The Female May Play More Roles in Biological Heredity Than the Male Does: Female-Relayed Intact Cell and Cytoplasmic Inheritance §

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Abstract

For more than a century, modern genetics has led to the impression that female and male play an equal role in biological heredity, and the importance of cytoplasmic inheritance has been ignored. This is due to the Modern Synthesis, which unified Darwinian natural selection and Mendelian genetics in the mid-20th century, fully discarding Lamarck's theory. Recently, six models of pregnancy-associated eukaryotic cell transmission between mother and offspring have demonstrated their significance in biology and ecology from the fimpological perspective. [1, 2] Based on these models, a model called 'female-relayed whole cell and cytoplasmic inheritance' further illustrates that both fertilized oocyte-mediated cytoplasmic inheritance (FOMCI) and pregnancy-associated whole-cell-inheritance (PAWCI) can be transmitted to the offspring generation by generation along the pregnancy-associated female path, and that both FOMCI and PAWCI are determined by reproductive female offspring, not by reproductive male offspring. Clearly, modern genetics lacks FOMCI and PAWCI and therefore is not enough to reflect the full content of biological heredity, in which, the female may actually play more roles than the male.

Key words: biology; ecology; evolutiology; fimpology; integral cell inheritance; cytoplasmic inheritance; cell transmission; stem cells; eukaryote; female; male; pregnancy

Introduction

Heredity, the natural phenomenon of transmitting traits from one generation to the next, was first observed at the individual level of macroorganism. For over thousands of years, much practical experience has been accumulated on humans, non-human animals, and plants in this regard. However, during this time, there was little understanding of heredity and it was thought that traits were transmitted through the simply blending of maternal and paternal characteristics. This changed in the 19th century when heredity began to be understood at the cellular level. After the emergence of cell theory found by

the German botanist Matthias Schleiden, the German physiologist Theodor Schwann, and German physiologist Rudolf Virchow, the link between cells and biological heredity was established in the 19th century, particularly with the recognition of Virchow's 'omnia cellula e cellula' (every cell comes from a cell).[3, 4] Describing and understanding the distribution and taxon, as well as the reproduction and inheritance of extant macrobiological species, were the early goals and task of traditional macrobiology. Virchow's cells-mediated inheritance was later replaced by Weismann's germ cells-nuclear inheritance, and finally, DNA-centered genetics was formed based on Mendel's laws. In the 21st century, the idea that males and females play equal roles in biological heredity has been challenged. This article aims to further illustrate that females may play more roles in biological heredity than males do.

Mendel's study on heredity at the macroorganism level

Gregor Mendel (1822-1884), an Austrian monk, began his independent study on the inheritance of morphological characteristics in peas in the 1860s. During his experiments with pea plants in a monastery garden, Mendel solved the problem of explaining the distribution pattern of phenotypical characteristics of intra-species in a series of generations. He became convinced that although invisible, there might be tiny independent factors determined the traits, such as shape, colors and height of pea plants. Intriguingly, although Mendel's laws including the twin-unit theory of heredity and the dominant-recessive relationship, were published only six years after the publication of *The Origin of Species*, his discovery went largely unrecognized for about 18 years after Darwin's death. Since its rediscovery in 1900, Mendel's laws have been considered the essential principles of modern genetics. It is worth noting that Mendel's experimental subjects were macroorganism pea plants, not cells or molecules, and therefore the hypothetical 'units of transmission' mechanism proposed by Mendel should not be interpreted solely by in term of nuclear inheritance or attributed solely to hereditary information located in chromatin or chromosomes. In fact, in Mendel's pea plant experiment, cytoplasmic inheritance cannot be ruled out. Therefore, modern DNA-centered genetics only reflects the partial, not the whole, significance of Mendel's study on heredity at the macroorganism level. Interestingly, while conducting his original research on the hybridization of peas, Mendel received no financial support from the official scientific community, and his was even been ignored for 35 years before it was rediscovered.[5]

Nuclear Inheritance to DNA-centered Inheritance

In the 19th century, it was believed that cells played an important role in transferring heredity between preceding cells and following cells, but it was unclear how this happened. It was the German biologist, August Weismann, who first proposed that the nucleus, a round body near the center of the cell, described by Scottish botanist Robert Brown, might contain hereditary material. Following Weismann's nuclear inheritance hypothesis, biologists soon discovered that the hereditary material within the nucleus is

chromatin, which normally looks like a ball of tangled string, but turn into rod-like chromosomes during cell division. Chromosomes can show a unique banding pattern after special dye is applied.

Until to the 1950s, scientists had not solved the mystery of nuclear inheritance — what are the basic molecular functional units of chromatin, and how do they transmit hereditary information? In 1953, British biophysicist Francis Crick and American biochemist James D. Watson published their breakthrough in Nature outlining their model for the structure of deoxyribonucleic acid (DNA), which carries hereditary information or genes.[6–8] In other words, genes form the informational units of the DNA molecule, and specific proteins are the products of corresponding genes. The double-helical structure of DNA was one of the most important discoveries in the 20th century, and it is now clear that chromosomes contain packages of DNA (deoxyribonucleic acid) information that act as a blueprint for the human body, as well as non-human animals, plans, fungi, bacteria, archaea, protozoa, and some viruses.

Cytoplasmic inheritance—fertilized oocyte-mediated cytoplasmic inheritance (FOMCI)

Since Weismann's time, nuclear inheritance has held the dominant position in biological heredity, which was further strengthened by Crick and Watson's discovery. In contrast, cytoplasmic inheritance was not prominent during most time of the 20th century, although it did attract some attention from scholars in the 1950s.[9–11] Unfortunately, the importance of cytoplasmic inheritance could not be revealed in traditional biology, especially after Lamarck's theory was fully discarded by the Modern Synthesis in the mid-20th century. However, cytoplasmic inheritance was still mentioned by some authors.[12–14] For instance, Nora and colleagues proposed that the higher risk for congenital heart diseases in the offspring of their mothers who had a congenital heart disease might be the result of cytoplasmic inheritance rather than Mendelian heredity Law.[13] Moreover, 60 years ago, Waddington coined the term 'epigenetic' to describe how environmental modifications to DNA could occur without changes in the nucleotide sequence.[15–17] This process of epigenetic modification has been extended from DNA methylation to acetylation of histone proteins in chromatin, imprinting, and post-translational modifications. The significance of epigenetics has now gone beyond its original role in evolutionary biology, and has been extended into medicine. Epigenetics is associated with multiple human diseases, such as cancer, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral diseases.[16, 18]

After entering the 21st century, cytoplasm, the essential environment of the nucleus, began to re-attract researchers' attention.[19, 20] Cytoplasm, as the environment of nuclear, also contains many other entities or elements, such as mitochondria and spindle, of which mitochondria is the most studied.[21–23] Currently, the data on cytoplasmic inheritance in mammals mainly comes from studies on mitochondrial DNA molecules (mtDNA).[14, 21, 24–28] In the past decades, the success in cloning animals by nuclear transfer revealed the importance of harmonious nuclear-cytoplasmic interaction in oogenesis, ovulation and embryogenesis.[22, 27, 29–38] The importance of cytoplasmic factors in the development of

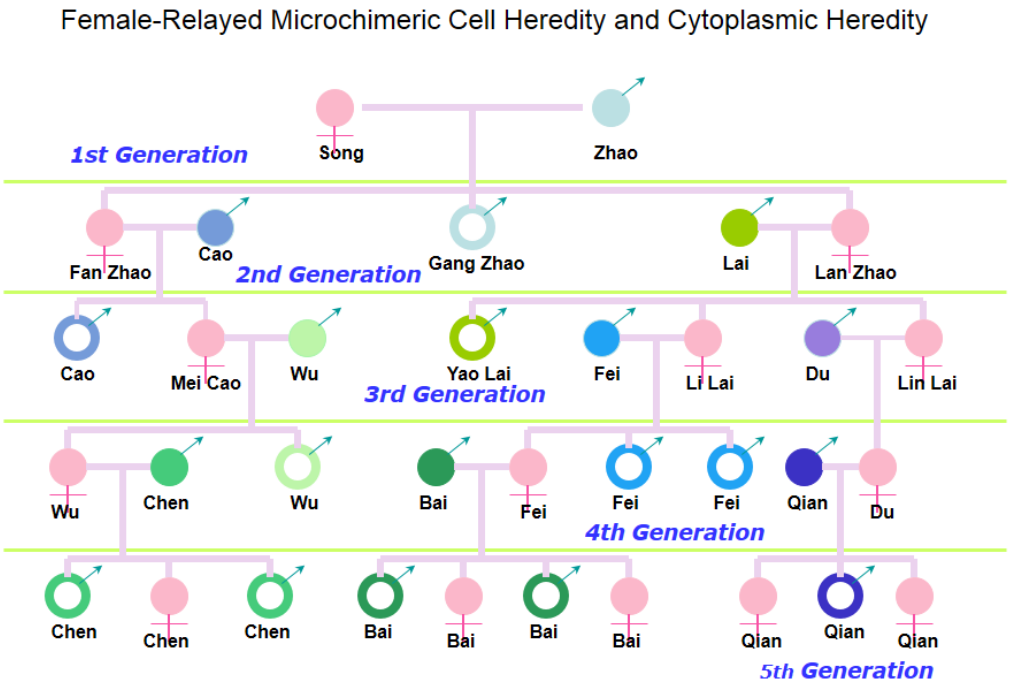
transplanted nuclei was demonstrated in a study on two different species of fish.[39] Sun and colleagues transferred carp nuclei into goldfish enucleated eggs and showed that these cloned fish displayed some developmental traits similar to those of the goldfish,[39] providing another solid experimental evidence to support the hypothesis that cytoplasm, as the environment of the nucleus, may play an important role in bio-heredity. Recently, Wang and colleagues showed that mouse oocytes at different developmental stages including the germinal vesicle stage, the metaphase II (MII) stage, and the fertilized oocytes (zygotes), exhibited different protein compositions,[40] which, remarkably opened a new window to study Evo-Devo. Therefore, cytoplasm, an essential cellular component plays an indispensable role in non-DNA molecule-associated inheritance, such as "epigenetic transgenerational inheritance," and 'prion-mediated inheritance'.[41–48]

Pregnancy-associated whole cell inheritance (PAWCI)

Early studies reported that fetal cells could be detectable in maternal circulation 1 to 5 years after delivery.[49] Bianchi and colleagues reported that fetal cells persisted in the mother's body for as long as 27 years,[50] and even lifelong.[51, 52] Maloney and colleagues showed that maternal cells even persisted in healthy offspring for as long as 49 years.[53, 54] Therefore, pregnancy-associated eukaryotic cell transmission actually reflects a whole-cell associated biological heredity. Maurel and Kanellopoulos-Langevin pointed out that microchimeric maternal cells may provide the third path for heredity.[19] Recently, six models of pregnancy-associated eukaryotic cell transmission between mother and offspring have demonstrated from a fimpological perspective that there is a complex eukaryotic cellular transmission system during gestation and lactation, which has further enriched our understanding on PAWCI.[1, 2]

A model for female-relayed whole cell and cytoplasmic inheritance

Here, I propose a theoretical model called *Female-Relayed Whole-Cell and Cytoplasmic Inheritance* (FRICCI) for illustrating fertilized oocyte-mediated cytoplasmic inheritance (FOMCI) and pregnancy-associated whole cell inheritance (PAWCI), which further indicates that both the male and the female play a distinguished role in biological heredity. If the fetus is male, the obtained maternal oocyte cytoplasm and eukaryotic stem cells from pregnancy-associated cell transmission during gestation and lactation would not be able to be transferred to the male fetus's next generation because there is no anatomic platform for cell transmission between the male and his future offspring, and the heredity that the male can contribute is only the delivery of DNA molecules in spermatozoa to his next generation via Mendel hereditary law. In contrast to the male, if the fetus is female, in addition to well-known DNA molecular heredity, the female has been theoretically and experimentally shown to play unique roles in FOMCI and PAWCI.[2, 19, 39, 53–56] Therefore, at the eukaryotic cell level, FOMCI and PAWCI are two unique roles played by the female in biological heredity, which actually constitute a challenge faced by modern genetics and the Modern Synthesis.[57]



In the Figure, Mrs. Song and Mr. Zhao, as the first generation, had three offspring: two girls (Fan Zhao and Lan Zhao) and one boy (Gang Zhao). When Mr. Gang Zhao has offspring, no matter if they are girls or boys, he can only transfer sperm-DNA acquired via Mendel's Law from his parents Mrs. Song and Mr. Zhao, to his next generation, which will be created by the fertilization between Mr. Gang Zhao's sperm and another female's oocyte. Therefore, although Mr. Gang Zhao obtained FOMCI and PAWCI from his mother, Mrs. Song, he cannot transmit FOMCI and PAWCI to his offspring, or grandchildren of Mrs. Song. In other words, the heredity of Mrs. Song's FOMCI and PAWCI discontinues with her sons.

In contrast to Mr. Gang Zhao, the Misses Zhao, the two daughters of Mrs. Song are able to transfer FOMCI and PAWCI to their five children, the third generation. Moreover, among five offspring, there only are three daughters, named Mei Cao, Li Lai, and Lin Lai, who can transmit their maternally originated FOMCI and PAWCI to their offspring (the fourth generation). Females of the fourth generation transmit their maternally originated FOMCI and PAWCI to their children, the fifth generation. Therefore, in the theoretical model, Mrs. Song's FOMCI and PAWCI are transferred via a female path to Miss Wu, Miss Fei, and Miss Du in the fourth generation and to Miss Chen, Miss Bai and Miss Qian in the fifth generation. Clearly, in the modern societies, the patriarchy-dominated family name system and the family-based genealogical tree fail to reflect the real dispersal pattern of Female-Relayed Non-Nucleus Entities Inheritance (FRNNEI).

Concluding Remarks

Besides DNA-centered nuclear inheritance, fertilized oocyte-mediated cytoplasmic inheritance (FOMCI) and pregnancy-associated whole cell inheritance (PAWCI) have been attracting more attention than before for their unique role played in biological heredity, which have been supported experimentally and illustrated theoretically. The

model called "female-relayed whole cell and cytoplasmic inheritance" further illustrates that both FOMCI and PAWCI could be transferred to offspring generation by generation along the pregnancy-associated female path; and moreover, both FOMCI and PAWCI are determined by reproductive female offspring, but not by reproductive male offspring. Therefore, the female may play more roles in biological heredity than the male does. Moreover, in modern societies, the patriarchy-dominated family name system and the family-based genealogical tree fail to reflect the real dispersal pattern of FOMCI and PAWCI. The revival of the study on FOMCI and PAWCI from the biological, ecological and evolutiological perspective will undoubtedly expand our knowledge in the life sciences.

Abbreviations

PAWCI: Pregnancy-Associated Whole Cell Inheritance
FOMCI: Fertilized Oocyte-Mediated Cytoplasmic Inheritance
FRNNEI: Female-Relayed Non-Nucleus Entities Inheritance
FRICCI: Female-Relayed Integral Cell and Cytoplasmic Inheritance

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