REVIEW

The Conflict Between Mothers and Foetuses

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Abstract

Pregnancy is often perceived as a harmonious process between mother and children. However, evolutionary speaking, the interests of a pregnant female are not always the same as the ones of her offspring; some degree of conflict even exist between them concerning, for instance, the allocation of nutritional resources. Analysing pregnancy as a not fully cooperative process enables understanding of certain phenomena that would be incomprehensible otherwise. Examples of these phenomena are the enormous amounts of foetal hormones released in maternal blood and certain complications linked to pregnancy, such as diabetes and hypertension. This paper tries to use the notions of inclusive fitness and genomic imprinting to understand the particular phenomena that take place during mammalian pregnancy. The different "weapons" used by mothers and foetuses (placenta, hormones,...) are described here, and ways in which their unbalance can lead to severe complications are explained.

Introduction

What is the best example of cooperation between two beings? Many people will say that pregnancy is a good candidate. A mother's body changes drastically so that he womb can accommodate a little child, who in return will bring her comfort and joy. And physiologically, it seems that the mother's body and the placenta are coordinated in the best way, maximizing harmony and cooperation between the two organisms. However, does cooperation always represent the best picture of pregnancy? The best interests of the mother and those of her child might not always be exactly the same, in particular when it comes to the allocation of the mother's resources. Generally, having different interests over resources means for two different organisms that they will enter a conflict in order to receive or keep as much advantages as possible. Could there be a conflict between a mother and her unborn child?

The idea that an offspring could be selected to take more from a parent than they are selected to give was first expressed by Trivers [1]. Haig then argued that foetuses will be selected to get many nutrients for their own growth while their mothers will be interested in distributing fairly the resources available between all her offsprings and keep enough for her own survival [2]. Seeing pregnancy as a conflict between different interests sheds light on some processes otherwise are tough to explain, such as the enormous amounts of foetal hormones released in maternal blood and complications and diseases linked to pregnancy, like diabetes and hypertension. Therefore, this paper will argue that the mother-foetus conflict hypothesis is required in order to fully comprehend several aspects of pregnancy.

Inclusive Fitness

So what could be the best interests of a mother and a foetus during pregnancy? Both of them carry genes which will be selected only if they optimally increase the fitness of their carrier. The mother's fitness will be increased if she has as many offsprings living up to maturation as possible. This means that she will try to allocate the resources she has got evenly between all her children. In addition, as the offspring only carries half of her genes, her own survival will in general be more important than the one of one of her children. As a result, the mother's best interest is to give her foetus just the amount of resources required for their survival. On the other hand, the foetal genes will be selected if they permit growth and increase chances of living up to maturation. This means getting a lot of resources from their mother.

The conflict is even stronger in promiscuous species. To explain this observation, it is important to understand the concept of inclusive fitness, which considers the condition under which an allele can spread in a population. It includes two types of benefits that can favour an allele. Direct benefit takes

place when the allele selected directly increases the reproductive success, and thus the fitness of their carrier, through selfish or mutually beneficial behaviours. An indirect benefit requires improving another individual's fitness at the expense of one's own because they have the same genetic material [3]. Additionally, it is more interesting to help a close kin than one that only shares a small percentage of your genome. This leads to the concept of the coefficient of relatedness r, which defines the probability that an allele in the actor's genome is also present in the recipient's genome [3, 4]. In the case of the relation between a mother and her offspring, or between full-siblings, r is always equal to 1/2. So this means that in non-promiscuous species a foetus will not have interests in taking too much nutrients from their mother, as it could harm greatly the fitness of their full-siblings and therefore reduce their indirect fitness. The equation is different for half-sibling. They do not share the same father, so their coefficient of relatedness is only ¼. Genes favouring the uptake of more resources from the mother will be selected, as survival of half-siblings is less important for one's indirect fitness.

Genomic Conflicts

It appears that genes in the same individual can have diverging interests too. In promiscuous species, genes inherited from one's mother (matrigenes) have different interests than those inherited from the father (patrigenes) [5]. The genes matrigenes will want the foetus to take fewer resources as it would be disadvantageous for the mother and her other children. Patrigenes, however, are not shared either by the mother or one's half-siblings. Consequently, they will be selected to make the foetus take more resources from the mother, as it does not cost anything to the father and increases his chances of reproductive success. The result is an "intragenomic conflict" between the two types of genes.

The differentiation between patrigenes and matrigenes is made possible by a process called genomic imprinting, which is the epigenetic alteration of genes that can lead to their silencing in sperm and egg cells [5]. Approximately 100-200 human genes are imprinted by epigenetic mechanisms such as DNA methylation [6]. Several diseases in humans have highlighted the importance of genetic imprinting [6]. The placenta is a very good place for its action, as all nutrients exchanged between foetus and mother have to go through it. Indeed, most described imprinted genes are active in the placenta [6]. Experiments showed that several species of mice with two paternal or two maternal chromosomes instead of one from each parent did not survive through pregnancy and that the formation of their placenta was considerably altered. Malformations and high death rates were also observed in mice with uniparental chromosome duplications for at least 13 chromosomes. Interestingly, it was found that the extraembryonic tissues, including the placenta, were more developed in mice with additional paternal chromosomal material, and less in those with additional maternal one [6]. To understand that, it is important to take a close look at the placenta constitution and functions.

Placental Constitution and Implantation

In humans, the embryo inserts itself in the maternal endometrium approximately one week after ovulation. The arteries supplying the endometrium, called the spiral arteries, lengthen and become highly coiled during the days following the theoretical implantation. The decidua, the tissue that lines the maternal uterus and is in direct contact with the placenta, and endometrial glands form around the same time. If implantation has not occurred, decidual tissue, the endometrial glands and spiral arteries are gotten rid of during menstruation [2]. A few days before, the embryo differentiates in two layers: the inner cellular mass and an outer layer of trophoblast cells, which will constitute the parts of the placenta in direct contact with maternal tissue. Once the embryo is implanted, some of these trophoblast cells invade the mother's decidua either through an interstitial route or through the lumen of the spiral arteries, to aggregate around these arteries.

The action of the trophoblast cells in the decidua is to break down the smooth muscle of the arterial wall so that the mother cannot vasoconstrict these vessels anymore and thus cannot control the uteroplacental blood flow. The trophoblast cells then create a capillary network linked to the foetus by the umbilical cord, forming the intervillous space. This is the site where the exchanges between mother and foetus will take place. The maternal and embryonic vessels are always separated by several layers of trophoblast cells. Consequently, the foetus can control secretions of substances into maternal blood, while the mother cannot secrete anything without foetal

control [2]. It is clear that placentation shows that to a certain extent control is taken by the embryo over its mother, who cannot regulate the amount of blood and therefore nutrients she allocates to her child through vasoconstriction and can be subject to the effects of chemical substances. She has to develop mechanisms to limit this foetal control, leading to a certain degree of conflict. It is also understandable that paternal genes are more implicated in the placentation process, as their best interest is to take advantage of maternal resources.

It is notable that placentas in different mammalian species show a highly variable morphology in comparison to other tissues. For instance, in some species the trophoblast cells nearly do not affect the maternal tissues while in others, such as in humans, they breach it to have a direct access to maternal blood [2]. Why would placentas have such a low degree of homology, except for a need of continual adaptation? Trophoblast cells are required to adapt rapidly, as they are the front line of foetal-mother conflict. Indeed, this conflict leads to continual selection on genes counteracting maternal restriction measures [7]. Decidual tissues are also under strong selection to develop mechanisms counteracting excessive foetal uptake of resources.

During implantation, trophoblast cells secrete many proteases in order to breach the decidual tissues, while these tissues secrete inhibitors to slow the advance [2]. However, the decidua cannot be a strictly protective organ as decidual reactions only exist in species with invasive placentas and are taking place more often in those with highly invasive placentas [2]. There are three different units taking place in this conflict for resources: the genes of the mother and the patrigenes and matrigenes in the foetus. An example of maternal genes expressed in the decidua is the transforming growth factor-β (TGFβ), whose action is to prevent the degradation of the decidual matrix by inhibiting the action of the trophoblast cells [2]. This is a major event limiting spiral arteries changes that advantage the foetus. It is not sure why the foetus would be receptive to TGFβ, but the logical explanation would be that the receptors are expressed by matrigenes, while patrigenes are responsible for the aggressive traits of the trophoblast.

Growth and Placental Hormones

The needs in nutrients of the foetus are usually limited at the beginning of pregnancy, before becoming compelling for the mother in the third semester, when most of the growth and lipid uptake happens. At that moment, the amount of maternal blood available for exchange of nutrients has mainly been determined by the intervillous space formation during the first semester [8]. It is therefore during the first trimester of pregnancy that most conflicts about nutrients uptake are inferred to happen, even if it is a time when the embryo does not have much needs. The stage at which the trophoblast cells would stop their invasion and the extent of this invasion are determined by a conflict between patrigenes against matrigenes and maternal genes.

Traits other than TGFβ that influence the invasive phenotype of the placenta have been observed. An example is the expression of the gene encoding for IGFII (Insulin Growth-Factor II), that takes place in the invasive portion of the placenta. IGFII has been shown to be only expressed by the paternally-derived gene in mice and human placentas [2]. On the other hand, IGF2R, a gene antagonizing the effect of IGF2, has been demonstrated to be only maternally expressed. Mice that were born with a deletion of the paternal copy of IGF2 were born small, and those born without the maternal copy of IGF2R were born too large [2].

Some hormones secreted in very high amounts by the foetus in maternal bloodstream during gestation and acting on maternal receptors, like human placental lactogen (hPL) or pregnancy-specific glycoprotein (PSG), also provide evidence for the conflict theory. The seemingly inconsistently huge quantities of hormones released can be explained as a way for the foetus to manipulate maternal physiology [2]. These hormones are a determinant of trophoblast invasion, length of maternal gestation, modulation of mother's vasculature and several other processes enhancing maternal investment. As a reaction to increased levels of hormones, mothers were and are selected to develop mechanisms to decrease the response, such as by decreasing the amount of corresponding receptors [2]. Foetuses in turn were selected to release even more hormones, sometimes until it reaches extremely high amounts [9]. For example the secretion of hPL reaches levels up to 15µg/ml during the final weeks of pregnancy [9]. This hormone increases the amount of free glucose

in the blood by binding receptors that cause an increased maternal insulin resistance. However, it is not beneficial for the mother to give more glucose than required to her offspring. She therefore reacts by increasing her production of insulin, leading foetuses to be selected to produce even more hPL. This observation is puzzling, but explainable by the conflict theory, that states that the high amount of hPL released are not per se necessary but the unfortunate result of a co-evolutionary arms race.

Diseases and Complications of Pregnancy

Several symptoms and complications related to pregnancy exist and it is difficult to find an explanation for a number of them if pregnancy is seen as a fully cooperative process. However, the mother-foetus conflict theory provides much insight. Diabetes due to pregnancy, for instance, can be explained by this theory. Pregnant women's glucose blood concentration is situated on a continuum, and depends on the genes of the mothers and those of their offsprings. Glucose intolerance can be developed by women who cannot produce enough insulin to compensate for receptors resistance induced by foetal hormones. Furthermore, the foetus might have developed mechanisms to decrease insulin concentration in the blood [2]. Foetus would thus ensure access to more glucose to grow bigger, and this can happen at the expenses of their mother, who undergoes diabetes.

Foetuses can also decrease the uteroplacental vessels resistance in order to receive more blood flow. Maternal genes developed countermeasures, one of which simply being the coiling of the spiral arteries, as lengthening of a vessel decreases blood flow. Maternal blood pressure sometimes rises during the second half of pregnancy. Furthermore, the placenta probably also releases factors in maternal blood, that lead to vasoconstriction of non-uteroplacental vessels. This results in an increase in blood pressure in some place the mother's vasculature, but also a bigger share of the blood flow going to the spiral arteries. In some cases, this leads to hypertension and preeclampsia (hypertension with proteinurea). Preeclampsia has been shown to have a familial component, so interactions between matrigenes and patrigenes might also be involved [2]. Preeclampsia is one of the main causes of mortality in pregnant women and can also cause complications for the child after birth, and its best explanation might well be maternal-foetal conflict.

Conclusion

The maternal-foetal conflict theory is useful to understand certain processes happening during pregnancy. Conflicts arising between maternal and fetal genes and between matrigenes and patrigenes are a likely consequence of different interest in the distribution of maternal resources, particularly in promiscuous species. Maternal genes and matrigenes would develop counter-mechanisms to avoid being extracted too much resources, while paternal genes and patrigenes would selected to do the exact opposite. This can lead to a co-evolutionary arms race that can cause damage and surprising manifestations. As a consequence, it appears necessary in order to grasp a complete understanding of pregnancy to analyse its conflictual dimension and not always see it as a fully harmonious and cooperative process.

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