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COMMENTARY

# The mitochondrial-derived peptide MOTS-c: a player in exceptional longevity?

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## Summary

**Mitochondrial-derived peptides (MDP) are encoded by functional short open reading frames in the mitochondrial DNA (mtDNA). These include *humanin*, and the recently discovered *mitochondrial open reading frame of the 12S rRNA-c* (MOTS-c). Although more research is needed, we suggest that the m.1382A>C polymorphism located in the MOTS-c encoding mtDNA, which is specific for the Northeast Asian population, may be among the putative biological mechanisms explaining the high longevity of Japanese people.**

**Key words: aging; centenarians; longevity gene; longevity regulation; mitochondria; mitochondrial DNA; mitochondrial DNA abnormalities; molecular biology of aging.**

## Background

The number of people aged ≥60 years is expected to almost triple by 2050, with the '*oldest old*' group (>85 years) being the most rapidly expanding segment in Western societies (Waite, 2004). Among long-lived individuals, those who reach exceptional longevity (EL, *i.e.*, centenarians (≥100 years) and supercentenarians (SCs, ≥110 years)) are arguably the paradigm of successful aging (Andersen *et al.*, 2012). Several genetic factors might contribute to EL, as suggested by the differences found in the frequency distribution of several genetic variants among centenarians compared with their ethnic-matched referents of younger ages (Alexe *et al.*, 2007; Ruiz *et al.*, 2012; Garatachea *et al.*, 2014). Factors related to inflammation (Basile *et al.*, 2012), metabolism (Emanuele *et al.*, 2014) or nutrition (Pareja-Galeano *et al.*, 2015), among others, can also influence the likelihood of reaching EL.

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Japan has clearly the longest life expectancy in the world, as well as the highest number of SCs, as we recently reviewed (Santos-Lozano *et al.*, 2015). Thus, Japanese long-lived people represent an interesting model to study the biology of EL, and to gain insight into the nature *vs.* nurture debate.

## Mitochondrial haplogroups and EL

Mitochondrial DNA (mtDNA) can influence EL (He *et al.*, 2014). The 16,569-bp human mtDNA contains 13 genes that codify proteins involved in mitochondrial oxidative phosphorylation (OXPHOS), as well as 2 rRNA and 22 tRNA genes that are necessary for protein synthesis within mitochondria (Mercer *et al.*, 2011). Mitochondria are one of the most important players to understand the aging process at the cellular level as they are both the main source and target of oxidative damage (Gomez-Cabrera *et al.*, 2012). Mitochondrial dysfunction is in fact a main hallmark of aging, which is partly caused by accumulation of mtDNA damage as we age (Lopez-Otin *et al.*, 2013). Thus, because mtDNA haplotypes or haplogroups (*i.e.*, characteristic clusters of tightly linked mtDNA polymorphims that form continent-specific genotypes) might influence individual susceptibility to mtDNA damage, they could also influence EL in a continent- or ethnic-specific manner (Pinos *et al.*, 2012). For instance, the association between mtDNA and EL is controversial in Spanish people, with Pinos *et al.* reporting no association between mtDNA haplogroups and EL (Pinos *et al.*, 2012) but Dominguez-Garrido and co-workers finding that the Caucasian haplogroup J (which would be associated with lower mtDNA damage) might confer a higher chance to attain high longevity (85+years) compared with other haplogroups in Northern Spaniards (Domínguez-Garrido *et al.*, 2009). On the other hand, although mtDNA haplogroups D4b2b, D4a, and D5 are not associated with type 2 diabetes (Fuku *et al.*, 2007), they are linked with EL in Japanese population (Alexe *et al.*, 2007; Bilal *et al.*, 2008). We also showed that the mtDNA m.1382A>C polymorphism, which is specific for the ancestor haplogroup D4b2, is associated with EL in the Japanese population (Alexe *et al.*, 2007).

## Mitochondrial-derived peptide MOTS-c

Mitochondrial-derived peptides (MDP) are encoded by functional short open reading frames in the mtDNA. These include *humanin*, a 24-amino acid peptide encoded in the 16S rRNA region with strong cytoprotective actions (Hashimoto *et al.*, 2001) and the recently discovered *mitochondrial open reading frame of the 12S rRNA-c* (MOTS-c), which is a 16-amino acid peptide that regulates insulin sensitivity and metabolic homeostasis (Lee *et al.*, 2015). We have recently suggested that MOTS-c might also be involved in the aging process (Alis *et al.*, 2015).

The aforementioned m.1382A>C polymorphism is located in the MOTS-c encoding mtDNA, that is a 51-bp short open reading frame in the 12S rRNA region, from positions m.1343 to m.1393 (Table 1). The m.1382A>C variation causes a Lys14Gln replacement in the MOTS-c peptide equivalent to nucleotide position 1382 of the mtDNA; this is likely to have functional consequences, as the physicochemical





Aging Cell

**Table 1** The m.1382A>C polymorphism in the mtDNA region 12S rRNA (highlighted in bold) causes Lys14Gln replacement in the mitochondrial-derived peptide MOTS-c

| Nucleotide position* | Nucleotide sequence | Aminoacid (3-letter code) | Aminoacid position |
|---|---|---|---|
| 1343 | atg | Met | 1 |
| 1346 | agg | Arg | 2 |
| 1349 | tgg | Trp | 3 |
| 1352 | caa | Gln | 4 |
| 1355 | gaa | Glu | 5 |
| 1358 | atg | Met | 6 |
| 1361 | ggc | Gly | 7 |
| 1364 | tac | Tyr | 8 |
| 1367 | att | Ile | 9 |
| 1370 | ttc | Phe | 10 |
| 1373 | tac | Tyr | 11 |
| 1376 | ccc | Pro | 12 |
| 1379 | aga | Arg | 13 |
| **1382** | **[A>C]aa** | **Lys>Gln** | **14** |
| 1385 | cta | Leu | 15 |
| 1388 | cga | Arg | 16 |
| 1391 | tag | Stop | |

*Position number based on the entire mtDNA sequence.

difference between the original and the altered aminoacid residues is relatively high, with a Grantham value of 53, that is, above the average value (=50) that differentiates radical from conservative single amino acid replacements (Grantham, 1974). This amino acid replacement is also predicted to have a functional effect with the PROVEAN (PROtein Variation Effect ANalyzer) tool (http://provean.jcvi.org), that is, yielding a score of −4.000, below the specifically predicted cutoff score (=−2.5) above which the variant would be 'neutral' (Choi *et al.*, 2012). The m.1382A>C polymorphism is specific for the Northeast Asian population and may be among the putative biological mechanisms explaining the high longevity of Japanese people. Further, MOTS-c is an important 'mitokine', with this term referring to mitochondrial-derived signals that impact other cells in an endocrine-like manner (Fig. 1).

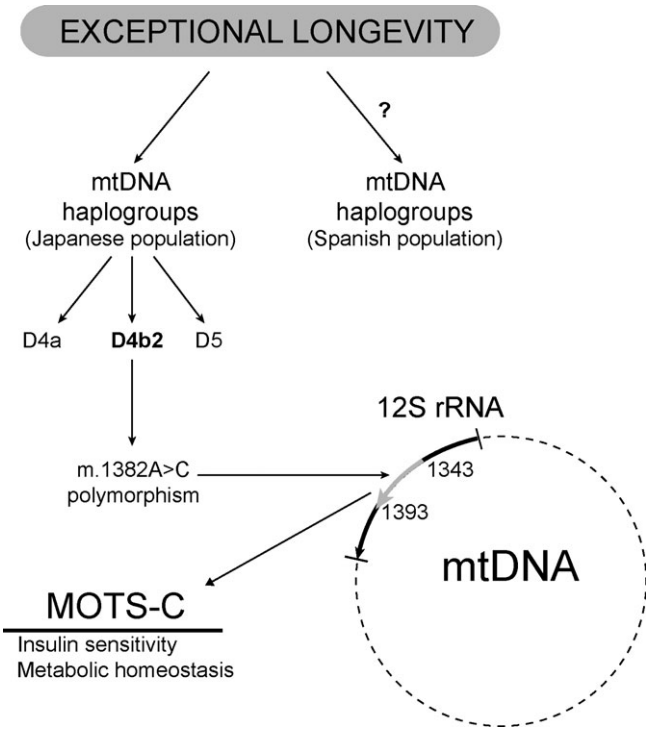


**Fig. 1** Putative biological link between the novel mitochondrial-derived peptide MOTS-c and exceptional longevity through the m.1382A>C mtDNA polymorphism. See text for abbreviations.

## Conclusions

We suggest a biological link between MOTS-c and extended lifespan through the putative endocrine action of this mitokine. Further mechanistic research is needed to determine the functional significance of the m.1382A>C polymorphism and the potential influence of MOTS-c in the human aging process.

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## Author's contributions

All authors have: (i) made substantial contributions to conception and design (NF, HP-G, HZ, RA, AL, NH, YA); (ii) drafted the article (NF, HP-G, HZ, RA) or revised it for critically for important intellectual content (AL, NH, YA); and (iii) gave final approval of the version to be published (NF, AL, NH, YA).

## Conflict of interest

None declared.

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