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Review

Cadence of procreation: Orchestrating embryo–uterine interactions

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ABSTRACT

Embryo implantation in eutherian mammals is a highly complex process and requires reciprocal communication between different cell types of the embryo at the blastocyst stage and receptive uterus. The events of implantation are dynamic and highly orchestrated over a species-specific period of time with distinctive and overlapping expression of many genes. Delayed implantation in different species has helped elucidate some of the intricacies of implantation timing and different modes of the implantation process. How these events are coordinated in time and space are not clearly understood. We discuss potential regulators of the precise timing of these events with respect to central and local clock mechanisms. This review focuses on the timing and synchronization of early pregnancy events in mouse and consequences of their aberrations at later stages of pregnancy.

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Contents

1. Introduction

In mammals, the beginning of a life commences with the union of a sperm and an egg through the process of fertilization. The fertilized egg then undergoes several rounds of mitoses to form a blastocyst. These developmental events in the embryo are synchronized with proliferation and differentiation to specific uterine cell types guided by ovarian estrogen and progesterone (P_4) in a spatiotemporal fashion to render the uterus receptive for blastocyst implantation. These events are sequential and dynamic, conferring activation of both embryonic and maternal genes in a timely and coordinated fashion that set up reciprocal interactions between these two entities requisite for successful implantation. Failure to orchestrate these coordinated interactions at scheduled times lead to defective or unsuccessful implantation. Implantation across eutherian species occurs within a precise and transient time frame known as the window of uterine receptivity to implantation (window of implantation). The onset and duration of this window varies across species. Defects around the time of implantation may compromise pregnancy outcome by

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steering adverse ripple effects through the remaining course of development [1].

2. The window for implantation is transient

Rodent models have helped us to better understand the mechanisms that direct uterine receptivity and nonreceptivity. In mice, the active states of the uterus with respect to implantation are classified as prereceptive, receptive, and refractory (nonreceptive); these states are defined by observations of uterine responses to transferred blastocyst in pseudopregnant mice and are generally directed by ovarian P_4 and estrogen secretion [2,3] While the uterus is prereceptive on days 1–3 (day 1 defined as finding the vaginal plug), it becomes receptive to implantation on day 4 of pregnancy or pseudopregnancy and lasts for only ~24 h. If blastocysts are transferred late on day 5, the uterus becomes refractory to implantation with gradual degeneration of blastocysts until the estrous cycle is reset after hormonal withdrawal. Similarly, the uterus is receptive for a short period spanning 7–9 days after ovulation (cycle days 21–23) during the mid-luteal phase in women. After this time, the uterus becomes and remains refractory (nonreceptive) for the remainder of the luteal phase.

3. Stages of implantation progress in a discrete sequence

When the mouse embryo reaches the blastocyst stage, it gains the ability to attach to the receptive luminal epithelium once the uterus has been primed with P_4 and superimposed by a small amount of estrogen. If this condition of embryo–uterine synchrony is met, engagement of cell adhesion molecules at the uterine luminal and blastocyst trophectoderm epithelial surfaces initiates the implantation process. These adhesion molecules then transduce signals necessary to sustain embryonic and maternal contributions to support fetal development [4].

For implantation to ensue, the uterine luminal epithelial closure is essential on day 4 of pregnancy (day of uterine receptivity) in mice. This luminal epithelial closure is P_4 dependent, but independent of embryonic participation, since this occurs in pseudopregnant mice with uterine steroid hormonal milieu similar to that of pregnant females during the periimplantation period [5]. In rodents, the process of implantation is classified into three stages: apposition, adhesion/attachment, and penetration [6,7]. Close apposition of the blastocyst trophectoderm with the luminal epithelium within a specified implantation chamber (crypt or nidation) is followed by the adhesion stage. This latter stage initiates further intimate and molecular exchanges between the two epithelial cell types, leading to the attachment reaction. The attachment reaction is coincident with localized increased endometrial vascular permeability at the site of the blastocyst, as determined by the visualization of blue bands along the uterine horn after an intravenous injection of a macromolecular blue dye (uterine blue reaction) [3]. In mice, successive events spanning the luminal closure to the attachment reaction occur starting from day 3 afternoon and are complete by day 4 of pregnancy [8,9].

The attachment reaction in mice and rats occurs on the evenings of day 4 and 5, respectively, and day 6½ in rabbits [10–12]. This reaction is assumed to occur approximately on day 8 in humans and baboons, day 9 in macaques, and day 11 in marmoset monkeys [13,14]. In large animals, the attachment reaction occurs on day 13 in pigs, day 16 in sheep, day 19 in goats, and day 20 in cows [2]. Finally, penetration involves the invasion by the trophectoderm through the epithelium into the stromal bed. Stromal cell differentiation to specialized decidual cells (decidualization) becomes robust with the demise of the luminal epithelium at the attachment site.

4. Spatial orientation for implantation: crypt formation

Blood vessels enter the uterus from the mesometrium, assigning a mesometrial-antimesometrial (**M-AM**) axis to the uterus. In mice, implantation occurs within a crypt (nidus) toward the antimesometrial pole of the uterus, and discrete implantation sites are spaced evenly with respect to adjacent sites along the uterine horn. How the uterus and embryo communicate to spatially coordinate implantation is not fully understood. Mouse blastocysts are oriented with their inner cell mass (ICM) directed toward the mesometrial pole, whereas the ICM in humans is directed toward the antimesometrial pole. Initially, mouse blastocysts are situated into crypts with random orientation of their ICMs. The underlying mechanism by which the orientation of a blastocyst is directed at the time of implantation remains elusive.

5. Implantation strategies are diverse across eutherians

In 1884, Bonnet classified implantation based on histological analyses of cell–cell interactions between the blastocyst and uterus, grouping strategies into three categories: central (rabbits, ferrets, and marsupials), eccentric (mice, rats, and hamsters) and interstitial (guinea pigs, chimpanzees, and humans) [15]. Nearly one century later, Schlafke and Enders classified implantation in certain species into intrusive, displacement, and fusion types from their ultrastructural studies [16]. Humans and guinea pigs show an intrusive type of implantation in which trophoblast cells penetrate through the luminal epithelium, reaching and extending through the basal lamina. In contrast, rodents exhibit a displacement type of implantation: the luminal epithelium is freed of the underlying basal lamina, facilitating the passage of trophoblasts through the epithelium. In rabbits, the fusion type of implantation allows trophoblast cells to unite with the luminal epithelium to form symplasma.

Interestingly, implantation is shallow in large animals, such as pig, sheep, cow and horse in which the entire trophoblastic surface of elongated blastocysts makes the attachment contacts along the luminal epithelial surface [17]. In these animals, less-invasive blastocysts with remarkable elongation occurring on day 12 of pregnancy exhibit longer free-floating status within the uterus than in species with more invasive conceptii. The growth of extra-embryonic tissue contributes to this elongation, enabling the embryo access to an efficient supply of nutrition from uterine secretions until the attachment reaction occurs. Trophectoderm invasion through the luminal epithelium and basal lamina into the stroma is required to provide nutrition to the developing embryo by establishing a vascular connection with the mother. This process varies considerably from species to species with respect to timing (heterochrony) and cytological features [16]. The significance of diverse implantation strategies and timing displayed by different species suggest diversification of species-specific adaptation. However, one common feature is the enhanced endometrial vascular permeability at the site of blastocyst attachment in many animals examined. It is believed that this increased permeability also occurs in the endometrial bed in human implantation, but has not been experimentally documented due to ethical restrictions.

6. Implantation requires coordinated action of ovarian hormones

The master regulators that specify the transient window of uterine receptivity are primarily the ovarian hormones P_4 and estrogens. While both hormones are crucial for implantation in mice and rats, ovarian estrogen is not essential for implantation in many species such as pigs, guinea pigs, rabbits, and hamsters.

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