The Cost of Being Male
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CO_2 reservoir could nearly double Mars' atmospheric mass, the resulting climate alterations would be modest, and as pointed out by Phillips *et al.*, would involve effects of dust raising and extent and longevity of seasonal frosts, as well as the enhanced CO_2 pressure. These ice reservoirs are not the path to a "warm, wet" Mars. Indeed, the limitations of the depth of CO_2-ice reservoirs (*13*, *14*) probably require that high former CO_2 pressures needed for much warmer conditions must involve carbonate or other rock reservoirs, in addition to ice deposits. The new findings of large, and possibly multiple, buried CO_2 reservoirs show how complex a seemingly simple cold finger system can be. Mars' cold trapping is clearly affected by seasonal kinetics, changing dust loading of the atmosphere, obliquity and other orbital cycles, and longer-term evolution of Mars geology. There is much yet to learn about this simple system. The north-south polar asymmetry is but one example of continuing puzzles.

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EVOLUTION

The Cost of Being Male

Mitochondrial mutations influence nuclear gene expression more in male *Drosophila* than in females.

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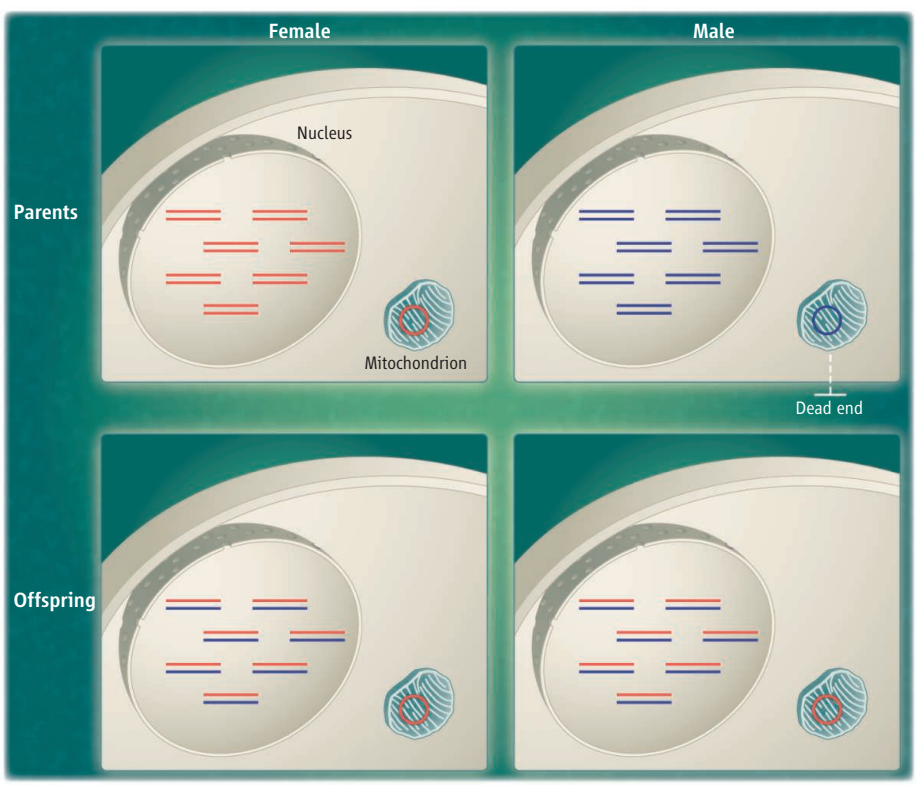
Although we often hear of "the human genome," human cells, like all other eukaryotic cells, actually contain two genomes. The nuclear genome, which garners most of the attention, is composed of the chromosomal DNA within the nucleus and encodes tens of thousands of proteins. The mitochondrial genome, which is present in the organelles that serve as the major site of energy production in the cell's cytoplasm, consists of a circular piece of DNA that encodes fewer than 20 proteins. The two genomes must function together for the cell to survive. However, because the two genomes differ in their mode of inheritance, their interaction may not be completely harmonious. On page 845 of this issue, Innocenti *et al.* (*1*) report experimental findings from the fruit fly demonstrating a sex-specific breakdown of the cooperation between the nuclear and mitochondrial genomes. In this case, it is the males who get the short end of the stick.

Upon reproduction, both mother and father pass half of their nuclear genomes to their offspring. An exception is the Y chromosome, which is passed only from father to son. In contrast, the mitochondrial genome is inherited maternally. That is, it is passed only from the mother to the offspring of both sexes (see the figure). Viewed from the mitochondrial genome's perspective, males are an evolutionary dead end: Regardless of the mitochondria's effect on a male's survival or reproductive success, they have no chance to contribute their genetic information to the next generation. This implies that natural selection will be inefficient at removing mitochondrial mutations that have a negative impact on male, but not female, fitness (*2*). Thus, mitochondrial genomes are expected to harbor more mutations that are deleterious to males than to females. This phenomenon is referred to as the "male mutational load" or, more colorfully, "mother's curse" (*3*).



Dead-end males. Males are an evolutionary "dead end" for the mitochondrial genome. Although offspring (**bottom**) inherit the nuclear genome from both parents (**top**), they inherit the mitochondrial genome only from the mother. This can lead to the accumulation of mitochondrial mutations that have a deleterious effect in males, but not in females.

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In their study, Innocenti *et al*. provide direct experimental evidence for an increased mitochondrial mutational load affecting gene expression levels in male *Drosophila*. They performed careful genetic manipulations to create strains of *Drosophila* that differed only in their mitochondrial genomes. They then used DNA microarrays to measure differences in nuclear gene expression associated with the different mitochondrial genomes. They performed their experiments separately on males and females. The results were striking: In females, exchanging mitochondrial genomes altered the expression of only a handful of nuclear genes; in contrast, in males, more than a thousand genes showed a significant change in expression. Assuming that most changes in gene expression are deleterious (*4*), this indicates a much greater mutational load in males than females. Additional support for this interpretation comes from the expression profiles of the genes that were affected in males. There was a significant over-representation of male-biased genes (those that are expressed at a higher level in males than females) (*5*) and genes expressed specifically in male reproductive tissues. Furthermore, previous studies have shown that the expression level of many of the variable genes is associated with male reproductive output (*6*).

In addition to providing experimental validation of theoretical predictions, Innocenti *et al*. provide at least a partial explanation for the observed difference in gene expression polymorphism between males and females in natural populations of *Drosophila*. Previous studies have shown that, in general, male-biased genes are more variable in expression among individuals than female-biased genes, and that there is greater gene expression polymorphism among males than among females (*7*–*9*). Because individuals in natural populations harbor genetic polymorphism within their mitochondrial genomes, it is reasonable to assume that this polymorphism contributes to the observed variation in nuclear gene expression.

Recent studies have shown that another genetic element with sex-specific inheritance, the Y chromosome, also makes a large contribution to gene expression polymorphism among males (*10*). Like the mitochondrial genome, the Y chromosome encodes very few proteins. However, the Y chromosome contains a large amount of noncoding DNA (known as heterochromatin), and it is this heterochromatin that appears to modulate the expression of many nuclear genes (*10*, *11*). Y-chromosomal polymorphism has a disproportionate effect on genes whose products localize to the mitochondria (*11*). This raises the possibility that the male nuclear genome coevolves with the mitochondrial genome to alleviate some of the deleterious effects caused by mitochondrial mutations.

There are at least two open questions regarding the influence of the mitochondrial genome on nuclear gene expression. The first is mechanistic. How does a tiny genome that encodes only 13 proteins affect the expression of hundreds of nuclear genes in a sex-specific manner? Thousands of nuclear gene products are required for proper mitochondrial function, but further research is needed to elucidate the complex interactions that underlie this ancient symbiosis. The second question pertains to the effect of male-deleterious mitochondrial mutations in females. Are these mutations slightly deleterious, neutral, or even beneficial to females? The effect in females is a critical parameter that determines the rate at which these mutations will spread in a population. It is also important for extrapolating the *Drosophila* results to other species that have much smaller effective population sizes, such as mammals. For example, if most of the mutations have slightly deleterious effects on female fitness, one would predict a greater male mutational load in humans than in *Drosophila*, because natural selection is expected to be less efficient in humans (*12*).

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DEVELOPMENT

Planarian Pluripotency

Jonathan M. W. Slack

Cellular and molecular details underlying tissue regeneration are revealed in the flatworm.

Many animals can regenerate tails, but few can regenerate heads, and how they do so is a fascinating problem. Tiny flatworms called planaria have long been famous for the ability to regenerate body parts (*1*–*3*) and as such, they are a valuable model system for elucidating mechanisms that control cell and tissue replacement, a process that is important for the survival of most organisms. On page 811 of this issue, Wagner *et al*. (*4*) examine the nature of the cells (called neoblasts) responsible for regeneration in planaria, and on page 852, Petersen and Reddien (*5*) reveal more about how the worm decides whether to regenerate a head or a tail.

Neoblasts are small undifferentiated cells that have long been thought responsible for normal growth and regeneration in planarians (*6*). Labeling of DNA synthesis shows that they are the only cells in the worm that undergo division (*7*). Neoblasts are often described as "stem cells," but unlike mammalian stem cell systems, little is known about them. In mammals, a tissue with continuous cell renewal contains a small number of stem cells that survive for the lifetime of the animal and generate all cell types of the relevant tissue. For example, the hematopoietic stem cells of the bone marrow generate all the cell types of the blood and immune system (*8*, *9*). The stem cells are found in special niches where the microenvironment maintains their self-renewal capability (*10*, *11*). But most dividing cells of renewal tissues are not stem cells, but progenitor cells, which have a finite potential to divide and are committed to form one subset of cell types. For example, the hematopoietic stem cell gives rise to a common lymphocyte progenitor cell, and this gives rise to progenitor cells for particular types of lymphocyte.

Given the lack of knowledge about the organization of the neoblast population, the question asked by Wagner *et al*. was simple: Are there any cells among the neoblasts that are fully pluripotent, or are all neoblasts committed to form particular subsets of differentiated cell types? The term "pluripotent" generally denotes the ability to develop into any cell type in the body, whereas "multipotent"

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