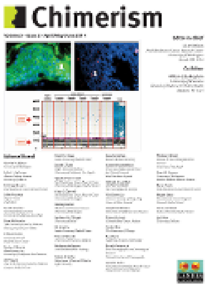

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ARTICLE ADDENDUM

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Does microchimerism mediate kin conflicts?

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Fetal microchimerism (FMc) is predicted to promote the fitness of the fetus and maternal microchimerism (MMc) to promote the fitness of the mother. Offspring and mothers benefit from each other's health. Therefore, microchimeric cells should usually not be harmful to their host. However, the evolutionary interests of mothers and offspring diverge when there is competition among siblings for maternal investment. Fetal cells in mothers' bodies could benefit their own offspring at the expense of its sibs by promoting lactogenesis or by extending the interbirth interval. Maternal cells in fetal bodies could benefit from the suppression of sibling rivalry. Non-inherited haplotypes in MMc or sibling microchimerism (SMc) gain no direct benefit from their hosts' health and could be associated with substantial detrimental effects.

Keywords: breast cancer, inclusive fitness, infertility, interbirth intervals, kin conflict, microchimerism

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Fetal cells colonize maternal bodies during pregnancy and maternal cells colonize fetal bodies. The engrafted cell populations can persist for the remainder of the mothers' and offspring's lives. Moreover, the presence in a woman's body of her mother's cells (maternal microchimerism/MMc) and her offspring's cells (fetal microchimerism/FMc) raises the possibility of secondary engraftment. Fetuses could feasibly be colonized by cells derived from maternal grandmothers or older sibs (sibling microchimerism/SMc), perhaps even by cells of great grandmothers and matrilineal aunts and uncles (tertiary engraftment). As a result, most human bodies contain cells derived from two or more related genetic individuals. This intriguing phenomenon, of ubiquitous kin chimerism, has attracted little attention from evolutionary biologists even though inclusive fitness theory was developed to explain the evolution of interactions among kin.[1] A recent paper has taken a first step toward addressing this neglect.[2]

Gene expression is subject to selection not only for its effects on the individual in which the gene is expressed but also for its effects on other individuals who carry copies of the same gene. Inclusive fitness sums the effects of gene expression on all individuals whose fitness is affected weighted by their probability of carrying a copy of the responsible gene. From this perspective, engrafted cells are subject to natural selection for their effects on the inclusive fitness of their donor not their host.[3] Mother and child have a mutual interest in each other's well-being because a child's fitness is enhanced by having a healthy mother and a mother's fitness by the production of healthy offspring. Natural selection will therefore tend to eliminate negative effects of FMc and MMc on host health and favor positive effects.

An important caveat should be mentioned. All genes of an infant benefit from maternal health, even though some genes are absent from the mother, because all genes benefit from the mother's care of the infant. By contrast, only those of a mother's genes inherited by an infant benefit from that infant's survival. The effects of a non-inherited maternal haplotype (NIMH) on an offspring's fitness are irrelevant to the propagation of that haplotype except in so far as these effects have consequences for other individuals who carry the haplotype. Thus, an NIMH would increase in frequency if it caused the early demise of embryos without its copies if this sped the conception of replacement embryos with its copies.[4] Such an embryocidal effect could occur across the maternal-fetal interface or be mediated by MMc within fetal bodies. Parallel arguments apply to the effects of non-inherited sibling haplotypes, either mediated by FMc in the mother's body or by SMc in the bodies of younger sibs.

"Spiteful" effects of NIMHs are strongly disfavored by natural selection if the effects are also experienced by offspring that inherit the haplotype. Therefore, effects of maternal genes that do not discriminate between offspring with and without their copies should promote the health of all offspring because each offspring has an equal chance of inheriting a maternal gene's copies. Most maternal effects are likely to be of this benign type because of the rarity of genetic "self-recognition" and because natural selection at unlinked loci will tend to suppress haplotypic nepotism. The discussion that follows will assume maternal genes have non-discriminatory effects.

Siblings share genes. Therefore, genes of offspring benefit from a mother's continued reproduction. Maternal genes of an offspring obtain this inclusive fitness benefit from all of the mother's future offspring whereas paternal genes benefit from full-sibs but not from half-sibs sired by different fathers. The evolutionary interests of mothers and offspring are not identical, however, because natural selection favors offspring who value themselves more highly than their sibs.[5] Genes expressed in offspring will favor maternal investment in their own offspring relative to its sibs whereas genes expressed in mothers will favor allocation of care and attention to whichever offspring gains the greatest benefit. Thus, genes expressed in mothers (or MMc) will evolve to maximize the mother's number of surviving offspring whereas genes expressed in offspring (or FMc) will evolve to favor their own offspring's survival even at some greater cost to its sibs.

MMc might benefit mothers by reducing offspring demands, perhaps favoring a more sleepy and compliant child, or by reducing sibling rivalry and promoting sibling solidarity. FMc creates the possibility that mother–offspring conflict and sibling rivalry can be played out within the mother's body.[2] There are many ways that FMc could benefit fetuses prenatally, including mobilization of maternal reserves for use by the fetus, but there are fewer ways that FMc could cause mothers to discriminate postnatally in favor of the microchimeric cells' own offspring.

One route for postnatal manipulation of mothers would be for FMc to promote differentiation of alveolar epithelium in the maternal breast, or to inhibit mammary involution, thereby enhancing and maintaining the milk supply for the suckling infant.[2] By the production of growth or differentiation factors, a relatively small number of fetal cells could have a large effect on mammary differentiation and function. Consistent with this possibility, cells with Y chromosomes are commonly found in human breasts.[6,7] These cells could contribute to protection against breast cancer if their effects on lobular differentiation were to reduce the pool of mammary stem cells. An area for future study is the relation between microchimerism and inflammatory disorders of the breast. Expression of inflammation-associated genes is upregulated in parous breasts for at least a decade after pregnancy[8] and gigantomastia and sclerosing lymphocytic lobulitis are associated with autoimmune disease.[9,10]

Longer delays until the birth of a subsequent child reduce child mortality under conditions of resource scarcity.[11] Thus, FMc could benefit infants by delaying the birth of a younger sib.[2] There are multiple possible scenarios: fetal cells in the maternal breast could promote lactogenesis and longer duration of lactational amenorrhea (see above); fetal cells in the maternal ovary could interfere with ovulation; or fetal cells in the maternal endometrium could interfere with implantation of subsequent embryos. A recent study found foreign cells in the endometrium of parous women[12] and FMc is more readily detected in women who have experienced a pregnancy loss.[13] Discriminatory effects of maternal or paternal haplotypes of FMc against subsequent embryos that do not inherit their copies are worth consideration.[2]

A key question is whether immigrant cells perform specialized functions in host bodies or simply behave as they would in their body of origin. If cells do not distinguish between resident and immigrant roles, then cellular functions will be subject to selection on their average effects in the two roles weighted by the strength of selection in each role. Functions in the resident role would tend to predominate because resident cells vastly outnumber immigrant cells. If, on the other hand, immigrant cells have evolved specialist functions, then these functions would be expected to promote the fitness of the genetic individual from whom the cells originated. Microchimerism is an evolutionarily ancient phenomenon that has been detected in humans, monkeys, mice, rats, pigs, cattle, and dogs.[14-18] There has been ample time for the evolution of specialist functions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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