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Review Article

Cytokines, growth factors and macromolecules as mediators of implantation in mammalian species

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ABSTRACT

Implantation is one of the most critical steps in mammalian reproduction and implantation failure constitutes a major cause of infertility in both animals and humans. The mechanism of implantation is exclusively under the control of ovarian steroids progesterone and oestrogen whose actions are mediated in a complex phenomenon that involves a number of cytokines and growth factors. According to a plethora of literature on implantation in mammalian species, prominent of these cytokines and growth factor playing crucial roles in implantation include integrin, osteopontin, integrin, insulin-like growth factor and leukaemia inhibitory factor. Others are cluster domain 44, hyaluronan system and many non-adhesive molecules such as glycoprotein mucin 1. In this review, the specific roles played by these molecules are expatiated. Generally, they function as adhesive molecules that facilitate attachment of ligands/proteins on the trophectoderm to their respective receptors on endometrial luminal epithelia or vice versa. Sometimes, they also function as signalling molecules that enhance communication between implanting blastocyst and receptive endometrium. This is of particular importance in embryo culture and embryo transfer where *in vitro* derived blastocyst unlike the *in vivo* condition, is not exposed to these substances and hence, their absence may be partly responsible for the low implantation rate observed in the surrogate. Appreciation of the roles played by these cytokines, growth factors and molecules as revealed in this review will spur further research on these topics, facilitate their inclusion in embryo culture media (if positively required) and are considered as vital aspect while developing strategies to improve fertility.

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1. Introduction

Sub-fertility is a pervasive problem affecting both human and animal species. In humans, available evidence suggests that pregnancy loss predominantly during pre-implantation and the first few weeks of pregnancy is one of the major causes of subfertility. According to the global statistics presented by Boivin and Bunting [1], an estimate of over 72 million women between the ages of 20–40 years are infertile. In domestic animals, subfertility is a limitation to animal production and is one of the main issues for dairy cows selected for milk production [2]. An estimate of 60% pregnancy loss occurs in dairy cattle, with a significant number observed during early stages of embryo development [3]. Fertilization rates in cattle are around 90%, however, one-third of embryos fail to survive the first 18 days of pregnancy [4]. This implies that reproductive losses in dairy cows due to early embryo death are 3–4 times greater than losses due to fertilization failure. In spite of almost 100% fertilization rate in sheep [2], only 60–80% of the fertilized eggs proceed to live birth, while higher percentage of these losses occur before day 18 of pregnancy [5]. Collectively, this suggests that implantation failure constitutes a major source of pregnancy loss and infertility in both human and animal subjects.

The early stage of pregnancy is thus termed 'a critical period' because of the high risk of embryo loss. One event known to occur during this critical period is blastocyst implantation to the maternal endometrium. Implantation is a complex process and has been generally acknowledged as the most critical step in mammalian reproduction. In primate and human, embryo stays momentarily in the oviduct before being transported to the uterus between 72 and 96 h post fertilization, readily prepared for implantation. In domestic ruminants, definitive implantation is achieved by adhesion of the mononuclear trophoblast cells to the endometrial luminal epithelium and formation of syncytia by the fusion of trophoblast binucleate cells with the luminal epithelium. The protracted period of peri-implantation embryo has made the ruminant especially sheep a unique model for classical study on molecular mechanism of implantation in mammalian species generally [6].

The contact between the embryo and the maternal tissue soon after fertilization is crucial for subsequent development and survival of the embryo *in utero* because it creates the medium of interaction between the two entities and also generates the platform that eventually leads to the formation and development of placenta [7] which is necessary to facilitate the exchange especially of micronutrients and gases from the mother to the conceptus.

Endometrial cells undergo cyclic renewal, differentiation and eventually apoptosis and shedding (in primate) as well as secretory with the primary purpose of allowing implantation of a viable embryo in a conceptive cycle. Many of these physiological processes depend on the timely expression of cell adhesion, bridging and signalling molecules as well as disappearance of others (such as non-adhesive molecules) which maintain tissue microarchitecture by mediating cell-to-cell and cell-to-substratum attachments that constitutes endometrial remodelling. In other words, endometrial remodelling is a prerequisite for the uterus to attain structural and functional capacity during implantation. This remodelling occurs only during the receptive phase of reproductive cycle [8] and this period is termed 'window of receptivity' when attachment of blastocyst to the maternal endometrium is physiologically possible [9].

Window of receptivity in mammalian species is exclusively under the influence of ovarian steroids, progesterone and oestrogen [10–12]. High level of oestrogen at ovulation causes uterine cell proliferation while subsequent increase progesterone during dioestrus/pregnancy suppresses proliferation and causes cell differentiation in preparing the uterus for receptivity [13]. In addition to the steroids, a plethora of other molecules, including macromolecules, growth factors and pro-inflammatory cytokines mediate and modulate the actions of these steroid hormones to bring about the required changes in the uterine extracellular matrix [14]. Among these cytokines/growth factors playing crucial roles in implantation are integrins (ITG), osteopontin (OPN), insulin-like growth factor (IGF) and leukaemia inhibitory factor (LIF). Others are hyaluronan (HA) system, cluster domain 44 (CD44), and many other non-adhesive molecules such as glycoprotein mucin 1 (MUC1). To date, the list is inexhaustible and continues to grow, however, the molecular mechanism underlying the phenomenon of implantation still remains, in the word of Aplin [9], elusive. For the purpose of simplicity in this review, they are better classified as (i) adhesive and bridging molecules for those that initiate the visible actual attachment observed, (ii) signalling molecules that induce the transcription and translation of other genes and proteins that initiate communication/interaction between the receptive maternal endometrium and implantation-competent blastocyst and then (iii) the protective non-adhesive molecules on the endometrium that have to be removed before implantation could occur.

As reproductive biologists persist in their continued effort to understand the mechanisms underlying implantation process for a better development of strategies towards improving its success rate, our present understanding on the mechanism of implantation is still far from being complete. The objective of this review is to highlight the roles of ITG, OPN, IGF, LIF, HA system, CD44 and the non-adhesive MUC1 as mediators of implantation in mammalian species.

2. Methodology

The preliminary search strategy involved using the Unites States National Library of Medicine (https://www.ncbi.nlm.nih.gov/pubmed/) while matching the word implantation with cytokines, growth factors and adhesive molecules. The plenty of papers generated each time were selected based on their relevance to the subject matter of this review by going through the titles and abstract. These were read one by one and key references from them were also reviewed to generate a broad knowledge on the roles of ITG, OPN, IGF, LIF, HA, CD44 and MUC1 as mediators of implantation in mammalian species. Other relevant textbooks on the subject were also consulted to come up with a broad knowledge

Table 1
Sources and roles of cytokines, growth factors and macromolecules mediating and modulating implantation process in mammalian species.

Cytokine/growth factor	Sources/location	Proposed roles in implantation	References
ITG	Endometrium and blastocyst	Adhesive molecules	[146]
OPN	Placental and endometrial immune cells	Adhesive molecule	[35]
IGF	Oviduct/Endometrium	Metabolic indicator/ signalling	[63,147]
LIF	Endometrium	Signaling	[85,148]
HA	Endometrium and blastocyst	Adhesive molecule	[95,99]
CD44	Endometrium and blastocyst	Adhesive and signalling	[119]
MUC1	LE of endometrium	Anti-adhesive	[149]

CD44; cluster domain 44, HA; hyaluronan, IGF; insulin-like growth factor, ITG; integrin, LIF; leukaemia inhibitory factor, LE; luminal epithelium, MUC1; mucin, OPN; osteopontin.

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