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Multi-level and multi-scale integrative approach to the understanding of human blastocyst implantation

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ABSTRACT

Implantation is a complex process which results in fixation of zona pellucida free blastocyst to the maternal uterine endometrium. In the human, it involves progesterone mediated preparation of endometrium, age- and stage-matched development of pre-implantation embryo, and interaction between embryo and endometrium. In the present essay, we present the case to explain why there is a necessity of undertaking multi-level, multi-scale integrative approach to deconstruct the succession process of endometrial development to the climax of implantation.

1. Introduction

Restricting reproduction rate and use of reproductive energy for assuring the survivability and growth of offspring allowed significant advantage to higher vertebrates in evolution. Viviparity typically seen in eutherian mammals with the process of embryo implantation and nurturing individual offspring in the protected environment of uterus is an example of evolutive adaptation (Rothchild, 2003). Implantation is the process of adhesion or fixation of the blastocyst to endometrial surface of the uterus. It involves differentiation of the adhesion site to definitive site where the placenta eventually develops. Before the initiation of implantation, however, both embryo and endometrium need to undertake respective developmental process in time- and space-specific manner. This developmental process between these two interacting compartments renders them physiologically synchronous and conditioned with each other. Thus, in the human, maternal uterus becomes 'receptive' by mid-luteal phase, viable embryo develops into blastocyst, and zona pellucida free blastocyst becomes 'invasive', and both become suitably positioned (Fig. 1). In ecological terms, the pre-implantation developmental processes constitute the 'succession process' and implantation process is the 'climax'. The entire process of implantation however shows a great deal of species-specific variations and environmental niche selectivity. In some species, for example, there is 'diapause' resulting in natural, obligatory, or facultative delay in implantation. There are already several reviews available in this regard for the interested readers (Aitken, 1977; Dey and Lim, 2006; Renfree and Shaw, 2000).

From the view-point of functional morphology, the living primates as an Order are best considered in twelve Families. Based on available data of implantation process in various primates, it appears that there was a relatively smooth progression of implantation process and placental type from primitive and relatively simple forms in *Tupaiidae* (Tree shrew) to highly intrusive and complex ones in *Hominidae* (Human) that parallels the progression of the phylogenetic series (Napier and Napier, 1967). It is anticipated that the human blastocyst implantation and placenta typically had emerged from that in the chimpanzee (Napier and Napier, 1967; Ramsey, 1982) as the same is applicable for many human traits (Goodman and Sterner, 2010).[2]

Collectively, it appears that human blastocyst implantation is a complex process. Yet, it is imperative that we study the biology of blastocyst implantation at different levels and with different perspectives as closely as possible. It bears many promises, both proximate and not-so-proximate. For example, the knowledge of implantation can be of value to controlling fertility on its both arms and safeguarding mother and embryo, and shall add greater understanding to general physiology, biochemistry, cancer biology,

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[2] In this regard, we may take note of what Charles Darwin (1874) observed in regard to the bodily size and strength in his *The Descent of Man, and Selection in Relation to Sex*: there is a strong probability that the man is descended from the chimpanzee.

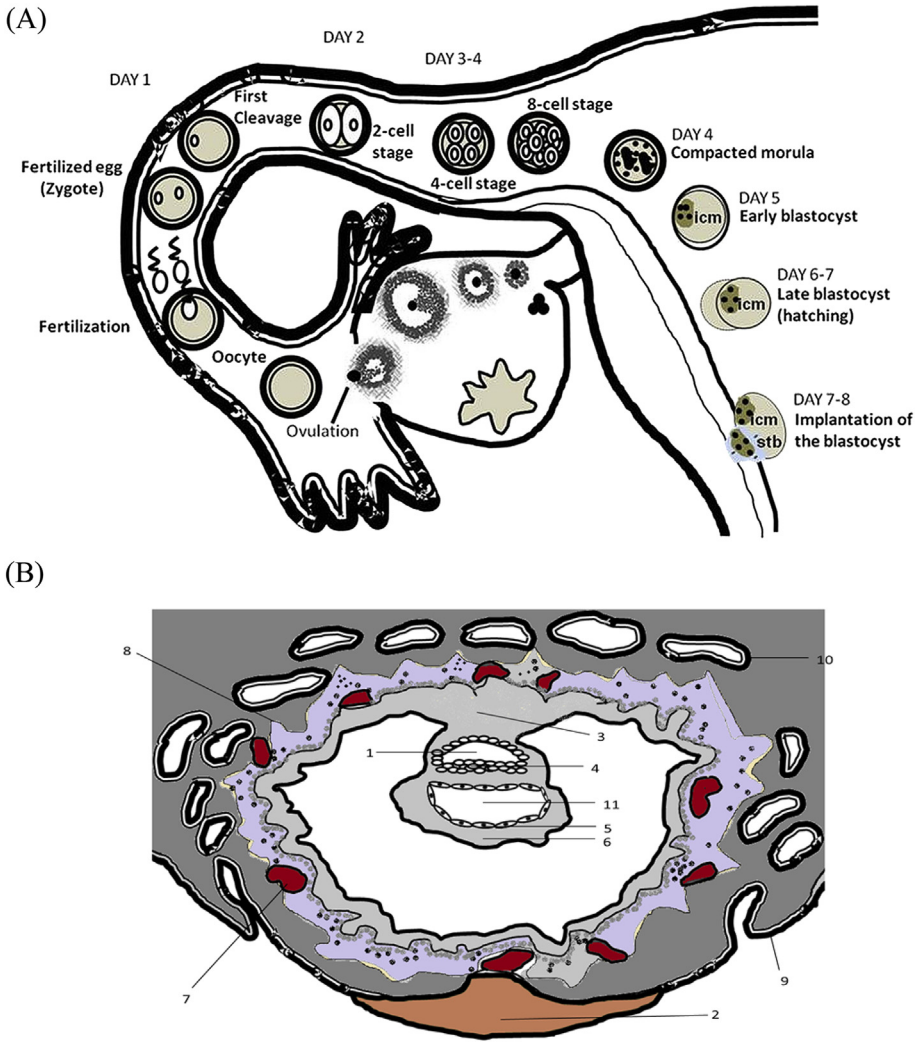

Fig. 1. Blastocyst implantation in the human. (A) Age- and stage-matched development of preimplantation embryo starting with fertilization on day 0 followed by blastocyst hatching on days 6–7 and blastocyst implantation on days 7–8 after ovulation in the human. Concomitantly uterine endometrium undergoes a series of physiological adaptive changes making it receptive to the blastocyst. icm, inner cell mass; stb, syncytiotrophoblast. (B) Typical implantation stage embryo on day 8–9 after fertilization. 1, amniotic cavity; 2, blood clot at the site of initial implantation; 3, body stalk, or connective stalk later forming the placental cord region with placental blood vessels; 4, embryonic ectoderm that contributes to embryonic and placental membrane development; 5, endoderm that contributes to embryo development; 6, mesoderm, consisting of both embryonic mesoderm (in the trilaminar embryonic disc) and extra-embryonic mesoderm (outside the trilaminar embryonic disc); 7, maternal endometrial capillaries; 8, trophoblast that contributes to placental development; 9, uterine epithelium the epithelial layer that lines the uterus; 10, uterine glands that secrete nutrients to support the initial growth both before and after implantation; 11, yolk sac which is the endoderm-lined and extra-embryonic mesoderm-covered cavity and it eventually contribute to the fetal gastrointestinal tract, blood and blood vessels.

endocrinology, genetics, pharmacology and immunology. In the present review, we shall take a look to the stock of knowledge in the area of human implantation biology and discuss why a multi-level and multi-scale integrative approach could be of help in deconstructing the succession process of blastocyst implantation in the human.

2. A quick scan of the trajectory of research in blastocyst implantation

Before we proceed further, we may take a quick overview of the trajectory of scientific researches on blastocyst implantation. In 1932, Carl Hartman wrote, “Attention may finally be called to a hiatus in our knowledge of the earliest changes invoked by the implanting egg on the uterine epithelium” (Quoted from Meyer, 1976). After more than two decades, in 1955, Warren Nelson commented about blastocyst implantation that, “We know little or nothing of the details of this mechanism” (Nelson, 1955). In early 1970s, Moses Chaim Shelesnyak’s group presented a model of ‘events and interactions in nidation’ as shown in Fig. 2 (Shelesnyak and Marcus, 1971). Yet, in 1976, R.K. Meyer wrote, “The mechanism of implantation of the fertilized ovum into the uterus is a challenging, unsolved problem, in spite of the many investigations directed toward its elucidation. For more than seven decades of this century many investigators have studied various aspects of the phenomenon from various points of view. Approaches which have been employed are: morphological, histological, histochemical, physiological, and phamacological” (Meyer, 1976). In 1993, Hans-Werner Denker labeled the process of implantation as ‘a cell biological paradox’ (Denker, 1993). John Aplin remarked in an article in 2006 that the molecular mechanism of implantation is still ‘elusive’ (Aplin, 2006). It is implicit in these elegant papers that the level of investigations has steadily progressed from macro- to micro-level, and then to cell biology and molecular biology levels over the last