PROGRESS IN

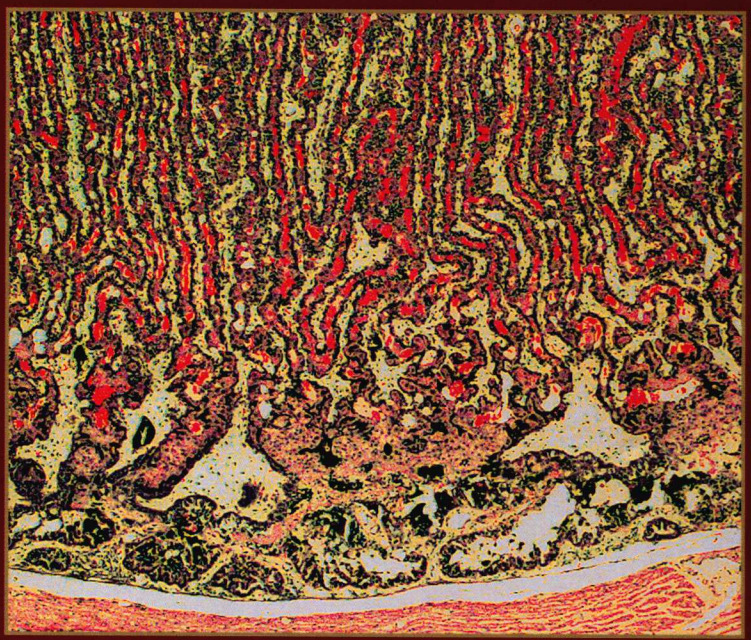
MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE

VOLUME 145

MOLECULAR BIOLOGY OF PLACENTAL DEVELOPMENT AND DISEASE

EDITED BY

WILLIAM R. HUCKLE



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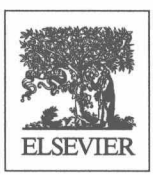

ACADEMIC PRESS

An imprint of Elsevier

elsevier.com

Academic Press is an imprint of Elsevier
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
125 London Wall, London EC2Y 5AS, United Kingdom

First edition 2017

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ISBN: 978-0-12-809327-6
ISSN: 1877-1173

Publisher: Zoe Kruze
Acquisition Editor: Alex White
Editorial Project Manager: Helene Kabes
Production Project Manager: Magesh Mahalingam
Cover Designer: Vicky Pearson Esser

Typeset by SPi Global, India

PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE

Molecular Biology of Placental Development and Disease

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PREFACE

What an extraordinary tissue is the placenta—that developmental project undertaken jointly by mother and her unborn, its extraembryonic offshoots invading an accommodating endometrium, ultimately serving both parties as cellular gatekeeper, trafficker of nutrients and molecular signals, immune protector, vascular network, endocrine organ, and more—only to disappear at birth. Little wonder that the placenta is subject after birth to a host of traditional practices around the world, many being a ritual acknowledgment of the vital roles that we understand the tissue to play biologically. Particularly appealing is the belief, held in one form or another by several cultures, that the placenta is able to serve as an ethereal, twinned guardian throughout the child's life, and so must be accorded due reverence and proper handling at the time of birth.

While the folklore surrounding the placenta undoubtedly dates back many centuries, this organ presently receives what some might consider long overdue reverence of a scientific nature. In 2011, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the US National Institutes of Health began a series of workshops, involving hundreds of scientists and other stakeholders and aiming to set research priorities for the years to follow. Emerging from these discussions, and stemming in part from the broad recognition of the potential lifelong consequences of an individual's experience in utero, was the launch of the "Human Placenta Project" by the NICHD in 2014. To date, three rounds of Requests for Applications based directly on the stated goals of the HPP have been issued, including calls titled "Novel Tools to Assess Human Placental Structure and Function, Using Omics to Define Human Placental Development and Function Across Pregnancy, and Assessing Human Placental Development and Function Using Existing Data." Close to 40 grants have been awarded, additional workshops have been held to exchange findings and refine goals, and interested readers invited to follow the progress of the HPP in detail at http://www.nichd.nih.gov. This endeavor promises to bring to bear the powerful new tools of ultrasensitive transcriptional profiling, epigenetics, noninvasive imaging, and computational modeling in service of improving the prospects for prevention, diagnosis, and treatment of the numerous pregnancy complications that involve the placenta. It is reasonable to expect that the HPP will do justice

to the vision articulated by NICHD leaders Drs. Guttmacher and Spong, writing in an October 2015 supplement to the *American Journal of Obstetrics & Gynecology* devoted to expert reviews on placental biology and disorders: "The HPP is designed to rectify the long-neglected need to understand the human placenta across gestation. If successful, it should change how we understand and manage pregnancy and all that grows from pregnancy."

The success of the HPP will of course be built upon long-standing and diversified expertise in placental research. The aforementioned journal, together with *Placenta* (the *Official Journal of the International Federation of Placenta Associations*), other serials, and the professional societies and conferences that serve the reproductive biology, theriogenology, fertility, endocrine, immunology, and vascular biology communities, are rich with basic and clinical investigations that define our state of the art. I am pleased that many of the investigators responsible for building this knowledge base have joined me in the assembly of Volume 145 of *Progress in Molecular Biology and Translational Sciences (PMBTS), Molecular Biology of Placental Development and Disease.*

The volume begins with two chapters of an introductory nature, the first reviewing the comparative developmental anatomy of placenta in species most relevant to clinical medicine and basic research (Hafez), and the second giving an overview of experimental models used to investigate placenta formation and function (Huckle). Next comes a set of four chapters that address molecular mechanisms by which the cells of the extraembryonic membranes proliferate, differentiate, form syncytia, and invade and remodel the uterine wall: "Transcription factors that regulate trophoblast development and function" by Baines and Renaud, "The phylogeny of placental evolution through dynamic integrations of retrotransposons" by Imakawa and Nakagawa, "Contribution of syncytins and other endogenous retroviral envelopes to human placenta pathologies" by Bolze, Mommert, and Mallet, and "Role of exosomes in placental homeostasis and pregnancy disorders" by Salomon and Rice. These chapters describe the remarkably complex and precise feats of transcriptional coordination that ultimately produce a fully developed, functional placenta. Even more startling is the contribution made to that process by the expressed products of retroviruses incorporated into mammalian genomes in the dim evolutionary past. The volume concludes with a pair of chapters that address the placental function at the fetal–maternal interface in addition to developmental questions: "Novel regulators of hemodynamics in the pregnant uterus" by Clark, Pru, and Pru and "Regulation of placental amino acid transport and fetal growth" by Vaughn, Rosario, Powell, and Jansson.

It is my hope that readers will find in this volume new reasons to be intrigued by the placenta as a biological phenomenon, as well as an appreciation for the ways that cutting-edge molecular biology is being engaged to ameliorate serious and frequently occurring complications of pregnancy. I am grateful to Professor P. Michael Conn, editor of the PMBTS series, for the opportunity to assemble this volume, to the contributing authors for sharing their expertise, and to Ms. Helene Kabes, Mr. Alex White, Mr. Magesh Mahalingam and their colleagues at Elsevier for unfailing professionalism and patient guidance through the editorial process.

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CONTENTS

CHAPTER ONE

Comparative Placental Anatomy: Divergent Structures Serving a Common Purpose

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Contents

Abstract

The placenta, one of the most important transient organs, forms by the apposition of fetal membranes and maternal tissues. Its role is to mediate physiological exchanges between mother and fetus. The word "apposition" covers a wide range of structural variations. It includes approximation, adhesion, interdigitation, or actual fusion between

Progress in Molecular Biology and Translational Science, Volume 145
ISSN 1877-1173
http://dx.doi.org/10.1016/bs.pmbts.2016.12.001

fetal and maternal tissues.[1] Formation of the placenta establishes hemotropic nutrition for the fetus: essential metabolites must be provided to maintain the growing fetus, and these must come to it via the maternal circulatory system.[2,3] Equally important, the placenta also provides oxygen and removes metabolic waste products from fetal blood. Nutritive and excretory roles of the placenta are not its only functions: it also has immune and endocrine activities.[4] Nutrient and gas transport, waste removal, immunological protection of the fetus, and hormonal secretion influencing the maternal metabolism are all complex functions. They may also to some extent be conflicting purposes; hence, the placenta is a complex fetal organ. It is structurally adapted to perform its roles somewhat differently in different species, but the set of functions remain the same. Understandably, the placenta has been the subject of extensive research, and it will continue be an important topic thanks to its complexity. The intent of this chapter is to provide a simple description of placental anatomy using classic categories and to describe anatomical species variations in humans, important domestic animals, and the major laboratory species.

THE PLACENTA

The placentae of eutherian mammals have features in common, ones that facilitate essential functions, but there are of course unique species-associated configurations. While the placentae of different species have many structural variations, the overriding necessity of fulfilling its essential functions means that different systems are designed to achieve the same purpose.

The process of placentation starts with a small area of maternofetal apposition, which in time increases in size, in response to the growth of the fetus. The development of the placenta begins with the implantation of the blastocyst into the wall of the uterus.

1. FETAL MEMBRANES

Understanding the development of fetal membranes is necessary before discussing the anatomy of the completed placental organ. Fetal membranes provide the basis for the formation of structures essential to the physiological maintenance and protection of the embryo. Fetal membranes (also referred to as extraembryonic membranes, despite the fact that they are really embryonic in origin) are formed from and are continuous with the three embryonic layers: ectoderm, mesoderm, and endoderm[5]. The prefix "extra" is used in context of "outside of" the embryo proper. Fetal

membranes are formed from somatic or splanchnic mesoderm plus ectoderm or endoderm. For details, see Steven, 1975; Perry, 1981; Noden and De Lahunta, 1985; Mossman, 1987; Leiser and Kaufmann, 1994; Wooding and Burton, 2008.[3,5–9]

There are four fetal membranes: the chorion, the amnion, the yolk sac, and the allantois (Fig. 1). The chorion and amnion are derived from the somatopleure (i.e., trophoblastic ectoderm and extraembryonic somatic mesoderm). The yolk sac and allantois are derived from splanchnopleure (the endoderm and extraembryonic splanchnic mesoderm).

The following general description applies to human and domestic animals, including the horse, pig, ruminant, and carnivores, but species variations will be noted and specified. The development of fetal membranes in rodents is unique to those species, so the development of fetal membranes in mice and rats will be discussed in the section of the placenta of rodents.

A placenta is formed when fetal tissues acquire contact or fusion with maternal tissue for physiological exchange. In mammals this always involves the chorion and either the yolk sac or the allantois. The amnion remains avascular, and its function is chiefly mechanical.[7]

1.1 Yolk Sac

The yolk sac is formed from hypoblast endoderm and extraembryonic mesoderm. The hypoblast separates from the inner surface of the embryonic disc in early blastocyst stage, forming an endodermal tube within the trophoblast

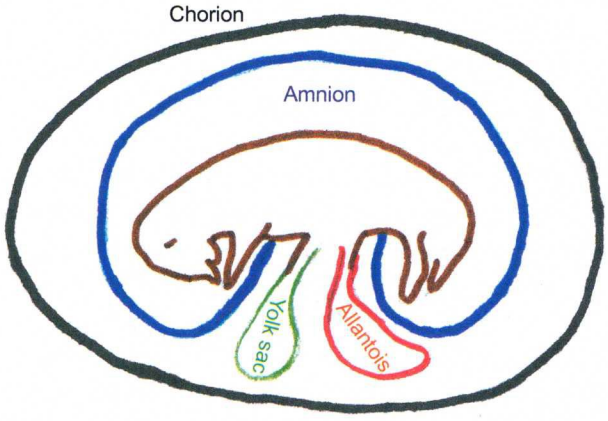

Fig. 1 Schematic simplification of fetal membranes early in fetal life. *Redrawn after Leiser R, Kaufmann P. Placental structure: in a comparative aspect.* Exp Clin Endocrinol. *1994;102:122–134.*

tube. The hypoblast tube is invested with splanchnic mesoderm after its formation and splitting.

The yolk sac is the part of the tube outside the embryo. The yolk sac is one of the components of a choriovitelline placenta; the other component is the chorion. It is the connection between the yolk sac and the chorion on the abembryonic side that forms the choriovitelline placenta, that is, the apposition of yolk sac endoderm, fused somatic and splanchnic mesoderm, and the trophoblast. This combination of embryonic structures is termed a "trilaminar omphalopleure." This connection is formed early in gestation in the horse and in carnivores; it remains functioning in the horse for a longer period than in any other mammal (for the first quarter of the total gestation period), and it is the primary source of nutrients during that period. The yolk sac/chorion connection is broken down later in carnivores, except in the extremities where it remains functioning well after establishment of the chorioallantoic placenta. The apposition between the yolk sac and the chorion is transitory in ruminants and pigs, but it is nevertheless functional for a short period.

In humans, the primary yolk sac is formed in a similar fashion as in domestic animals. With fetal growth, however, it is displaced to the abembryonic pole and ultimately degenerates. The space that constituted the primary yolk sac becomes the definitive yolk sac. It is small to begin with, provides very limited nutritive function, and regresses early, but it is still important in respect to other functions. The yolk sac mesoderm is a major site of hematopoiesis, and the yolk sac endoderm is the source of primordial germ cells.

The yolk sac and its vitelline vessels provide temporary nourishment early in embryonic life. The nutritive role of the yolk sac is later taken over by the allantois, after the latter has developed. In most species, the yolk sac's degeneration leaves no visible remnant at birth. The attachment between chorionic and yolk sac mesoderm at the extremities in carnivores persists until birth and can be seen as a tubular structure extending throughout the length of the fetal membranes.

1.2 Allantois

The allantois is derived from splanchnopleure (endoderm and splanchnic mesoderm). It arises as a diverticulum of the hindgut and gradually fills the entire extraembryonic coelom (exocoelom) in most species. The allantois does not extend to the area where the connection of yolk sac and

chorion exists in the horse and carnivores, nor where the mesamnion is located in the pig and ruminants. In humans, the allantois is vestigial, but in a functional sense, the human placenta is a chorioallantoic type (see later). The vessels of the allantois vascularize the chorion and amnion, with allantoic arteries as branches of the two dorsal aortae. Allantoic veins or umbilical veins drain into the caudal (inferior) vena cava through the sinus venosus.

1.3 Chorion

The chorion is derived from trophoblastic ectoderm and extraembryonic mesoderm (somatopleure). There is an intimate association between the forming chorion and amnion. These form by folding in domestic animals and by so-called cavitation in humans, mice, and rats.

In domestic animals, the chorion and amnion are the products of bilateral folding of the extraembryonic somatopleure. This arches dorsal to the embryo and continues to grow. Fusion of the chorioamniotic folds occurs at the mesamnion or chorioamniotic raphe. Dorsal fusion results in formation of two layers of somatopleure separated by the exocoelom: the outer somatopleure becomes the chorion and the inner somatopleure the amnion. Thus, the chorion is lined by mesoderm from inside, and amnion is lined by mesoderm from outside. This ensures that the chorionic trophoblasts face the endometrium.

When complete separation of the chorion and amnion occurs, the exocoelom fully surrounds the amnion. When this happens, the fetus is born covered with the amnion, as in the case of the horse. If the dorsal connection (mesamnion) persists, which is the case in pigs and ruminants, the fetus is born without being covered by the amnion.

In humans, the chorion is simply the original trophoblast, which becomes lined by somatic mesoderm. The chorion is relatively avascular; blood perfusion is achieved instead by the allantoic vessels. But the chorion (vascularized by the allantois) is the essential component of chorionic villi. The chorioallantoic placenta is the permanent functional placenta in domestic mammals and humans, taking the place of the transitory choriovitelline placenta.

1.4 Amnion

The formation of the amnion is associated with the formation of the chorion as described earlier. The amnion is the outer membrane, created