A Theory of the Extended Phenotype of the Mitochondrion

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Abstract

A mitochondrial perspective on the evolution of sex (meiosis) is considered. Rather than viewing mitochondria as passive entities taken up by an archaeal host that remains in the driving seat, mitochondria are viewed as the key force driving the process. The proto-mitochondrion is presumed to have manipulated its archaeal host to engage in sex in order to replicate itself in a more and more beneficial environment. Such a perspective appears capable of providing possible answers for a number of long standing issues in biology: the existence of sexual recombination, the existence of multiple mating types and the preference for having two primary mating types, uniparental mitochondrial inheritance, and the existence of multiple nuclear chromosomes.

1 Introduction

This paper presents a mitochondrial perspective of the evolution of the eukaryotic cell creating a Theory of the Extended Phenotype of the Mitochondrion (TEPM). It is not that the nuclear genome is unimportant, but that it might be over-emphasized, and that by giving due consideration to the role of the mitochondrion a clearer picture of the eukaryogenesis emerges.

The phrase "extended phenotype" was developed by Richard Dawkins to refer to phenotypic effects beyond the boundary of the organism[7]. The extended phenotype of the mitochondrion is the phenotypic effects of the mitochondrion beyond the outer mitochondrial membrane. The effects of the huge amount of energy provided by the mitochondrion, and the mitochondrion's role in programmed cell death are two examples of the extended phenotype of the mitochondrion. This paper considers additional possible extended phenotypic features of the mitochondrion, and in particular a role in the evolution of sex.

After briefly reviewing theories of eukaryogenesis, this paper develops a theory of a mitochondrial driven eukaryogenesis, and then compares predictions of the theory to observations of asexual eukaryotes and uniparental mitochondrial inheritance.

2 Evolution of the eukaryotic cell

The eukaryotic cell is widely believed to have evolved from a symbiotic relationship between an archaeon and an alphaproteobacteria, with the alphaproteobacteria becoming the mitochondrial organelle.

Exactly how an alphaproteobacteria ended up living inside an archaeon isn't certain:

- The viral eukaryogenesis hypothesis posits the eukaryotic cell evolved from a virus, archaeon, and alphaproteobacteria[2]. Difficulties with the viral eukaryogenesis hypothesis include viruses would need to evolve the means to replicate by themselves if they are to eventually evolve into gametophytes, and the lack of any known double stranded DNA viruses with segmented genomes so the theory doesn't explain the origin of chromosomes.
- One more plausible line of reasoning starts with the archaeon's development of the cytoskeleton component actin[3, 9, 19]. Actin filaments would have allowed the archaeon to extend its plasma membrane to engulf large particles, which it would then attempt to digest, leading to the development of phagocytosis[34]. When that ingested particle happened to be a living cell, the ingested cell would evolve in such a way as to attempt to resist the full phagocytic effects of ingestion. An example of this is provided by *Rickettsia conorii*, an alphaproteobacteria and intra-cellular pathogen, which enters the host by inducing host phagocytosis, and then escapes from the phagosome into the host's cytosol[30].

Once inside the archaeon the alphaproteobacteria would have had three possible ways to propagate. It could replicate until the host cell bursts and then find new host cells to infect, or it could attempt to ensure that it is faithfully propagated to each descendant of the host cell. This is similar to the lytic and lysogenic cycles of bacteriophages and viruses. Additionally the alphaproteobacteria could use actin based motility to spread from cell to cell. An example of this is again provided by the rickettsia. The typhus group rickettsia cause host cell lysis, while the spotted fever group spread from cell to cell by means of actin filaments[12]. It is worth noting that spotted fever rickettsial infection doesn't necessarily lead to host cell death, because avirulent strains of the spotted fever group exist that are capable of coexisting with their host in what might be described as a parasitic endosymbiosis.

The host might be expected to be evolving defenses against the alphaproteobacterial parasites. These defenses are unlikely to be complete (we are still vulnerable to rickettsia today), but are likely to be substantial. The exception being if the endosymbiant provides a benefit to the host. This is the case with the mitochondria, which through oxidative phosphorylation increases the ATP available to the host by roughly a massive 15 fold over the glycolysis of anaerobic fermentation[25].

3 An active germline replicator perspective

An active germline replicator is an entity of which copies can be made and whose nature has some influence over the probability of it being copied[7].

Both the archaeal host and the alphaproteobacterial proto-mitochondrion are active germline replicators. The germ cells and zygotes of eukaryotes might be described as low fidelity active germline replicators. Germ cells and zygotes make copies of themselves in an environment made up of other germ cells and zygotes. The strategy they employ may involve creating zygotes, germ cells, somatic cells, and multicellular organisms, but in the end they produce more copies of themselves. They are low fidelity replicators in the sense that the DNA sequences of the copies only partially reflect the original due to homologous recombination of allelic sequence differences.

To be pedantic, it is the DNA that forms the active germline replicator, and the proto-mitochondria or alphaproteobacteria is just a vehicle for the replicator, but is easier to speak in terms of replicating proto-mitochondria than to spell out every time that it is the DNA of the replicating proto-mitochondria that is the replicator, with the rest of the mitochondrion existing because it assists in making copies of the replicator.

An important question in biology is how can active germline replicators (the archaea and alphaproteobacteria) combine to make other active germline replicators (those of eukaryotes).

4 The problem of sex

Sex (meiosis) is troubling to biologists. At the macro level it appears to have advantages, but at the micro level it is difficult to understand how it evolved, and why it continues to exist.

First there is the mechanical cost of meiosis, which is greater than reproduction via mitosis. Second there is the two-fold cost of sex, or the cost of males. Third, sex involves an organism sharing 50% of its resources with a stranger, with only hope as to what it might receive in return. Consider a selfish mutation that doesn't hold up its end of any quid pro quo associated with sex, such as an allele that favors itself during meiosis. Such a mutation might be expected to spread within a population, even if it is harmful to the success of the species.

Reported advantages of sex include the ability to combine the best mutations from several organisms, resistance to parasites, the ability to repair double-stranded DNA breaks, clearance of deleterious mutations, and an increase in the speed of evolution.

Genetic information wants to be stable. It is widely believed that information is primarily stored as DNA rather than RNA, because DNA is more stable. The mitochondrial genome mutates 10-100 times faster than the nuclear genome. Thus it seems reasonable to expect genes would prefer to be encoded on the nuclear genome. This agrees with what is observed, with a majority of mitochondrially targeted genes located on the nuclear genome. Too much stability would however be problematic, as there then wouldn't be enough genetic variation for evolution to work with. Sex increases the size of space over which evolution can work from the genome of a single organism, to the genome pool of a entire species.

5 A proposed evolution of sex

It is proposed here that sex evolved as a means for mitochondrial active germline replicators to replicate themselves inside of more and more suitable hosts. The mitochondria are engaged in the ultimate selective breeding experiment, crossbreeding those host nuclear chromosomes that proved successful in previous generations.

The proposed route to sex involves an actin propelled alphaproteobacteria attempting to spread from cell to cell by punching a hole in two apposed archaeal cells' membranes, much like the spotted fever group rickettsia do. If the plasma membranes were to then to heal by joining around the points of apposition on the rim of the two holes, you would end up with a single cell containing alphaproteobacteria and two copies of the archaeal genome. This would be much like the mitochondria and two copies of the nuclear genome found in eukaryotic cells today. When the cell next replicated the two archaeal genomes would become four genomes, which would be followed by cell division. All it would take is for this to be followed by a second cell division, and you would have something that is starting to resemble meiosis – minus the important reassortment of genes. Reassortment of genes would however occur if the circular chromosomes were broken into distinct lengths – primitive nuclear chromosomes.

Reassortment of genes would bring huge benefits to the organism. Suddenly evolution can occur in parallel across all the genomes in the population, and the best features of each merged, instead of all having to be evolved along a single linage. Add in to the process recA, the key gene for recombination, which is already found in both archaea and alphaproteobacteria, and you have full blown meiosis[18]. At first the process would be messy, with multiple archaeal cells sometimes merging, and chromosomes and proto-mitochondria not getting distributed among descendants evenly. Frequently failures would occur, but the sequence of steps leading to tightly regulated meiosis is precisely the sort of thing evolution is good at climbing.

An evolution of sex like the one described would explain why there are no anciently amitochondrial species. The mitochondria was there at the start of eukaryogenesis.

The possibility that the alphaproteobacteria that evolved into the mitochondrion had a broad host cell range has the potential to explain the difficulty of determining the archaeal ancestor of the eukaryotic cell. There need not be one single ancestor. Indeed a prerequisite to the evolution of sex is not only that the archaeal hosts be in close apposition, but that the archaeal host live in multi-species community, as opposed to a single species colony. This is true of the archaea, which are frequently found to form biofilms[10]. If the archaeal hosts formed a simple colony, there genomes would be near identical, and there would be little benefit to sex.

An actin-based alphaproteobacteria motility model of eukaryogenesis is a simple theory that is compatible with the idea of mitochondria replicating themselves inside more and more suitable hosts, but it isn't the only possible compatible theory. Other theories on the emergence of meiosis would be compatible, provided it is the mitochondria that is originally driving the process.

6 Talking about sex

Who benefits from sex? In this theory, sex evolved for the benefit of the proto-mitochondria. The mitochondria are manipulating their environment (the archaeal host) in order to make it more probable the mitochondria will survive.

Do the nuclear genes of the originally archaeal host benefit from sex? This is arguable, and will likely depend on the species. More importantly this isn't the reason sex evolved. Sex comes with great costs, and there is strong pressure for nuclear genes and genomes to reproduce selfishly, asexually. This later point is no different than a multi-player prisoner's dilemma. Everyone might benefit from cooperation, but an individual genome gains a strong initial advantage by defecting.

Why did the nuclear genes participate in sex then? The nuclear genes benefited from their association with, and the energy provided by, the mitochondrion: the primary beneficiary of sex.

Note that although sex may have benefits for the resulting eukaryotic cell, it need not. Sex could be harmful to the success of the eukaryotic cell, but so long as the mitochondrion benefits it would still occur. This is in contrast to existing theories on sex, which attempt to divine how nuclear genes of the eukaryotic cell benefit.

How does the mitochondria cause sex? Today, this is hard to see. Whatever mitochondrial genes that once existed to cause sex, say by riding an actin filament and punching a hole in two cell membranes, may have long since migrated to nuclear genes, and have probably been replaced by other nuclear genes. Today the interests of the mitochondria and competing nuclear genes are tightly aligned, making it difficult to separate the interests of one from another.

All the nuclear genomes capable of supporting a given set of closely related mitochondrial genomes, say the mitochondrial genomes of some species, might be viewed as forming a nuclear genome pool "owned" by those mitochondrial genomes, or as a resource of those mitochondrial genomes that is supporting those mitochondrial genomes. These mitochondrial genomes are in competition with other mitochondrial genomes, and benefits from the crossbreeding of the nuclear genomes they own. The larger the nuclear genome pool, the more opportunities the mitochondrial genomes have to survive.

If sex was lost in some species this would reduce the fitness for the embedded mitochondria relative to the mitochondria of other species as they would no longer benefit from the crossbreeding of the nuclear genomes. It would represent a rapid evolutionary dead end for the species. An exception to this might occur if the mitochondria is delivering little or no value to the resulting organism, such as in anaerobic environments. Here there would be a higher hurdle to climb before sex became beneficial, and so sex might be expected to more commonly be stably lost.

Expanding on this last point, let n be the nuclear genome pool size, m be the amount of energy provided by the mitochondria per nuclear genome per unit of time, and let o capture any other species specific variation. Let the mean inclusive fitness of a sexual species be $\bar{w}_s(n, m, o)$. The fitness of an asexual species is independent of the genome pool size, so let the mean inclusive fitness be $\bar{w}_a(m, o)$. Sex is advantageous to species most of the time, so:

$$\bar{w}_s(n, m, o) > \bar{w}_a(m, o) \text{ for most } o \text{ when } n, m \text{ large enough.} \quad (1)$$

If you view sex as involving a trade-off between the fixed costs of sex, $c(o)$, and multiplicative benefits to the species of genome pool scale evolution, $b(n, o)$, then:

$$\bar{w}_s(n, m, o) = b(n, o)\bar{w}_a(m, o) - c(o). \quad (2)$$

If m is zero, $\bar{w}_a$ is at a minimum. There are still all of the fixed costs of sex, but with minimal benefits, so:

$$\bar{w}_s(n, m, o) < \bar{w}_a(m, o) \text{ for many } o, n \text{ when } m = 0. \quad (3)$$

7 Asexual eukaryotes

A nuclear gene that prevents sex might be expected to propagate within a species, but represents an evolutionary dead end. The benefits of sex will be lost, and the species will be out-competed by other species. This is consistent with the observation that it is very rare for a taxon higher than a species to consist entirely of asexual species[20]. The only reported exception appears to be the bdelloid rotifers:

- The bdelloid rotifers are famous as a class of ancient asexual eukaryotes. Bdelloid rotifers appear to engage in inter- and intra-species horizontal gene transfer[8, 11]. This may go some way to explaining why the bdelloid rotifers don't need to engage in sex. They get the benefit of the introduction of new genes to an existing organism through other means. However, it would appear there may be a mitochondrial angle to the story. The bdelloid *Rotaria rotatoria* mitochondrial genome has been sequenced[21]. The mitochondrial small and large ribosomal subunit sequences are 521 and 529 nucleotides respectively. This seems very small to be a functioning ribosome, particularly for the large subunit. A review of the mitochondrial large subunit sizes of 3,200 species only turned up 6 sequences that were putatively smaller. All 6 had adjacent non-coding regions, possible suggesting they were incompletely identified. Thus it is conceivable that bdelloid rotifers have lost a functioning mitochondrial ribosome, along with the loss of sex, and would then require some nuclear component to assist in the translation of the mitochondrial genome. This might seem unlikely, but so does a large subunit size of 529 nucleotides. Finally it should be noted that the non-bdelloid rotifer *Brachionus plicatilis's* mitochondria is highly unusual in that it contains two chromosomes[29]. Whether this odd arrangement was a stepping stone to the bdelloid's asexuality isn't known. Summarizing, something is going on with the mitochondrion in bdelloid rotifers.

Two taxa that were once thought to be asexual are aphids of the genus *Trama*, and the darwinulid ostracods[22]:

- *Trama* was reportedly a genus of asexual aphids, but with the report of sex in *Trama troglodytes*, this is no longer the case[4].
- Like Trama, the darwinulid ostracods were long thought to be asexual, but males have now been found in one species, suggesting any loss of sex might have been more recent[27].

If the loss of sex is represents an evolutionary dead end, ancient asexual species should be rare. They are. Besides the bdelloid rotifers and darwinulid ostracods the only other well known ancient asexuals appears to be the arbuscular mycorrhizal fungi[22]:

- *Racocetra castanea* is an ancient asexual arbuscular mycorrhizal fungus. Like the bdelloid rotifers, *Racocetra castanea* might have found an alternative to sex. In mycorrhizal fungi offspring receive hundreds of nuclei from the parent[16]. Thus there is a population of individually mutating nuclear genomes that might provide some of the benefits of sex seen in other organisms. Whether there are any concomitant changes to the mitochondrial genome isn't known as it doesn't appear to have been sequenced.

Lastly it is worth considering a few other taxa within which sex appears to has been lost:

- Further evidence that the mitochondria has something to do with sex is provided by the microsporidia. Microsporidia are a group of fungi that lack mitochondria. They do however have an organelle called a mitosome, that appears to have been derived from the mitochondrion[32]. Mitosomes appear to have lost their organellar DNA. This makes the fact that some species of microsporidia are asexual interesting. Even more interesting is the fact that this loss of sex doesn't appear to have occurred in one ancient ancestral lineage, but to have occurred several times in different lineages[14]. It seems more than a coincidence that the loss of sexuality has occurred in the absence of mitochondrial DNA.
- Diplomonads and trichomonads are two taxa of excavata that have lost their mitochondria[26]. Despite some diplomonads having genes for meiosis, they are not known to be sexual[23]. Trichomonads are also believed to be asexual[6]. Once again the loss of mitochondria and the possibility for asexuality go hand in hand.

In conclusion there seems to be a relationship between missing or unusual mitochondrial systems and asexuality. More specifically, asexuality rarely transcends taxa larger than a species, asexuality frequently appears to be an evolutionary dead end with very few ancient asexuals, and asexuality is particularly common in amitochondrial species. This is consistent with the theory that has been developed.

8 Mating types

Sex is almost synonymous with there being two primary mating types. But why? Being capable of mating with a large number of other different mating types, or any other appropriate cell, would

make it easier to find a suitable partner. Having only two mating types seems like the worst possible option.

If you take the perspective that sex wasn't evolved for the good of the eukaryotic cell, but for the good of the mitochondria, two gamete mating types makes sense. The two mating types then are "seeks to propagate mitochondria", and "will suppress propagation of mitochondria when mating with the same species". These then evolved into the oocyte and sperm in anisogamous species. Just as it is difficult to imagine an evolutionary path for sex to evolve if you consider nuclear chromosomes, it is difficult to see how two cells that both want to propagate their mitochondrial chromosomes would want to mate. Similarly two cells that both suppress propagation of their mitochondrial chromosomes wouldn't want to mate. The only combination that makes sense is seeks to propagate mitochondria mating with suppresses propagation of mitochondria. The mitochondria benefits from this arrangement because it get to be transmitted into a better host.

9 Non-maternal inheritance of mitochondria

As predicted by the theory, uniparental (maternal) inheritance of mitochondria is the rule in eukaryotes, but there are a few exceptions worth examining[1]:

- Biparental inheritance. The yeast *Saccharomyces cerevisiae* is known to undergo biparental inheritance that is dependent on the location on the zygote where buds form[33]. The yeast *Schizosaccharomyces pombe* is also known to display biparental inheritance. What distinguishes these two species is they are both capable of undergoing mating type switching in which a haploid cell of one mating the switches to the other mating type[13]. It seems as if this sex reversal might destroy the advantages of uniparental mitochondrial inheritance.
- Mating type hierarchies. The myxogastria are slime molds that after forming a zygote engage in multiple nuclear replications and divisions without any corresponding cell divisions. The myxogastrid *Physarum polycephalum* has multiple mating types and a corresponding hierarchy of mitochondrial dominance[15]. Another myxogastrid *Didymium iridis* also has multiple mating types and for many mating types the mitochondrial inheritance pattern is uniparental with one particular parent favored, but for a few crosses it is biparental[28]. Having multiple primary mating types apparently disrupts the usual pattern of mitochondrial inheritance.
- Paternal inheritance. Paternal inheritance of mitochondria is known to occur in some interspecies crosses, and in several plants with uncommon sexual strategies[5]. This makes sense. Outside of the species the paternal mitochondria isn't bound by the same evolved rules of decorum that are designed to help the mitochondria of that species, and so might seek to propagate. Meanwhile the presence of paternal inheritance in several plant species with uncommon sexual strategies highlights the link between sex determination and mitochondrial inheritance.

How did sex evolve? Section 5.
For whose benefit is sex? Section 6.
Why is evidence for eukaryotes prior to incorporation of the mitochondrion lacking? Section 5.
Why do eukaryotes have multiple nuclear chromosomes? Section 5.
Why is the mitochondrial genome of the bdelloid rotifers so anomalous? Section 7.
Why are amitochondrial species more likely to be asexual? Section 6.
Why do mating types exist? Section 8.
Why are there typically only two mating types? Section 8.
Why are mitochondria typically inherited uniparentally? Section 8.
Why is paternal inheritance of mitochondria common in inter-species crosses? Section 9.

Table 1: Questions addressed by the Theory of the Extended Phenotype of the Mitochondrion.

Why does separate mitochondrial DNA continue to exist?
What is happening to the mitochondrial ribosome of bdelloid rotifers?
How does mating type switching in yeast destroy the need for uniparental inheritance?

Table 2: Some questions raised by the Theory of the Extended Phenotype of the Mitochondrion.

10 Discussion

Most attempts to understand the evolution of the eukaryotic cell have focused on the nuclear chromosomes, treating the incorporation of the mitochodrion as an energy providing afterthought. In terms of size the mitochondrial genome is small, but in terms of what it brings to the equation, a 15 fold increase in ATP, it is large, and thus it should have been expected to play a major role in the evolution of the eukaryotic cell. Treating the mitochondrial genome as a selfish replicator provides a new way of looking at the eukaryotic cell, and with it a new understanding. Sex might have evolved as a means for the proto-mitochondria to propagate itself into a more and more competent host. There is a close relationship between "for the benefit of the mitochondria" and "for the benefit of the species". And the whole eukaryotic cell can even be viewed as the extended phenotype of the mitochondria. This isn't the only way the eukaryotic cell should be viewed, but it adds an interesting new perspective.

TEPM is capable of addressing a number of questions in biology as shown in Table 1. Some of these questions already have one or more existing plausible answers. However these are all single point theories that address one question. By the principle of parsimony there is considerable advantage to replacing them by one single theory.

The theory also raises a number of new questions and enhances the importance of some existing questions as listed in Table 2.

The key genes responsible for the actin propulsion of the spotted fever group rickettsia are RickA and Sca2[24]. Whether orthologs of either of these genes were present in very early eukaryote mitochondria isn't known. A quick Blast search fails to turn up any matching sequences in existent eukaryotes.

Mitochondria are key players in Programmed Cell Death (PCD). They are the source of Reactive

Oxygen Species (ROS) that are capable of triggering PCD[17]. And most of the pathways for PCD flow through mitochondria[31]. A number of computer simulations were performed. They showed the possibility of an evolutionary advantage to engaging in PCD if it is known that the nuclear and mitochondrial genomes are a poor energy producing match. In such cases it can be better to engage in PCD and remove the poor match from the gene pool than to reproduce and engage in meiosis. It is possible a poor match could be detected by the production of ROS by complexes I and III of the electron transfer chain. Thus it might be theorized that mitochondria engage in PCD in unicellular species and in the germline as a result of mito-nuclear incompatibilities. Despite this there is currently a lack of experimental evidence to support mitochondria engaging in PCD on this basis under normal physiological conditions.

11 Conclusion

Taking a mitochondrial perspective on the evolution of the eukaryotic cell delivers a new theory. The biology of the eukaryotic cell is unchanged, but the way one looks at something affects how it is perceived. A mitochondrial perspective results in some changes of perception that may make some things clearer. The proto-mitochondria is viewed as having manipulated its host to provide a more suitable environment to live in. Sex may be viewed as having been an adaptation for the benefit of the proto-mitochondria.

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