Mammalian Placentation: A Tribute to E.C. Amoroso's Contributions to Placenta Development

Rodney D. Geisert and Thomas E. Spencer

Abstract Establishment of viviparity in mammals evolved through not only the long-term retainment of the fetus within the maternal uterus but differentiation and expansion of cell layers to form functional membranes to exchange O_2/CO_2 and nutrients between the placenta and maternal circulations. Development of a fetal placental vascular circulation to interact with the maternal uterus is critical to the survival of all species. However, the fascination with the mammalian placenta is the robust variation in types, form, attachment, invasiveness, structure, cell differentiation, endocrine function, and regulation of the maternal immune system. Despite the obvious role of the placenta to support fetal development, mammals have evolved multiple strategies to give live birth at term. The placenta and the maternal–fetal interface during pregnancy can be quite simple to very complex. Professor E.C. Amoroso contributed greatly to the study of comparative placentation in animals. His paper "Placentation" in Marshall's Physiology of Reproduction published in 1952 remains the standard for comparative placental anatomy today. The present volume on "Mammalian Placentation" brings together current reviews for leading experts to diversity of placentation in a number of mammalian species. Chapters will discuss viviparity, blastocyst formation, and placentation in the cow, pig, horse, mouse, dog, primate, human, elephant, and marsupials.

Keywords Implantation · Placentation · Mammal · Viviparity

The development of viviparity in mammals as well as some invertebrate species required the adaptation of the placenta to serve as a functional conduit for interplay

R. D. Geisert (✉)
Division of Animal Sciences, S121 Animal Science Research Center, University of Missouri, Columbia, MO, USA
e-mail: geisertr@missouri.edu

T. E. Spencer
Division of Animal Sciences, S135 Animal Science Research Center, University of Missouri, Columbia, MO, USA
e-mail: spencerte@missouri.edu

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between the semi-allograftic fetus with the maternal uterus. Although primarily recognized for his work on pulmonary circulation in the sixteenth century, the Italian anatomist and surgeon, Realdo Columbo utilized the Latin word for cake "*placenta uterina*" (Greek *plakoenta*) which means flat or plate to describe the large round vascular structure he observed attached to the uterus during pregnancy of women. Although the "placenta" protects the fetus from maternal immune rejection and provides oxygen and nutrient flow to support a fetus to term across all the species; structural differentiation of this fetal–maternal interface is very varied among species.

In the absence of an adequate supply of yolk to support embryo development in oviparous and ovoviviparous species, mammalian viviparity evolved through the differentiation of extraembryonic cells which contribute to placental formation. Initiation of placental development occurs before hatching from the zona pellucida when the outermost cells of a morula form tight junctions to establish cellular polarity. Compaction of the morula establishes outer and inner cells which positions the Na^+/K^+ ATPase system to move fluid into the extracellular space of the compact morula to forming a blastocyst (Fig. 1a). Cellular positioning within a morula induces differential transcriptional activity of the Hippo and Ras signaling pathways to dictate formation of the inner cell mass (ICM) and trophoblast of the preimplantation embryo (Senner and Hemberger 2010; Cockburn and Rossant 2010; Artus and Chazaud 2014). Blastocyst development is somewhat conserved across viviparous mammals and is the direct prelude to formation of the placenta. However, depending upon the species, blastocyst hatching from its zona pellucida can either lead to attachment and invasion through the surface epithelium to implant within the endometrium (examples: rodents, primates, humans) or continued growth (Fig. 1b) and expansion (Fig. 1c) throughout the uterine lumen (examples: ruminants, pig, horse) where trophoblast (Greek trephein meaning to feed; and blastos meaning germinato) comes into direct contact with endometrial epithelium and secretions to support development to term. Continued cellular differentiation and expansion of the ICM (epiblast) provides the extraembryonic mesoderm and endoderm (hypoblast) layers, from its posterior region (Perry 1981), that combine with the trophectoderm to contribute to formation of the classical placenta membranes (Fig. 1d). Mammalian viviparity requires not only the development of the placenta but also the retention of the embryo within the uterus for an extended period before birth, maintenance of pregnancy via progesterone production by the maternal corpus luteum and later the placenta, secretions from the uterus including endometrial glands, O_2, and nutrient exchange between the maternal and placental vasculatures, and modification of the maternal immune system at the placental/uterine interface.

Placentation of mammals can be classified by gross morphology (placental shape) and the number of cellular layers (cellular microstructure) that separate the placenta and uterine vasculature (Grosser 1909; Mossman 1937). Although placental development undergoes gross morphological changes from early to late gestation, the mammalian placenta is classified into four basic groups: Diffuse (pig, horse), Cotyledonary (ruminants), Zonary (dog, cat, elephant), and Discoid (mouse, rat, rabbit, primate, and human). However, the amount of placental erosion or cellular

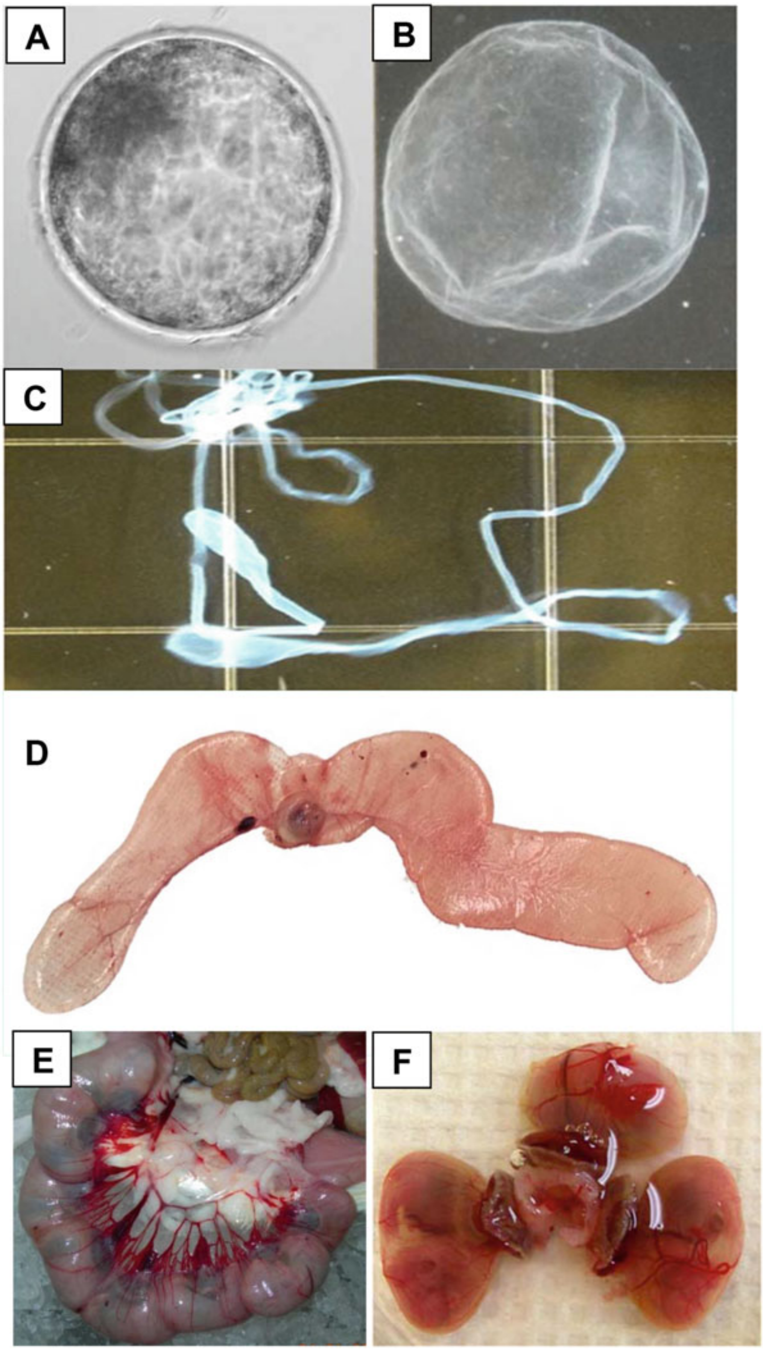

Fig. 1 Transitions in embryo development for formation of the mammalian placenta. (**a**) Day 7 pig blastocyst enclosed in the zona pellucida. (**b**) Day 10 spherical (5 mm) pig conceptus. (**c**) Rapidly elongating trophoblast of a day 12 pig conceptus expanding within the uterine horn. (**d**) Diffuse pig placenta (day 35) containing embryo enclosed in the amnion and the fluid filled chorioallantois. (**e**) Pregnant day 18 rat uterus displaying invasive placentation. (**f**) Day 18 rat discoid placentae

Fig. 2 Emmanuel Ciprian Amoroso. (Photograph obtained from RV Short's tribute to EC Amoroso published in Biographical Memoirs of Fellows of the Royal Society (Short 1985))

layer displacement of the maternal endometrium provides a more accurate description of placentation as provided by the impressive illustrations made by EC Amoroso (1952). The pig (Diffuse) has an *epitheliochorial* type of placentation where the expanded chorion only attaches to the surface epithelium of the endometrium but does not erode or invade into the uterus. Although ruminants (Cotyledonary) initially have epitheliochorial type of attachment to the uterine surface epithelium, binucleate cells migrate from the chorion and fuse with the endometrial surface epithelium to form a syncytium which is classified as *syndesmochorial*. Species such as the dog and cat (Zonary) have an endotheliochorial type of placenta that invades into the endometrium eroding all maternal layers but the endothelium of the maternal capillaries is not breached. The *hemochorial* placentation in the mouse, rat (Fig. 1e, f), primate and human represents the most invasive type of placentation where the placenta blood vessels are directly bathed by maternal blood.

E.C. Amoroso, known as Amo by his friends and colleagues, (Fig. 2) contributed so much to our early understanding and knowledge of placentation across a great variety of species. He was born in the Port of Spain, Republic of Trinidad, where his eye sight was affected by exposure to typhoid fever at a young age which makes his work in placenta histology and illustrations even more remarkable. Amoroso spoke seven languages and was renowned for his elegant, captivating, and acclaimed lectures around the world. Although his work was not solely focused on placental development, he studied and published manuscripts investigating over 28 species. Professor Amoroso's classic, seminal chapter "Placentation" published in the 3rd edition of Marshall's Physiology of Reproduction in 1952 followed the work of many German anatomists (O. Grosser, O. Krolling and H. Strahl) and others (R. Assheton, H.W. Mossman, and A. Robertson) who pioneered understanding comparative placentation in mammals. His 184-page chapter (Amoroso 1952) is a masterpiece of intellectual information on comparative placentation. The chapter contains 88 figures, ~124 hand-drawn illustrations, and histological sections with over 434 references. Professor Amoroso's chapter covered adaptations in viviparity and ovoviviparity of fish, amphibians, and reptiles but mainly focused on comparative mammalian placenta including marsupials. The following quote taken from Professor Amoroso's chapter provides his keen interest in the placenta.

> The mammalian ovum, in all except the Monotremata, is small and does not contain a sufficient supply of nutriment for the developing embryo. It is retained for a longer or shorter period in the uterus, where, by special modifications of the uterine mucosa and a part of the ovum, a placenta is formed, and a transmission of nutriment from the mother to the embryo is made possible. Accordingly, the normal mammalian placenta may be defined "as an apposition, or fusion, of the foetal membranes to the uterine mucosa for physiological exchange" (Mossman 1937). The changes in the maternal and embryonic tissues vary greatly in the several orders, and even in the groups of the same order, but in all they are sufficiently complicated to render their explanation a matter of great difficulty. It is doubtful in any anatomical structure has given rise to keener or more prolonged controversies than the placenta (Amoroso 1952).

Professor Amoroso contributed greatly to our understanding of placentation in the pig, horse, cat, dog, rabbit, mouse, rat, guinea pig, primates, and human and contributed to early work in elephant placentation. Prior to his passing in 1982, Professor Amoroso made the following quote to his colleagues:

> Consider the past for what is relevant to the present; consider the present what is relevant to the formation of the future; consider the future for what may most enlarge man's freedom and fulfilment (Weaver 1982).

Several review papers concerning the mammalian placenta have been published since Professor Amoroso's extensive chapter (Perry 1981; Roberts et al. 2016). The following chapters on viviparity, blastocyst formation, and placentation in the cow, pig, horse, mouse, dog, primate, human, elephant, and marsupials attempt to build on the past, understand the present, and continue to progress towards bettering reproduction of animals and mankind honor the enormous contributions made by Professor Amoroso.

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