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The tripartite immune conflict in placentals and a hypothesis on fetal→maternal microchimerism

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SUMMARY

There is a two-way traffic of immune cells through the placenta; and fetal immune cells are often present in the maternal body even long after giving birth. We present an adaptationist theory to interpret fetal→maternal microchimerism and the diverse set of concomitant medical phenomena. We handle fetal, maternal, and paternal adaptive interests separately and in interaction with one another. Fetuses may benefit from immunological information gathered by migrant cells in the maternal body, and also from improved maternal defence. However, they may be jeopardized by a selfish maternal usage of fetal→maternal microchimerism – i.e., some mothers get pregnant only to improve their immune system and then to abort. The use of microchimeric cells by the maternal immune system may contribute to the adaptive benefits of female choosiness and polyandry. While fathers may enjoy an indirect benefit from enhanced fetal and maternal health, they also face the risk of wasting sexual efforts due to selfish pregnancies of cheating females. Paternal alleles acting via clones of microchimeric cells in the maternal body could launch an immunological attack against the non-kin sperm in the female genitalia, or against the non-kin fetus in the womb. Furthermore, an intraspecific version of Zahavi's Mafia Hypothesis could explain a potential interaction between the abortion of fetuses and a subsequent rise of an autoimmune disease. We suggest that males may be capable to provoke microchimerism-induced autoimmune-like diseases in the mother in revenge of selfish pregnancies. This hypothetic paternal threat could increase the maternal costs associated to selfish pregnancies. From a medical point of view, we propose new interpretations for autoimmune-like diseases, infertility, miscarriage, and also for the prevailing connections among them. Specifically, we argue that miscarriages may cause autoimmune diseases, a reversed causality as compared to the currently accepted one.

Introduction

Microchimerism is the presence of genetically disparate cells in the body of the host individual. A common type of this is the occurrence of fetal cells in the mother even long after parturition, i.e., fetal→maternal microchimerism. The presence of fetal T and B lymphocytes, monocyte/macrophages and NK cells appear to be quite prevalent (50–75%) in women years or even decades after delivery. On the contrary, maternal→fetal microchimerism, a phenomenon not discussed here, appeared to be about half as prevalent [1].

Though fetal→maternal microchimerism is studied almost exclusively in humans, it seems likely to also occur among other placental mammals (Eutheria). Here we intend to outline potential adaptive costs and benefits that may channel the evolution of this phenomenon in placentals, and, in particular, in humans. Since the adaptive interest of the mother, the father, and the fetus may well be contradicting within this context, we will discuss these potential interests separately from various viewpoints.

Fetal costs and benefits

There is a two-way traffic of immune cells through the placenta. Though no experimental evidence is available yet, we cannot exclude the possibility that fetal T-cells and B-cells migrate out into the maternal body, may gather biochemical information on currently prevalent pathogens, and may migrate back into the fetus. Thus, the offspring might not necessarily be immunologically naive at the moment of birth and soon after. The newborn offspring might enjoy the benefits from the former immunological experiences gathered by its own cells.

However, fetal immune cells live in the mother's body not only during pregnancy, but some of them may even remain there for decades. Half of their genome is paternally derived, carrying also the father's resistance alleles, and these cells actively contribute

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to the immune surveillance of malignant cells [2], and, at least potentially, to an improved defence against infectious pathogens. Naturally, the mother's improved immune capabilities yield an indirect benefit for the fetus as well.

Moreover, the fetal benefit may also have a direct component. Provided the mother's immune system is ineffective against a particular infection, while the fetus happens to carry effective paternal resistance alleles, it is in the fetus's direct interest to launch a preventive strike against the pathogens far away in the maternal body before they infect the fetus itself.

As explained below, however, fetuses may potentially be jeopardized by a strange maternal usage of fetal→maternal microchimerism: they may happen to be created and aborted to serve the pure and selfish immunological interest of their mothers.

Maternal costs and benefits

As mentioned above, mothers may potentially improve the efficacy of their immune system by means of paternal resistance alleles obtained via fetal→maternal microchimerism. However, not all females are physiologically prepared to give birth to an offspring; some of them may simply lack the adequate nutrient and energy resources for this effort. This prompts the question of whether or not females ill suited to give birth may still engage in 'selfish pregnancies'. It seems possible, at least theoretically, that they seek sexual contacts to obtain paternal resistance alleles only, and then they abort the embryo itself soon.

Females tend to be the 'choosy' sex of mammals, while males compete with one another to get access to females. The evolution of female preferences for healthier males is traditionally explained by three parallel arguments. Healthier males (i) pass more reliable resistance alleles to the offspring, (ii) are less likely to transmit sexually transmitted diseases to females, and (iii) are capable of providing better care and defence for the offspring [3,4]. In addition to this, we propose a fourth reason why to choose a healthy mate; we suggest that the evolution of female mammals' preferences for healthier males is partially driven by females' benefit of using paternal resistance alleles directly.

Similarly, several potential benefits of polyandry had already been proposed by former authors [5–7]. In parallel with all these benefits, we propose that polyandry may be beneficial for female mammals in their efforts to increase the diversity of resistance alleles they may obtain by means of microchimerism.

Fetal immune cells often appear to contribute to maternal autoimmune diseases in humans. In the strict sense, however, we should rather use the term 'graft-versus-host disease', provided clones of fetal cells are truly involved [8]. We propose that microchimera-induced 'autoimmune diseases' arise in relation to their adaptive function; women utilise paternal resistance alleles obtained via fetal immune cells to exhibit enhanced immune responses. The risk of 'autoimmune diseases', that may also be modified paternally as explained below, acts as a potential cost for mothers.

Paternal costs and benefits

Fathers may enjoy a fitness benefit provided fetal→maternal microchimerism enhances fetus health, as suggested above. Moreover, presuming it also improves maternal health more often than it harms, a father may enjoy further benefits from enhanced maternal care available for his offspring. On the contrary, however, males may a face the risk of wasting their sexual efforts on the selfish pregnancies of 'cheating' females. We can't resist the temptation to develop further speculations along this line of arguments.

At least theoretically, paternal alleles acting via clones of microchimeric cells in the maternal body could launch an immunological attack against the non-kin sperm in the female genitalia, or – alternatively – against the non-kin fetus in the womb. Thus, a father – or a male mammal, to speak more generally – could reduce rival males' further chances to fertilise the same female in the future.

Furthermore, here we propose an intraspecific version of the Mafia Hypothesis to explain a potential interaction between the abortion of fetuses and a subsequent rise of an autoimmune disease. Zahavi [9] proposed in his hypothesis that an aggressor (a cuckoo) applies force to ensure that the victim (a host bird) must make a decision. Given the 'mafioso'-ensured context, the target host bird has two choices; it either provides care to the cuckoo's nestling together with its own nestlings (which is bad for the victim), or the aggressor takes revenge by destroying the host's nestlings (which is worse for the victim). Soler et al. [10] generalized this hypothesis for interspecific host-versus-pathogen conflicts. We adopt this logic to outline a sexual conflict scenario in placentals; i.e. to suggest that males may be capable to provoke a microchimerism-induced 'autoimmune disease' in the mother – in revenge of 'selfish pregnancies'. This hypothetic paternal capability could reduce paternal costs related to 'selfish pregnancies'.

Implications

As clarified above, fetal, maternal and paternal adaptive interests may overlap in several points, or markedly differ from one another at other points. This mixture of interests may give rise to a complex tripartite game of cooperation and a conflict taking place within the maternal body. The maternal body, thus, appears to enjoy some advantage, by providing the physical scene of cooperation and conflict. To a high degree, the maternal body needs to cooperate with the fetus inside, though not always and not necessarily. Similarly, it may rely on the help of fetal lymphocyte clones to a certain degree, although these cells may also turn against it to serve paternal interests. Once the maternal body turns to fight against fetal microchimeric cells, fetal cells may, of course, still exhibit immunological mimicry and evasion strategies to confuse the maternal immune system. This effect may even lead to maternal autoimmune diseases in the strict sense.

Predictions of our interpretation differ markedly from those of former views that had arisen in clinical practices, which either claimed that fetal→maternal microchimerism was a harmful phenomenon, or that it was a beneficial one [11]. We cannot offer a similarly simple interpretation. On the other hand, however, we claim that this evolutionary view of tripartite cooperation and conflict may lead to a better understanding of at least two interacting groups of diseases; namely female autoimmune-like diseases, as well as the phenomena of infertility and miscarriage. At present, the hypothesis outlined above is supported only by circumstantial evidence.

The covariance of autoimmune diseases and reproductive failures is a well documented phenomenon, traditionally interpreted as the former causing the latter. Over the last decade, however, this view has proven to be increasingly hard to maintain, since new results indicate that infertility, pregnancy loss, and pregnancy complications precede autoimmune symptoms at least in case of rheumatoid arthritis and systemic lupus erythematosus [12,13]. To save the prestige of the traditional view, it has been suggested that autoimmune diseases may even obstruct reproductive efforts in their early preclinical phase, before the onset of the disease itself [14]. Here we propose an opposite causality; we argue that miscarriages can cause subsequent graft-versus-host reactions by the fetal cell clones as grafts that predispose women to suffer from autoimmune-like symptoms.

Similarly, our view offers testable new interpretations of reproductive failure symptoms like infertility and habitual abortions. We propose that microchimeric cell lines exhibiting an immunological

activity in the maternal body may well serve the reproductive interest of the father of a former fetus, and as such, intervene with the adaptive interest of both current parents.

Above, we gave a list of hypothetical features that could be adaptive for fathers, mothers and fetuses respectively. We must caution, however, that there are inherent biological and environmental constraints on adaptive evolution. Potentially adaptive characters are not necessarily produced by evolution, furthermore, existing characters are not necessarily adaptive. Future studies on humans and other Placentals will either confirm or falsify the existence of the potentially adaptive features described here.

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