiennes ou polypeptidiques. Le tissu endométrial est également doté de propriétés dynamiques, qui couvrent à la fois sa capacité à contrôler la trajectoire développementale de l'embryon indépendamment de la qualité de celui-ci (*driver*) et sa capacité à réagir comme un biosenseur précoce de la capacité de développement à terme de l'embryon. Dans la mesure où ces propriétés dynamiques peuvent être altérées par l'environnement pré- et post-conceptionnel, il apparaît crucial de déterminer comment les signaux hormonaux maternels et leurs actions biologiques sont impactés par les facteurs environnementaux (alimentation, stress, infections) afin de réduire voire de prévenir la portée de leurs effets néfastes sur la physiologie de l'endomètre et ainsi garantir la fonctionnalité optimale de ce tissu.

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Mots clés : Gestation ; Implantation ; Endomètre ; Stéroïdes

In mammals, a complex sequence of biological processes and the successful overcome of several critical points are involved in the birth of a viable and healthy progeny. Implantation appears as a critical step of pregnancy, associated with a high rate of embryo loss in all mammalian species studied so far. In humans, reproductive efficiency has been shown to be rather low, with a probability to achieve pregnancy estimated to 20–30% [1]. In addition to endogenous factors (such

as genetic mutations) that could be detrimental for pregnancy development, various environmental insults (nutrition, pollution and endocrine disruptors, infections stress) have been identified as factors that may affect gamete quality and fertilization, journey of the early embryo through the oviduct, cellular interactions between endometrium and hatched blastocyst or conceptus, foeto-placental development and parturition [2,3]. In addition, using assisted reproductive technologies (ART) and embryo transfer may alter the biological properties of the embryo with a subsequent impact on later stages of pregnancy [4]. Therefore, inadequate maternal compartment and/or in vitro

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manipulations of embryos affect the two way interactions that take place between the mother and the embryo when pregnancy initiates, precluding completion of successful pregnancy or affecting long-term health status of the offspring [5]. Focusing on ovarian steroids as essential components of maternal systemic signals required for pregnancy, this paper presents a brief overview on how these hormones regulate endometrium functionality in normal conditions and adversely alter its interactions with the embryo when maternal physiology is perturbed.

1. Endometrium as an essential tissue for progression and issue of pregnancy

In terms of contribution to pregnancy, mammalian females not only produce gametes (oocytes) but they also host the whole gestation in the reproductive tract (oviduct and uterus) until term. Whereas *in vitro* production of embryos and embryo transfer have demonstrated the oviduct to be a dispensable organ for supporting progression of pregnancy to term, no surrogate biological or artificial system has been derived for the uterus [6]. In normal physiological conditions, the uterus and its internal part referred as the endometrium constitute the maternal site for embryo implantation. The adult endometrium is a complex tissue that consists of stromal cells, luminal and glandular epithelial cells, endothelial and vascular smooth muscle cells, as well as a complex network of leukocytes populations. The endometrium is a fascinating and unique tissue that exhibits remarkable plasticity, with regeneration, reparation and remodelling occurring during estrous cycle, following pregnancy failures, and after parturition. As the biological interface dedicated to the interactions with the embryo then with the foeto-placental unit, the endometrium represents a critical tissue for normal fertility and reproductive success in all mammals. Recent data have demonstrated that the endometrium is able to:

- drive the developmental trajectory of the embryo then of the foetal-placental unit [7];
- and react to embryos that display distinct capacities to term development [8–10].

Therefore, the mammalian endometrium is a highly dynamic tissue endowed with driver and sensor properties [11] that are controlled by maternal factors in the absence of conception and by maternal factors and embryonic signals when pregnancy occurs.

2. Steroids and regulation of implantation

Although implantation itself is a dynamic and tightly regulated process occurring between a competent embryo and the synchronized endometrial tissue, events priming the endometrium for implantation are maternally driven. Hormonal regulation of implantation starts with a set of maternal factors that are produced distantly from the endometrium and will sequentially act on this tissue to make it receptive to embryo that will implant during a specific period (referred to window of

implantation) at the blastocyst stage in many species (e.g. primates, rodents, rabbit) or as an elongated conceptus in ruminants and pig [12].

In mammalian species with invasive implantation (primates including humans, rodents, rabbit), endometrial receptivity refers to a post-ovulatory process that includes decidualization of stromal endometrial fibroblasts, abundant secretory activities of endometrial glands, afflux of immune cells including specialized NK cells and spiral arteries remodelling. These events are necessary for supporting apposition, adhesion, penetration and invasion of the embryo into the endometrial wall [13]. In species with superficial implantation (ruminants, horse, pig), decidual transformation of stromal fibroblasts does not occur but endometrial receptivity in these species shares conserved molecular pathways and common genes with endometrial receptivity associated with invasive implantation [14,15], including some decidualization-related factors [16].

Progesterone-induced differentiation of oestrogen-primed endometrial stromal cells allows their transformation into secretory decidual cells. By regulating cytokines secretions and production of cell-surface proteins of endometrial cells, decidual cells control the invasion of trophoblast as well as the type and functions of immune cells in order to create a local immune privileged environment indispensable for embryo implantation and placental development [17]. In contrast to most mammals, decidualization of the human endometrium does not require embryo signalling and occurs at each cycle, irrespective of the presence or absence of an embryo. Based on the use of:

- endometrial biopsies across menstrual cycle;
- murine models with endometrium-targeted gene depletion;
- and *in vitro* treatment of endometrial stromal fibroblasts, a wealth of publications has presented molecular changes (transcriptomic, epigenomic, lipidomics and proteomic analyses) associated with endometrial receptivity and decidualization in primates and rodents [18,19], leading to the identification of potential biomarkers for endometrial receptivity in women [20,21].

In all mammalian species, a large array of estrogen (E2) and progesterone P4-dependant immune related genes have been identified (e.g. indoleamine 2,3-dioxygenase [IDO], *Progesterone-Induced Blocking Factor* [PIBF], Toll-like receptor family [TLR]), indicating that E2 is globally a pro-inflammatory steroid whereas P4 is an anti-inflammatory and immunosuppressive factor. Overall, cyclical changes in the sex steroids production influence a variety of endometrial genes, which act to protect this tissue against pathogenic agents, while simultaneously preparing it for implantation [22].

3. Maternal perturbations of endometrial function and consequences for pregnancy

Mice carrying null mutation for genes encoding steroid hormone receptors (*Esr1*, *Esr2*, *Pr-A*, *Pr-B*) and downstream target

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