Placenta 40 (2016) 40–51

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

What was the ancestral function of decidual stromal cells? A model for the evolution of eutherian pregnancy

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ARTICLE INFO

Article history:
Received 21 December 2015
Received in revised form
15 February 2016
Accepted 21 February 2016

Keywords:
Decidual stromal cells
Endometrial stromal cells
Eutheria
Extended gestation
Origin of placental mammals

ABSTRACT

In human and mouse, decidual stromal cells (DSC) are necessary for the establishment (implantation) and the maintenance of pregnancy by preventing inflammation and the immune rejection of the semi-allograft conceptus. DSC originated along the stem lineage of eutherian mammals, coincidental with the origin of invasive placentation. Surprisingly, in many eutherian lineages decidual cells are lost after the implantation phase of pregnancy, making it unlikely that DSC are necessary for the maintenance of pregnancy in these animals. In order to understand this variation, we review the literature on the fetal-maternal interface in all major eutherian clades Euarchontoglires, Laurasiatheria, Xenarthra and Afrotheria, as well as the literature about the ancestral eutherian species. We conclude that maintaining pregnancy may not be a shared derived function of DSC among all eutherian mammals. Rather, we propose that DSC originated to manage the inflammatory reaction associated with invasive implantation. We envision that this happened in a stem eutherian that had invasive placenta but still a short gestation. We further propose that extended gestation evolved independently in the major eutherian clades explaining why the major lineages of eutherian mammals differ with respect to the mechanisms maintaining pregnancy.

1. Introduction

Evolution of pregnancy is one of the salient attributes of eutherian mammals. Distinctive features of eutherian pregnancy include invasive placentation (at least ancestrally), extended gestation, maternal recognition of pregnancy, and the origin of decidual stromal cells (DSC).

DSCs are a novel cell-type that originated along the stem lineage of eutherian mammals [39,50]. In many eutherian mammals, DSC differentiate from a population of fibroblast-like cells in the uterus called Endometrial Stromal Fibroblasts (ESF) in a process called decidualization. In many eutherian mammals ESF decidualize during pregnancy, and in some eutherians, including humans, also during the secretory phase of a sterile sexual cycle [29]. Human ESF decidualize in response to progesterone and cyclic-AMP (cAMP).

Differentiation of DSC from ESF involves extensive reprogramming of gene regulatory status [8] and changes to the genome-wide patterns of histone-modification [71]. They also acquire a distinct cellular morphology—increased size, globular or polygonal appearance compared to the spindle-like appearance of their precursor fibroblasts, and increased accumulation of fat and glycogen granules as well as secretion of extracellular matrix [52].

1.1. Functions of decidual stromal cells

The functions of DSC have been studied extensively in model systems such as rodents and *in-vitro* grown human endometrial stromal cells. In human and mouse DSC form a physical barrier between the invading syncytio-trophoblast and the maternal tissue. Failure to form this barrier in human leads to a pathological invasion of myometrium by the trophoblast, a condition called *placenta accreta* that can be fatal to the mother [30]. The presence of glycogen and lipid granules suggests a nutritive function toward the fetus [52]. In addition DSC produce a variety of signaling molecules including prolactin, prostaglandins, relaxin, IGFBP1 (Insulin-Like Growth Factor Binding Protein 1) and many more. These hormones and

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http://dx.doi.org/10.1016/j.placenta.2016.02.012
0143-4004/

paracrine factors are important for maintaining maternal physiology in a state conducive to pregnancy [81]. In humans there is also evidence that the decidua plays a role in embryo selection, ensuring that only viable blastocysts can implant successfully [45].

Eutherian blastocyst implantation is an inflammatory process [19,77] and inflammation is necessary for successful implantation. Never the less soon after implantation the local endometrial environment becomes anti-inflammatory, a step necessary for the maintenance of pregnancy, mediated, in part, by a switch of the decidual cell cytokine profile [65].

The fetus expresses paternal antigens that can be identified by maternal immune system as 'non-self'. Yet, the semi-allograft fetus is not rejected by the maternal immune system. How this fetal-maternal immune tolerance is brought about is a long-standing puzzle in reproductive biology. In the last few years, DSC have been recognized as critical mediators of immunological tolerance at the fetal-maternal interface in human and mouse [26].

In the mouse, through epigenetic silencing of the chemokines, *Cxcl9* (C-X-C Motif Chemokine 9) and *Cxcl10* (C-X-C Motif Chemokine 10), DSC limit the influx of cytotoxic T-cells into the endometrium, thus minimizing the interactions between the trophoblast and effectors of the immune system [55]. Uterine variants of natural killer cells (uterine Natural Killer cells or uNK cells) and macrophages are distinct from their circulating counterparts in being less cytotoxic and active players in remodeling of uterine vasculature to accommodate invasive placentation. Acquisition of their distinct status in the endometrium is mediated by Interleukin-15 (IL15) secreted by decidual cells [26,40]. Conditioned medium from DSC, supplemented with IL15, converts peripheral natural killer cells to their uterine phenotype [36], and co-culture of CD34-positive hematopoietic precursor cells with DSC converts the precursor cells into uNK cells [74]. Decidualization in mouse creates an environment that prevents the growth of lymphatic vasculature in the endometrium, trapping dendritic cells in the endometrium [15]. Dendritic cells are antigen-presenting cells that must traverse to a lymph node through lymphatic vasculature to present antigens to lymphocytes. This important event in the activation of the adaptive immune system is thus interrupted by decidualization, at least in mouse.

Evidently, in human and mouse, DSC play a critical role in modulation of the uterine environment to facilitate and maintain the extended gestation in the face of immunological and physiological challenges of an invasive placenta.

1.2. Evolutionary origin of decidual stromal cells

DSC originated along the eutherian stem lineage as inferred by phylogenetic ancestral state reconstruction [50]. The evolution of functional interactions between certain transcription factors necessary for DSC differentiation also occurred at the same time in phylogeny, supporting this inference. DSC differentiation is dependent on functional cooperative interactions between HOXA11 (Homeobox A11) and FOXO1 (Forkhead Box O1) [43], and between FOXO1 and CEBPB (CCAAT/Enhancer Binding Protein, Beta) [13]. These cooperative interactions evolved along the stem lineage of eutherian mammals: reconstructed ancestral eutherian versions of these transcription factors have the ability to up-regulate the expression of DSC markers, while the reconstructed ancestral therian versions lack this ability as do the proteins of outgroup species, opossum, platypus and chicken (HOXA11: [9]; CEBPB: [44]).

While mammalian viviparity and direct fetal-maternal contact and interaction likely evolved in the stem lineage of therian mammals (i.e. prior to the ancestor of both marsupial and eutherian mammals), the fetal-maternal interaction is qualitatively different between metatherian (marsupial) and eutherian mammals. Highly invasive forms of placentation that lead to a sustainable accommodation of the fetal allograft are unique to eutherian mammals [53].

Placentation has been categorized into three major types based on the maternal tissue coming in direct contact with the trophoblast: epitheliochorial, endotheliochorial and haemochorial. Epitheliochorial (trophoblast is in contact with the luminal epithelium of endometrium) placentation is non-invasive because the fetal tissue does not breach the uterine luminal epithelium [32]. It is found in cattle, sheep, pig and horse and their relatives like dolphins and whales. Endotheliochorial (trophoblast is in contact with maternal endothelium) and haemochorial (trophoblast is in contact with maternal blood) are invasive forms because fetal tissue breaches the luminal epithelium and establishes a direct contact with endometrial stroma. Endotheliochorial placentation is found in carnivores, elephant etc. and haemochorial placentation is found in primates, rodents, armadillo etc. [53]. Phylogenetic ancestral state reconstructions have inferred that the eutherian ancestor possessed an invasive form of placentation. Disagreement remains whether it was endotheliochorial [50] or haemochorial [22,79]; what is clear, however, is that placentation was invasive in the eutherian ancestor [47]. In either case, the ancestor of eutherians had a placenta where the trophoblast of the conceptus was in direct contact with the endometrial stroma. See Fig. 1 for a phylogeny of mammals and Fig. 2 for the evolution of mode of placentation in Eutheria.

DSC are typically found in species that exhibit invasive placentation, with the possible exception of armadillo and other xenarthrans, discussed below. After their origin in the eutherian stem lineage, DSC are reconstructed to have been lost in the lineage leading from the laurasiatherian ancestor, the same lineage in which invasive mode of placentation was lost [50].

When DSC originated is relatively clear, based on multiple lines of evidence mentioned above. However, which evolutionary forces drove their origin, what their ancestral function was, and which ontogenetic and gene regulatory changes made their origin possible are open questions. It is important to address these questions for at least two reasons. First, how and why evolutionary novelties such as novel cell-types originate is a fundamental question in evolutionary biology [4,76]. Secondly, understanding how and why DSC originated can inform efforts to dissect the mechanistic basis of reproductive pathologies.

In order to understand the origin and ancestral function of DSC, research on rodent and primate model systems needs to be supplemented with data on the other major lineages of eutherians, in particular Afrotheria (tenrec, hyrax, elephant, manatee etc.) and Xenarthra (armadillo, anteater, sloth etc.). Primates and rodents are members of one of the four major eutherian clades, Euarchontoglires. Given that DSC originated in the eutherian stem lineage, it is imperative that any inferences concerning their origin be drawn from studies on taxa that bracket the entire diversity of eutherian descent: Xenarthra, Afrotheria and Laurasiatheria, in addition to Euarchontoglires.

To this end, we reviewed the literature on DSC in Eutheria, with specific attention to Xenarthra (armadillo) and Afrotheria (tenrec and hyrax). A surprising observation about DSC is that they are generally present in the peri-implantation phase, but tend to disappear in later stages of pregnancy. The latter observation is incompatible with the hypothesis that maintenance of extended pregnancy is a shared derived eutherian function of DSC.

2. The life cycle of DSC and its implications for their ancestral function

2.1. DSC do not generally persist until the end of gestation

In species that have decidual cells, their numbers dwindle as