Placenta (2005), **26**, 689–708
doi:10.1016/j.placenta.2004.11.010

CURRENT TOPIC

Animal Models of Placental Angiogenesis

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Paper accepted 20 November 2004

The study of the development of the fetal membranes is an ancient one, and the importance of placental vascular development to placental function has long been recognized. Animal models have been important in these studies, as they allow for controlled experiments and analysis of multiple time-points during pregnancy. Since the demonstration nearly 20 years ago that the placenta produces angiogenic factors, the major factors regulating placental angiogenesis have been identified. These major factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), the angiopoietins (ANG), and their receptors. Recently, sophisticated computerized image analysis methods have been developed to establish the pattern of placental vascular development in sheep. The maternal placental capillary bed develops primarily by increased size of capillaries, with only small increases in capillary number or surface densities. In contrast, the microvasculature of the fetal placenta develops primarily by increased branching, resulting in a large increase in capillary number and surface densities. These observations help to explain the relatively large increase in umbilical blood flow and nutrient delivery to the fetus that occurs during the last half of gestation. In addition, expression of mRNAs for VEGF, bFGF, ANG, and their receptors have recently been correlated with normal placental vascular development in sheep, and further refinement of these mathematical models is warranted. Lastly, the recent development of animal models of compromised pregnancies, including those resulting from maternal nutrition (both restriction and excess), multiple fetuses, environmental stress (heat stress and high altitude), and fetal and maternal breed effects, has already indicated that reductions in placental vascular development and expression of angiogenic factors are probably a root cause of fetal growth restriction. With these methods and models now in place, we should soon be able to establish the mechanisms involved in both normal and abnormal placental angiogenesis.

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Keywords: Vascular development; Angiogenesis; Placenta; Fetus; Fetal growth; Animals; Animal models

> "The [umbilical] vessels join on the uterus like the roots of plants and through them the embryo receives its nourishment." Aristotle, *On the Generation of Animals*, ca. 340 BC

INTRODUCTION

In the last two decades, the importance of vascular growth to the normal and abnormal function of the female reproductive organs has become increasingly recognized. For example, only 15 articles per year were published on angiogenesis in female reproductive organs during the 6-year interval from 1985 to 1990, whereas during 1996–2001 more than 180 articles per year were published [118]. Because the total number of articles concerning the female reproductive organs changed only moderately during these same intervals (approximately 52,000 vs. 68,000, total), articles on angiogenesis represented 1.62% compared with only 0.17% of all articles published on the ovary, uterus, or placenta in 1996–2001 vs. 1985–1990 [118]. The dramatic 12-fold increase in the number of scientific articles published on angiogenesis in the female reproductive organs is similar in magnitude to the 14-fold increase in the total number of articles on angiogenesis (nearly 2500 per year from 1998–2003).

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0143–4004/$–see front matter
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Importance of animal models

In this review, we will focus on non-primate animal models that have been used to study placental angiogenesis. For a discussion of angiogenesis in the primate placenta we refer the reader to several excellent recent reviews [1–4]. However, when appropriate we will discuss how results using non-primate animal models compare with those in primates.

Since ancient times, study of the fetal membranes has been an important area of investigation within the broader discipline of embryology [5]. Recognition that the fetal membranes must be important for embryonic and fetal development no doubt resulted from the observation that fetal membranes occur in all vertebrates, and in fact placentas of some type occur in all vertebrate classes and subclasses except Cyclostomata (hagfishes and lampreys), Aves, and Monotremata [6]. In addition, as Needham [5] points out, the placenta, or afterbirth, is a "readily observable biological phenomena," and thus in many ancient cultures it came to be treated with reverence and was imbued with important properties. For example, in ancient Egypt the placenta was viewed as the "seat of the external soul" and thus was assigned great importance [5].

Study of the human placenta, or of human embryos for that matter, was confined to anatomical descriptions until the advent of biochemical and tissue culture methods early in the 20th century [5]. Thus, animal models have been central to the study of the placenta since the earliest times, and much of our knowledge of placental anatomy and physiology continues to be derived from comparative studies in animals. Fortunately, the power of comparative animal models in solving complex biological problems is widely recognized. Nevertheless, almost 50 years ago, Donald Barron opined, "Obstetricians, by and large, deprive themselves to a surprising degree of sources of information which could be available to them from animal experiments … animal experiments are carried out to obtain vistas and to get ideas of the mechanisms of biological operation [7]."

The Egyptians and the Chinese developed practical methods to incubate fertilized chicken eggs about 3500 years ago, which led to the use of the developing chick as the most important model organism for embryological research from that time forward, and thereby chicken embryology came to provide the foundation for embryological study in all vertebrates [5,8,9]. For example, the term "yolk sac" was derived from study of the chick embryo, as were the embryological terms "vitelline" and "lecithal," both of which refer to yolk. Thus, even though it contains no recognizable yolk, the initial fetal membrane of mammals is still referred to as the yolk sac, or vitelline membrane [8,9].

Despite having only limited access to placentas, the ancient philosophers recognized the correct function of the placenta and umbilical cord. For example, ancient Indian medical texts refer to "vessels which lead chyle [or nourishment] from mother to fetus [5,10]." Empedocles of Akragas (ca. 444 BC) not only recognized the importance of the circulation but also described the vessels of the umbilical cord [5]. These ancient philosophers may have influenced Aristotle's view concerning the function of the umbilical vessels, as cited at the beginning of this review. Numerous others including Hippocrates (ca. 400 BC) and Galen (ca. 150 AD) shared this view, and also recognized that early development of the chick and mammals was very much alike, including development of the extraembryonic membranes [5].

During the Renaissance, many great artists including Michelangelo (ca. 1500) conducted dissections, primarily to increase their knowledge of human anatomy. Because of his careful and quantitative approach to the study of anatomy, and of biology in general, Leonardo da Vinci (ca. 1490) also became one of the great early biologists; in this regard he was well ahead of his time [5]. Nevertheless, the limited availability of human gravid uterine specimens led even da Vinci to make mistakes concerning placental anatomy. In his classical drawing of the gravid uterus of late pregnancy (titled, appropriately, "The babe in the womb;" [11]), he clearly depicted the uterus with its vascular supply, the fetal membranes and the umbilical cord and vessels, and the single placental disc, but mistakenly depicted fetal cotyledons interdigitating with maternal "crypts" [5,12], an arrangement we now know exists only in ruminants (e.g., antelope, cattle, deer, giraffes, goats, and sheep; for a more complete discussion of placental types, see [9]. Despite this error, da Vinci was perhaps the first to recognize that the fetal and maternal circulations were completely separate [5].

With the emergence of anatomy as a discipline during the Renaissance, numerous investigators, including the great anatomists Andreas Vesalius [13] and Regnier De Graaf [14], clearly depicted the extensive vascularization of the human gravid uterus and placenta, at least on a gross level. This work continued for several hundred years, and culminated with the beautiful drawings by Rymsdyk in William Hunter's *The Gravid Uterus* [15]. Nevertheless, in-depth anatomical and physiological studies continued to rely heavily on animal models [16–18], and even today most studies of placental function, including placental vascular function and growth, rely on animal models including primates, sheep, cattle, rabbits, and rodents [1,6,9,19,20].

Placental blood flow and the importance of placental angiogenesis

The importance of placental function is reflected by the close relationship between fetal weight, placental size (including placental villous surface area) and vascularity, and uterine and umbilical blood flows in many mammalian species [21–42]. Additionally, factors that affect fetal growth, such as maternal and fetal genotype, increased numbers of fetuses, maternal nutrient deprivation, environmental stress, or high altitude, typically have similar effects on placental size [25,26,42–58]. Fetal and placental weights also are reduced when the available uterine surface area is reduced experimentally [53,59].

In the numerous mammalian species that have been studied, fetal weight increases exponentially throughout gestation

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