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Review: Placenta, evolution and lifelong health

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ABSTRACT

The intrauterine environment has an important influence on lifelong health, and babies who grew poorly in the womb are more likely to develop chronic diseases in later life. Placental function is a major determinant of fetal growth and is therefore also a key influence on lifelong health. The capacity of the placenta to transport nutrients to the fetus and regulate fetal growth is determined by both maternal and fetal signals. The way in which the placenta responds to these signals will have been subject to evolutionary selective pressures. The responses selected are those which increase Darwinian fitness, i.e. reproductive success. This review asks whether in addition to responding to short-term signals, such as a rise in maternal nutrient levels, the placenta also responds to longer-term signals representing the mother's phenotype as a measure of environmental influences across her life course. Understanding how the placenta responds to maternal signals is therefore not only important for promoting optimal fetal growth but can also give insights into how human evolution affected developmental history with long-term effects on health and disease.

1. Introduction

Reproductive success (Darwinian fitness) is the cornerstone of evolutionary success and in placental mammals placental function is the cornerstone of reproductive success. This is because the placenta not only prepares the fetus for survival in the risky postnatal period but also provides signals which help the child fit the world in which it needs to grow and reproduce. Evidence for selective pressures on the placenta are seen in the diversity of placental structures across species [1]. Placental function is important for later health as poor fetal growth is associated with higher rates of chronic disease in adult life [2]. The selective pressures on the placenta over our evolutionary past will have acted to increase Darwinian fitness by increasing maternal and/or fetal fitness, whichever has the greatest long-term gain. We suggest that these changes will, in large part, have been to increase the fitness of the mother as, having reached reproductive age, she is more likely to reproduce successfully than an individual offspring. It must however be stressed that the needs of the mother and the fetus must be balanced, and this is illustrated by the effects of maternally and paternally imprinted genes within the placenta. Here we argue that understanding the evolutionary pressures on placental function may not only help us to identify the signals which regulate fetal growth but also those processes which influence the offspring's health in later life.

The placenta is the interface between the mother and the fetus and regulates the amount and composition of nutrients transported. Placental nutrient transfer can be altered by both maternal and fetal signals [3,4]. Those signals which have been identified tend to indicate processes acting over short time scales, such as maternal plasma nutrient levels [4]. We propose that in addition there is a set of signals which relate to aspects of the maternal phenotype, such as body composition, which reflect her past environment. These signals represent her capacity to support the pregnancy and assist the offspring to develop phenotypic attributes which best fit the environment in which it is likely to live. If the mother's capacity to support the pregnancy is limited these signals may initiate maternal constraint of fetal growth. Such constraint not only protects the mother's nutrient reserves, maintaining her ability to support the pregnancy, but also her future fertility. The placenta is ideally placed to mediate the partitioning of maternal nutrients between the mother and the fetus. In this way, when nutrient supply is restricted or is likely to be restricted the mother may be able to reduce transfer to the fetus, slowing its growth and reducing its future nutrient requirements. In other circumstances, such as maternal diabetes, the relaxed constraint can result in fetal overgrowth.

This review explores the evidence that the placenta has evolved to respond to longer-term signals which mediate maternal constraint of fetal growth and affect the offspring's phenotype in the context of evolutionary pressures on fitness.

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2. Evolution, development and future risk of disease

Fetal growth is an important determinant of lifelong health [2,5]. Epidemiological studies demonstrate associations between lower birth weight and adult hypertension, coronary heart disease and impaired glucose tolerance or insulin resistance [2]. Although most epidemiological studies have focused on birth weight, it is thought that birth weight itself does not underlie such relationships. Instead birth weight is a proxy indicator of the intrauterine environment, with a poor intrauterine environment being associated with lower birth weight. It is important to note that these relationships to lifelong health are not only seen in the lowest birth weight babies, but occur across the entire birth weight spectrum [6]. This indicates that the problem is not being born small, but developing in an intrauterine environment which leads to the baby being born smaller than it would otherwise have been.

The association between poor fetal growth and later risk of disease may be further exaggerated if there is mismatch between the maternal environment and the postnatal environment. For instance, a poor intrauterine environment may predispose the offspring to lay down fat in anticipation of a poor postnatal environment. If food is scarce in the postnatal environment this predisposition would be advantageous, but if there is mismatch and food is abundant this may lead to obesity and type 2 diabetes [2]. In countries where there is a rapid rural to urban transition this mismatch may have a substantial impact on future health [2].

Evidence for the placenta's role in determining fetal growth comes from observations that disruption of placental development causes growth restriction and that impaired placental nutrient transporter capacity precedes growth restriction [3,7,8]. As the placenta is a major mediator of fetal growth it is likely that placental function is related to future health of the offspring. This is not easy to demonstrate as, without good markers of placental function, it is difficult to generate epidemiological evidence for such a link. Initial small studies of placental weight, a surrogate indicator of placental transport capacity, generally showed associations between weight or the placental to birth weight ratio and cardiovascular disease, although there was some inconsistency [9]. More recently two larger studies have been completed based on records of tens of thousands of births. These studies suggest an association between a higher placental to birth weight ratio (interpreted as a disproportionately large placenta) and both higher blood pressure in childhood and increased rates of coronary heart disease in adult life [10,11]. In these pregnancies despite a relatively large placenta, the fetus appears not to have grown appropriately.

Evolutionary change in genotype by natural and sexual selection occurs over many generations, making it a poor mechanism for adaptation to fluctuations in environmental conditions. To meet such fluctuations, mechanisms have however evolved to allow developmental plasticity in response to environmental conditions. Environmental cues may be as simple as insufficient nutrient supply leading to reduced growth of fetal organs in ways which persist throughout life. For instance impaired fetal growth is associated with reduced nephron number which may predispose to hypertension in later life [12]. Alternatively, environmental signals may lead to epigenetic modifications of gene expression resulting in complex lifelong changes in phenotype. Some of these changes may act on the placenta itself so that effects on the fetus are indirect. A demonstration of this principle can be observed in rats in which the pattern of gene expression is influenced by maternal dietary folate content via changes in epigenetic processes [13]. Such processes may also affect the placenta itself: preliminary data in placental arterial endothelial cell culture from normal and IUGR pregnancies show changes in methylation and gene expression of the eNOS and arginase genes involved in nitric oxide production [14].

Given the placenta's role in mediating fetal growth and its position at the interface between the mother and the fetus it is in the ideal position to respond to maternal or fetal signals to modulate fetal phenotype (Fig. 1).

3. Maternal constraint

All the maternal nutrients transported to the fetus by the placenta represent a cost to the mother. In a healthy, well fed mother this is not necessarily a problem but in a mother without adequate food or nutrient reserves this may limit her ability to support the pregnancy or the infant after birth. It may also reduce her future fertility. Furthermore, if the fetus grows too big then the mother may have difficulty during delivery, potentially leading to maternal and fetal death. For these reasons it is thought that mechanisms exist by which the mother limits fetal growth to be appropriate to her stature and nutritional status. An obvious example of this is that twins are smaller at birth than singletons [15]. These mechanisms are referred to as 'maternal constraint' [16].

Evidence for maternal constraint in humans comes from studies showing that birth weight is more closely related to mother's than father's birth weight despite their equivalent genetic contribution [16]. This observation is supported by elegant embryo transfer studies in horses which demonstrate that embryos from large breeds are born smaller when transferred to the womb of a smaller breed and vice versa [17].

In humans maternal constraint becomes more important during labour given the relatively large size of the fetal head at term in relation to the size of the mother's pelvic canal. In populations

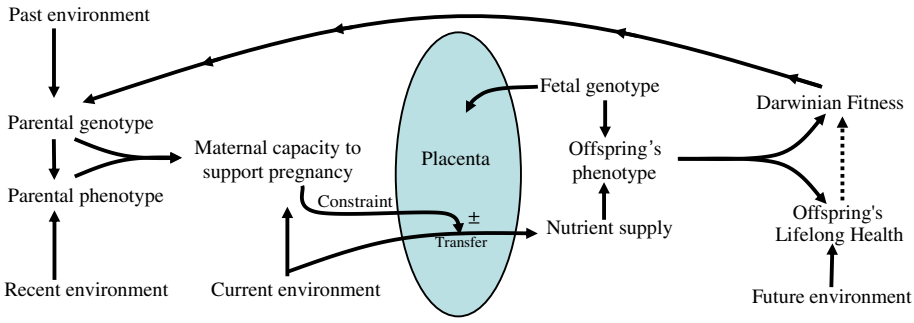

Fig. 1. Past environment is a determinant of maternal phenotype and maternal constraint. Maternal phenotype will determine her capacity to support the pregnancy and the extent of maternal constraint. Evolution will select for those factors which promote Darwinian fitness whereas the offspring's lifelong health will be determined by the interaction between birth phenotype and the environment it encounters throughout life. As Darwinian fitness is primarily determined by survival in infancy and age at puberty longer-term health problems will have a limited impact on selection.