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Review Article

Telegony, the Sire Effect and non-Mendelian Inheritance Mediated by Spermatozoa: A Historical Overview and Modern Mechanistic Speculations

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Contents

Telegony is the belief that the sire first mated to a female will have an influence upon some of that female's later offspring by another male. Although the reality of telegony was acknowledged by such authorities as Darwin, Spencer, Romanes and many experienced breeders, it has been met with scepticism because of Weismann's unfavourable comments and negative results obtained in several test experiments. In this article, alleged cases of telegony are provided. A search of the literature of cell biology and biochemistry reveals several plausible mechanisms that may form the basis for telegony. These involve the penetration of spermatozoa into the somatic tissues of the female genital tract, the incorporation of the DNA released by spermatozoa into maternal somatic cells, the presence of foetal DNA in maternal blood, as well as sperm RNA-mediated non-Mendelian inheritance of epigenetic changes.

Introduction

The subject of telegony is an exceptional, alleged phenomenon that enjoyed a remarkable career in the nineteenth century (Burkhardt 1979). Its principle is that females are impregnated by the first males to which they are mated, so that some of their subsequent offspring, regardless of their actual father, will show influence of the first male (Rabaud 1914). In modern parlance, the term 'sire effect' would cover such a phenomenon. Although the story of the son who resembles his mother's former husband has circulated among the people in China for generations, Charles Darwin was the first to summarize this phenomenon in biological science. In Chapter 11 of his book *The Variation of Animals and Plants under Domestication*, Darwin (1868) collected many alleged examples of 'the direct action of the male element on the female form'. He mentioned the case of Lord Morton's famous hybrid, from a chestnut mare and a male quagga. Not only the hybrid but also the offspring subsequently produced by the mare when mated to a black Arabian sire was more plainly barred across the legs than even the pure quagga. Darwin concluded that 'there can be no doubt that the quagga affected the character of the offspring subsequently begot by the black Arabian horse'. He considered it to be of special importance for understanding the mechanisms of heredity and development and advanced this case as one of several in support of his hypothesis of Pangenesis – a developmental theory of heredity (Darwin 1868; Liu 2008).

It is a historical fact that in the nineteenth century, the phenomenon of telegony commanded considerable respect, guided the practice of many animal breeders and played an important role in pre-1900 discussions of heredity. The reality of Morton's mare was acknowledged by such authorities as Louis Agassiz, Claude Bernard, Herbert Spencer, George John Romanes, Francis Galton, William Bernard Tegetmeier and many experienced breeders (Thomson 1908; Burkhardt 1979). Spencer (1893) regarded it as a major weapon in his debate with August Weismann over the reality of the inheritance of acquired characters. Scientists who made any pretence of understanding reproduction and heredity managed to find ways of explaining it. Unfortunately, modern biology has no place for it. Although xenia (pollen effects on seeds and fruits) has been well recognized by most plant biologists and is more alive than ever, telegony, a different case of the same general phenomenon in animals, has been met with scepticism (Burkhardt 1979).

A search of the literature of cell biology and biochemistry reveals several plausible mechanisms that may form the basis for telegony. Over the past several decades, convincing evidence has accumulated for the penetration of somatic cells by spermatozoa. The successful achievements in mammalian cell transfection by foreign DNA and the new findings of foetal DNA in maternal blood and sperm RNA-mediated non-Mendelian inheritance of epigenetic changes furnish a basis for telegony. Thus, it is timely to reconsider the case of telegony.

Reasons Why Telegony has been met with Scepticism

It was August Weismann who coined the term 'telegony'. Weismann (1912) was confident that if telegony was a genuine phenomenon, he could explain it without sacrificing his theory of the germ plasm. He suggested the possibility that 'spermatozoa had reached the ovary after the first sexual union had occurred and had penetrated into certain ova which were still immature.' When these ova mature, amphimixis might occur and coincide in time with the second coitus to which the subsequent offspring would be ascribed. But were this the explanation, one should sometimes find that offspring were produced without any second sire at all. No such phenomenon is known among higher animals. Thus, he was sceptical that the phenomenon was real. In his book *The Germ-Plasm*, he placed telegony under the heading 'doubtful phenomena of heredity'. He thought

that the recorded instances of telegony were based on a 'misconception' and suggested that experiments be conducted to test this question (Weismann 1912). We now know that some animals have sperm that live for years and the classic example is attine ants. But for most animals, the sperm has a relatively short life in the female genital tract. It is admitted that the life of the spermatozoa is limited to a few hours or days at the longest, and that their powers of fertilizing exist only during their life. None could possibly live to fertilize an egg secreted 1 or 10 years later. Thus, most people think that there is not a theoretical basis for telegony.

Realizing that 'no problem … claims wider attention at the present time than what is now generally known as telegony', Ewart (1899) conducted a series of experiments that were designed 'to repeat as exactly as possible Lord Morton's experiment'. He had no illusions that his work constituted a formal disproof of telegony but concluded that the striping of Morton's hybrid was best explained as a case of reversion. In addition, Daniel (1959) carried out a controlled breeding experiment with rats and with *Drosophila* to re-determine the validity of telegony. No evidence was obtained to support the view that previous matings can have any genetic effect on the offspring of later matings.

Possible Data in Respect of the Existence of Telegony

Many people thought that Morton's mare was a coincidence and not a causal connection. As a matter of fact, Darwin (1868) cited nine sources beside Lord Morton with respect to the idea of the influence of a previous sire on the offspring of a female's later matings. He gave a number of references to other cases, not only in horses but also in pigs, dogs and sheep. For example, a sow of Lord Western's black and white Essex breed was mated with a wild boar of a deep chestnut colour; and the 'pigs produced partook in appearance of both boar and sow, but in some the chestnut colour of the boar strongly prevailed.' After the boar had long been dead, the sow was mated to a boar of her own black and white breed – a kind that is well known to breed very true and never to show any chestnut colour – yet from this union the sow produced some young pigs that were plainly marked with the same chestnut tint as in the first litter. After Darwin's death, there appeared other examples of telegony in dogs, sheep, birds and human (see Table 1). It should be noted that some dog and sheep breeders, as a rule, still adhere to the idea, and several sheep breeders' associations even refuse to register lambs whose mother were ever 'impregnated' by mating with a common ram (Rabaud 1914; Mole 2006). Zhelnin (1964) observed the phenomenon of telegony in rabbits and argued that telegony did not occur rarely as was previously thought.

Table 1. Cases of telegony in animals and humans

Species	References
Horse	Morton (1821); Darwin (1868); Finn (1893)
Pig	Giles (1821); Darwin (1868); Finn (1893)
Sheep	Darwin (1868); Cornevin (1891); Finn (1893)
Dog	Darwin (1868); Cornevin (1891); Spencer (1893); Mole (2006)
Bird	Darwin (1868); Finn (1893)
Human	Lingard (1884); Flint (1888); Cornevin (1891); Hui (1989); Redfield (1903); Mei (2000)
Mice	Gorczynski et al. (1983); Cooper-Willis et al. (1985)
Rabbit	Zhelnin (1964); Sobey and Conolly (1986); Parer et al. (1995); Williams and Moore (1991)

Interestingly, a telegony phenomenon, or sire effect, has also been observed in the immune system of mice. When normal females that had borne at least three litters to males made tolerant neonatally were subsequently mated to normal, non-immune males, the offspring showed a hyporesponsive phenotype that did not differ from that of the progeny of fathers made tolerant neonatally. The response of this offspring was significantly lower than the response of mice born to normal females mated only to normal mates (Gorczynski et al. 1983). This type of observation has also been reported by Cooper-Willis et al. (1985). In addition, Sobey and Conolly (1986) demonstrated that male domestic rabbits, mating after recovering from myxomatosis, may transmit immunity to progeny born to the female in the next 7 months, including progeny sired by other males lacking immunity. This has been confirmed by later researches (Williams and Moore 1991; Parer et al. 1995).

Although always largely an animal breeders' issue, telegony is also invoked in ideas about human inheritance (Bynum 2002). A remarkable illustration of telegony in humans has been observed and recoded by Lingard (1884), in which a hypospadian, whose father and paternal grandfather were similarly malformed, contracted a marriage with a woman not related to him, who bore him three sons, hypospadians. He died a few years after the birth of his three sons. His widow within 18 months after his death contracted a second marriage, the husband in this instance not being a hypospadian and having no history of any such deformity in his family. By this marriage, she had four sons, all hypospadians. Sedgwick (1896) believed that this case might help to overcome some of the objections that have been urged against the influence of a previous marriage on the subsequent offspring by a second or even by a third husband. Thomson (1908) cited the case of a woman married to a deaf-mute, by whom she had one deaf-mute child. By a second normal husband, she had a deaf-mute child and then others who were normal. There is also evidence for telegony in modern China. For example, two Chinese women gave birth to children after they married their second husband. Interestingly, the appearances of their children closely resemble their first husband (Hui 1989; Mei 2000).

It should be mentioned that to confirm the existence of telegony, Romanes (1893) pursued investigations on three different lines: (i) He raised discussions on the subject in the principal breeders' and fanciers' journal of England and America. (ii) He entered into private correspondence with contributors of the largest experience and also with professional and amateur breeders and fanciers who addressed him directly on the subject. (iii) He started experiments with different animals. He concluded that 'my evidence is enough to prove the fact of a previous sire asserting his influence on a subsequent progeny, although this fact is one of comparatively rare occurrence.'

Previous Explanations for Telegony

To explain telegony, xenia, reversion, regeneration, prepotency (Mendelian inheritance), graft hybridization, sex-limited inheritance, the effect of use and disuse, the inheritance of acquired characters and many other facts pertaining to inheritance, variation and development, Darwin (1868) elaborated his 'provisional hypothesis of Pangenesis.' Darwin's Pangenesis had two basic postulates: first, that the cells of the body throw off gemmules (the embryonic form of our modern genes), which 'circulate freely throughout the system'; and second, that these gemmules are not only self-replicating and corpuscular but also able to penetrate other nascent cells and modify their subsequent development. Darwin (1868) maintained: 'it is certain that [the mother's] ovaria are sometimes affected by a previous impregnation, so that the ovules subsequently fertilized by a distinct male are plainly influenced in character'. He believed that in case of Morton's mare it was 'the diffusion, retention, and action of the gemmules included within the spermatozoa of the [first] male' that left the mare with a 'quagga taint' that continued to manifest itself in her later offspring. Darwin was not very explicit about this, but he did say more regarding the effect of pollen on the tissues of the mother plant. Darwin explained that in the case of xenia, 'the gemmules derived from the foreign pollen do not become developed merely in contact with pre-existing cells, but actually penetrate the nascent cells of the mother plant' (Darwin 1868).

In addition to Darwin's Pangenesis, there is another explanation, which is that the mother is influenced through the foetus during pregnancy and that the influence manifests on subsequent offspring. That is to say, the first sire impresses his own offspring with certain of his own characteristics; the offspring of this sire impresses the mother through the blood-current; the mother, in turn, transmits the peculiarities of the first sire to her subsequent progeny by means of the blood element she has received from her first offspring (Bell 1896).

A New Perspective on the Mechanism of Telegony

Penetration of spermatozoa into the somatic tissues of the female genital tract

In the early 1910s, Kohlbrugge published reports in which he claimed to have identified numerous spermatozoa in the mucosal cells of the uterus and uterine tube in the mouse, rabbit and bat. He maintained that modification of the mucosal cells could mediate a paternal influence upon the embryo, and he suggested that this influence, persisting from one pregnancy to the next, could be the mechanism of telegony (Kohlbrugge 1910, 1913). It should be mentioned that Austin et al. examined sections of uteri of the Great Horseshoe bat and the Common Pipistrelle, and their observations strongly suggest that spermatozoa do in fact enter the mucous membrane of the uterine tube in these animals. These observations are compatible with the possibility that the mucosa of the uterine-tube isthmus may be altered in some way by invading spermatozoa. They concluded that this could conceivably be brought about by transfer of genetic information in a manner analogous to that of bacterial transformation (Austin 1959, 1960; Austin and Bishop 1959). Since the first light-microscopic observations of the presence of numerous spermatozoa within the uterine mucosal cells, there have been numerous reports describing the penetration of spermatozoa into tissues, both maternal and embryonic (see Table 2). Recently, Brodsky and Ivanov (2009) proposed that spermatozoids may penetrate somatic cells *in vivo*, forming viable chimeric cells, which may survive in the body for a long time.

The incorporation of exogenous DNA into somatic cells

Darwin (1868) supposed that the gemmules derived from the spermatozoa actually penetrate the nascent cells of the mother animal. It has been suggested Darwin's so-called gemmules could include RNAs (particularly mRNA and small RNAs), circulating DNA, mobile elements, prions or as yet unknown molecules (Steele et al. 1998; Liu 2005). In our modern language, DNA/RNA may penetrate the somatic tissues of female animals. Interestingly, Watson et al. (1983) found that within 24–48 h after artificial insemination with spermatozoa, in which the DNA had been labelled with tritiated thymidine, a minimum of 9% of the radioactivity was transported across the uterine walls. In sperm-treated animals, the ovaries, the adrenals and a mesenteric lymph node exhibited strikingly large accumulations of radioactivity. They concluded that the lymphatic system could serve as a route for the dissemination of radioactivity originally associated with spermatozoa deposited in the uterus to maternal tissues. Ledoux and Charles (1972) demonstrated that if mice are killed 1 or 2 h after an I.V. injection of labelled

Table 2. Penetration of spermatozoa into somatic tissues and cells of the female genital tract (incomplete statistics)

Species	Results	References
Bat	Penetration of spermatozoa into uterine mucosa, fallopian-tube mucosa and oviducal epithelial cells	Kohlbrugge (1910, 1913); Austin (1959); Austin and Bishop (1959); Uchida et al. (1984) ; Rasweiler (1987)
Mouse	Penetration of spermatozoa into uterine mucosa, fallopian-tube mucosa and L cells	Kohlbrugge (1910, 1913); Lau (1975)
Rabbit	Penetration of spermatozoa into uterine mucosa and cervical mucosa	Kohlbrugge (1910, 1913); Austin (1960); Sievers-Altermann and Engelbrecht (1990)
Rat	Penetration of spermatozoa into uterine mucosa	Stein-Werblowsky (1973)
Hamster	Penetration of spermatozoa into fibroblast cells and ovary cells	Bendich et al. (1974); Lau (1979)
Dog	Penetration of spermatozoa into uterine tube and uterine glands	Doak et al. (1967); England and Pacey (1998); Rijsselaere et al. (2004)

DNA, this DNA can be recovered in the follicle cells of the ovary, in the vagina, embryos and tumour cells. The exogenous labelled DNA has therefore been transported by the blood and has become absorbed by cells of different tissues of the organism, without important destruction.

It has been known for years that naked DNA can be delivered to cells *in vivo* and result in gene expression, although the efficiency of gene transfer into skeletal or cardiac muscle is relatively low and variable (Wolff et al. 1990). In recent years, it has been demonstrated that naked plasmid DNA can be delivered efficiently into cells *in vivo* via electroporation, intravascular delivery and tail vein DNA injection (Herweijer and Wolff 2003). Bendich et al. (1974) demonstrated that penetration of somatic mammalian cells by spermatozoa occurred after simple admixture in culture. With sperm labelled *in vivo*, autoradiography revealed incorporation of DNA into nuclei of recipient cells, indicating release of DNA after entrance by sperm. Reid and Blackwell (1967) demonstrated that the pattern of saline elution of DNA prepared from cultured sheep macrophage cells is changed after these cells have been exposed to rat sperm. They believed that this altered pattern is because of the incorporation of intact sperm DNA by the macrophage.

Holmgren et al. (1999) raised the question whether DNA can be transferred from one cell to another via the phagocytosis of apoptotic bodies. They demonstrated that genomic DNA from apoptotic bodies is transferred to the nuclear compartment of phagocytosing cells and that this transferred DNA is stable over time. Thus, it is possible that apoptotic bodies, derived from spermatozoa, might be taken up by phagocytosing cells of the maternal tissues. It is now a well-established notion that mature spermatozoa act as vectors of genetic material, not only for their own genome but also for exogenous DNA molecules. This is called sperm-mediated gene transfer (Spadafora 2007). Although the sperms of the first sire cannot be supposed to persist and fertilize ova discharged long afterwards, it is conceivable that the DNA released by these sperms may persist and influence the ovaries and the ova, which does not amount to fertilization. During coition, millions of DNA-containing spermatozoa are deposited in the body of the female and those not used in fertilization are absorbed by it. If this foreign DNA could incorporate into somatic cells and influence ova, then later offspring might show this influence in their genetic constitution and thereby furnish a basis for telegony. Generally speaking, the transfection efficiency is low in nature. This might explain the rare occurrence of telegony.

Presence of foetal cells and foetal DNA in maternal blood

Circulating nucleic acids occur ubiquitously and are bioactive in living organisms. Two sources of circulating nucleic acids have been considered and discussed in the literature: dying cell, whether necrotic or apoptotic, and active nucleic acids release (Stroun et al. 2001; Gahan 2008). There is also increasing evidence that both circulating cells and free foetal DNA persist in the maternal circulation after delivery of the foetus (Lissauer et al. 2007). It has been demonstrated that foetal cells circulate in the bloodstream of most pregnant women and may persist for many years, and even decades, postpartum (Bianchi et al. 1996). Interestingly, male cells have also been identified in females with no history of male children or miscarriage. One possibility is the transfer of cells from the women's partner through sexual intercourse (Lissauer et al. 2007). Lo et al. (1997) demonstrated foetal DNA in plasma and serum from healthy pregnant women. Using quantitative real-time PCR, a surprisingly high mean concentration (6.2% of total plasma DNA) of foetal DNA was found in maternal plasma. Generally, gestational age correlates positively with amount of foetal DNA in plasma. Lo et al. (1998) reported foetal DNA concentrations to be low in the first trimester, rising in the second and third trimester. During the last 8 weeks of pregnancy, there is a sharp increase in foetal DNA in maternal plasma. It has been proposed that circulating foetal DNA is released from foetal and/or placental cells undergoing apoptosis (Bischoff et al. 2005). Invernizzi et al. (2002) found that cell-free foetal DNA could be present in maternal plasma decades after pregnancy.

The discovery of circulating foetal DNA in maternal blood not only has disclosed new strategies to perform non-invasive testing for prenatal diagnosis but also sheds a new light on the influence of hybrid embryo on its mother. We may suppose that the circulating DNA released by the hybrid embryo is transferred into the mother's body by circulation and later is incorporated into the mother's subsequent hybrid embryo by another male, thus being able to influence the characteristics of the subsequent offspring. There is also possibility that during pregnancy, whilst the embryo is developing and continuously releasing DNA into the maternal blood stream, the ovaries, and hence the primary oocytes, will stand a good chance of receiving this foetal DNA and so being transfected. This can be reinforced by the subsequent continued flow of foetal DNA in the maternal system after the foetus has been delivered (Gahan 2008). Hence, there is the possibility of transfected oocytes being fertilized at a later date by a second male.

Sperm RNA-mediated non-Mendelian inheritance

Recently, Krawetz et al. studied sperm from 10 fertile men and found that they contained some 3000 different kinds of mRNA. Some of them coded for proteins needed for early embryo development; others were previously unknown (Ostermeier et al. 2004; Ainsworth 2005). Rassoulzadegan et al. (2006) demonstrated that the genotypically wild-type ($Kit^{+/+}$) offspring of heterozygous $Kit^{(tm1\ Alf)}$ parents displayed the white spots characteristic of *Kit*-mutant animals. The modified phenotype was associated with decreased *Kit* mRNA levels and accumulation of non-polyadenylated RNA molecules. The sustained transcriptional activity at the post-meiotic stages resulted in the accumulation of RNA in spermatozoa. They were able to reproduce the phenotype by microinjection into fertilized eggs of either total RNA from $Kit^{(tm1\ Alf)}$ heterozygotes or *Kit*-specific microRNAs, both of which induced a heritable white-tail phenotype. This study of spotted mice suggested that as well as contributing their usual cargoes of DNA,

mammalian sperm and eggs might also transmit heritable genetic information in the form of RNA. It has been suggested that under certain conditions, spermatozoa can translate their mRNAs *de novo* and that spermatozoa RNA can potentially affect phenotypic traits in offspring (Miller 2007).

Thirty years ago, Steele presented a modern molecular view of Darwin's Pangenesis in his 'somatic selection' hypothesis, which states that mutant somatic information, if selected sufficiently for expression, will be transmitted to the germline in the form of RNA captured by endogenous retroviral vectors. Once in the germline, the RNA will be transcribed to DNA by reverse transcriptase and become integrated into the germline DNA (Steele 1979; Steele et al. 1998). Recently, it has been fully confirmed that RNA can act as a template for DNA synthesis in the reverse transcription of retroviruses and retrotransposons and guide genome rearrangement (Storici et al. 2007; Nowacki et al. 2008). More recently, Spadafora (2008) described the phenomenon of sperm-mediated 'reverse' gene transfer (SMRGT) and believed that such a mechanism would lead to the generation and non-Mendelian propagation of new genetic information by mature spermatozoa, independent from the information carried in the genome. Thus, plausible mechanisms now exist to explain the sire effects claimed to occur in the past under the phenomenon of telegony. Spermatozoa appear able to penetrate somatic tissues and could in theory deliver RNA to somatic cells where it could have regulatory and genetic effects. Further, retroviruses or retrotransposons may facilitate the transfection and reverse transcription of mRNA into cDNA leading to their integration into the female ovum genome and thus expression in the progeny.

Conclusion

Telegony is the belief that the sire first mated to a female will have an influence upon some of that female's later offspring by another male. Although Darwin and many famous nineteenth-century biologists held strong belief in telegony, it has been met with scepticism because of Weismann's unfavourable comments and negative results obtained in several test experiments. There are some data which raise the possible existence of telegony, although at present, there is no good experimental evidence. There are also possible molecular explanations which could be argued for this phenomenon that has not definitively been proven. The time has come when further progress in our understanding of heredity requires that we reconsider the case of telegony.

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Conflict of interest

None of the authors have any conflict of interest to declare.

Author contributions

Yongsheng Liu has written the manuscript and has participated in all phases.

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