PHILOSOPHICAL TRANSACTIONS B

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Invited reply

Cite this article: Speijer D. 2018 Response to Ghiselli F *et al.* (2018). *Phil. Trans. R. Soc. B* **373**: 20170278.
http://dx.doi.org/10.1098/rstb.2017.0278

Accepted: 4 September 2017

Subject Areas:
biochemistry, evolution, genetics, physiology

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The original article and the accompanying comment can be viewed at http://dx.doi.org/10.1098/rstb.2015.0530; http://dx.doi.org/10.1098/rstb.2017.0147.

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Response to Ghiselli F *et al.* (2018)

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I thank the authors (Ghiselli *et al*. [1]) for their interesting comments regarding my article [2]. They indeed further clarified some important points regarding both uniparental organelle inheritance (UPI), which we encounter almost exclusively as strictly maternal inheritance (SMI) and doubly uniparental inheritance (DUI) as well as 'role-reversal' of F-type mitochondrial DNA (mtDNA). Their data again illustrate the fascinating variety in mitochondrial inheritance.

The authors critically discuss their data to ask whether these support John Allen's 'division of labour' hypothesis [3], where male gametes maximize energy production for competitive advantages in motility, thus damaging mtDNA by mutagenic reactive oxygen species (ROS), coming from oxidative phosphorylation (OXPHOS). Non-motile female gametes, on the other hand, repress OXPHOS, keeping their mtDNA pristine. They 'clarify two discussion points: (i) the exceptions to the strictly maternal inheritance (SMI) of mitochondria and (ii) the claim that mtDNA is highly mutated in sperm and the supposed causal relationship between such damage and OXPHOS.'

Before responding to their arguments, it is worthwhile to very briefly summarize a possible evolutionary route to SMI. It is reasonable to suggest that the earliest eukaryotes had only few mitochondria (as found in some present-day unicellular eukaryotes), only later followed by a greater diversity/increase in organelle number, as exemplified by multicellular eukaryotes [4]. It is conceivable that a random distribution of mitochondria over daughter cells in these earliest eukaryotes would favour organelles that 'over replicate'. This could lead to over-abundances of mitochondria and necessitate 'organelle downregulation' upon cellular fusion. Thus, UPI could be an 'incidental consequence of the demise of organellar DNA, which provides some biochemical benefit.' [5]. Reduction of *overcapacity* mitochondria and mtDNA would be a clear benefit indeed. Such a basic reduction mechanism could then evolve to target organelles coming from only one parental source (a *later* development achieved by many quite different mechanisms). UPI evolved further with the development from isogamy to anisogamy and multicellular organisms differentiating between male and female gametes. SMI, in effect deleting the much more active 'paternal' mitochondrion, containing increased ROS-derived mtDNA damage, is the logical endpoint (see [2] and references therein).

So, what would this model predict when it comes to the two points mentioned by Ghiselli and colleagues? Exceptions to SMI might correlate with less selection for highly active sperm and there should be correlations between high OXPHOS activity and mtDNA damage, *if certain conditions are met*. I will try to show that their observations impact neither prediction. Alas, Ghiselli *et al.* only distinguish active/inactive mitochondria (sperm). This lack of nuance might have led them astray. One prediction of the 'division of labour' hypothesis is that if sperm has to *actively* compete to reach the egg first, SMI will not have the chance to disappear. Eukaryotes have developed many layers of adaptations to minimize mitochondrial ROS generation and damage, *but many of these reduce peak efficiency* (compare the role of uncoupling proteins in this respect [6]). So motile sperm using OXPHOS to swim do not necessarily generate large amounts of ROS-induced mtDNA mutations, as indeed illustrated by the long evolutionary persistence of DUI Ghiselli *et al.* correctly mention. However, I invoked the 'need for highly active sperm cells' (and, by the way, never 'claimed that … paternal mtDNA inheritance … can be explained by the *absence* of

mitochondrial activity in sperm'; my italics). When the energy for the final entry of the female is provided by the female incurrent siphon, such active competition seems absent.

This brings me to the second, and even more important, point of discussion, regarding the relation between OXPHOS activity and generation of mutagenic ROS. Here much is made of the fact that *lower* amounts of ROS (as compared with 'basal' ROS production) can be obtained during *high exercise activity*. The reference in this context is to Barja's excellent 'Updating the mitochondrial free radical theory of aging' [7]. Barja is *defending* the theory that mutagenic ROS (by mutating both mtDNA and nuclear DNA) are responsible for ageing. One of the many misconceptions he deals with is the naive vision of a *direct* relationship between mitochondrial ROS production and oxygen consumption; thus quoting him in this context seems a bit disingenuous. Mitochondrial ROS formation depends on membrane potential (Δp), kind of oxidative substrates, possibility of reverse electron transport to complex I and many other factors, besides overall activity. Thus, it is more than likely that, e.g. actively competing sperm using mitochondrial fatty acid oxidation would indeed generate large amounts of mutagenic ROS [8,9]. Finally, we have to keep in mind that when mitochondrial SMI appeared early on in eukaryotic evolution (as demonstrated by its almost universal presence), adaptations to lower endogenous ROS formation and cope with their effects were probably still evolving. This could have translated into even higher mtDNA mutation rates in male gametes at the time. Like the free radical theory of ageing, its cousin, the division of labour hypothesis, looks alive and well.

Data accessibility. This article has no additional data.
Competing interests. I declare I have no competing interests.
Funding. I received no funding for this study.

References

1. Ghiselli F, Breton S, Milani L. 2018 Mitochondrial activity in gametes and uniparental inheritance: a comment on 'What can we infer about the origin of sex in early eukaryotes?' *Phil. Trans. R. Soc. B* **373**, 20170147. (doi:10.1098/rstb.2017.0147)
2. Speijer D. 2016 What can we infer about the origin of sex in early eukaryotes? *Phil. Trans. R. Soc. B* **371**, 20150530. (doi:10.1098/rstb.2015.0530)
3. Allen JF. 1996 Separate sexes and the mitochondrial theory of ageing. *J. Theor. Biol.* **180**, 135–140. (doi:10.1006/jtbi.1996.0089)
4. Cole LW. 2016 The evolution of per-cell organelle number. *Front. Cell Dev. Biol.* **4**, 85. (doi:10.3389/fcell.2016.00085)
5. Bendich AJ. 2013 DNA abandonment and the mechanisms of uniparental inheritance of mitochondria and chloroplasts. *Chromosome Res.* **21**, 287–296. (doi:10.1007/s10577-013-9349-9)
6. Speijer D. 2014 How the mitochondrion was shaped by radical differences in substrates: what carnitine shuttles and uncoupling tell us about mitochondrial evolution in response to ROS. *Bioessays* **36**, 634–643. (doi:10.1002/bies.201400033)
7. Barja G. 2013 Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid. Redox Signal* **19**, 1420–1445. (doi:10.1089/ars.2012.5148)
8. Amaral A, Castillo J, Estanyol JM, Ballesca JL, Ramalho-Santos J, Oliva R. 2013 Human sperm tail proteome suggests new endogenous metabolic pathways. *Mol. Cell Proteomics.* **12**, 330–342. (doi:10.1074/mcp.M112.020552)
9. Speijer D. 2016 Being right on Q: shaping eukaryotic evolution. *Biochem. J.* **473**, 4103–4127. (doi:10.1042/BCJ20160647)