Commentary

Somatic mutations in mitochondria: the chicken or the egg?

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Abstract

Somatic mutations of mitochondrial DNA have been detected in various pathologies such as cancer, neurodegenerative diseases, cardiac disorders and aging in general. Now it has been found that patients with rheumatoid arthritis also have a higher incidence of mitochondrial mutations in synoviocytes and synovial tissue compared with patients with osteoarthritis. Furthermore, it has been shown that these mutations possibly result in changed peptides that are presented by major histocompatibility complex II and thus might be recognized as non-self by the immune system. Further studies will show whether these mutations are actually able to trigger autoimmune inflammation in rheumatoid arthritis or whether they must be considered epiphenomena of cellular damage in chronic inflammation.

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases. However, the pathophysiological mechanisms are still not fully understood and the etiology is simply unknown. Biomedical researchers have investigated various aspects of this intricate disease. Da Sylva and colleagues have now analyzed yet another piece in the 'RA-puzzle'. In a recent article in *Arthritis Research & Therapy*, this group analyzed the presence of mitochondrial DNA (mtDNA) mutations in patients with RA and their possible role in the pathogenesis of RA [1]. The sequencing of RNA transcribed from the mitochondrial *MT-ND1* gene showed a higher mutational burden (that is, changes per base pair) in RA cultured fibroblasts and RA tissue than in cells and tissue from patients with osteoarthritis (OA). More importantly, in RA tissue significantly more of these mutations resulted in non-synonymous amino acid changes than those in tissues of patients with OA.

Mutations in mtDNA have long been thought to have a role in the pathogenesis of various diseases. The 'classic' mitochondrial syndromes like Leigh syndrome or Leber's hereditary optic neuropathy are caused by inherited (germline) mutations of mtDNA. They comprise a wide spectrum of clinical symptoms that arise as a result of dysfunction of the mitochondrial respiratory chain, mostly affecting tissues that are highly dependent on oxidative metabolism such as the nervous system or the eye [2]. In contrast, tissue-specific accumulation of somatic (non-inherited) mtDNA mutations is best described in various types of cancer. Somatic mtDNA mutations have been found in breast cancer, colorectal cancer, renal cell carcinoma, malignant glioma and hematologic malignancies, to name only a few (reviewed in [3]). Furthermore, it was suggested that mtDNA mutations are involved in the development of cardiac disease [4] and neurodegenerative disorders such as Alzheimer's disease [5]. Finally, accumulated mtDNA mutations due to oxidative damage are considered to be responsible for one of the basic events of cellular life, aging itself [6].

The repeated detection of somatic mtDNA mutations in various diseases gives rise to the old 'chicken-and-egg' question. Do somatic mtDNA mutations actually provoke pathological states or should they be considered epiphenomena? In other words, why do somatic mtDNA mutations increase, and what consequences might they have? As a cause of the high incidence of somatic mutations in patients with RA, Da Sylva and colleagues suggest high levels of reactive oxygen species (ROS) followed by selective proliferation of synoviocytes that gained a survival advantage through the mutation. Several groups have demonstrated a role of ROS in RA by showing increased oxidative enzyme activity along with decreased levels of antioxidants and by confirming oxidative damage to hyaluronic acid, collagen and nuclear DNA [7]. Because Da Sylva and colleagues found no difference in the frequency of nuclear mutations (measured in a randomly chosen nuclear gene) between patients with RA and those with OA, they conclude that random damage, for example by ROS, cannot be the sole cause of mtDNA

MHC = major histocompatibility complex; MMP1 = matrix metalloproteinase 1; MnSOD = manganese superoxide dismutase; mtDNA = mitochondrial DNA; OA = osteoarthritis; RA = rheumatoid arthritis; ROS = reactive oxygen species.

mutations. The occurrence of nuclear mutations in RA has not yet been fully explained. Whereas some groups describe higher frequencies of mutations in p53 transcripts in RA than in OA [8], others could not detect any mutated p53 at all [9]. Data on mutations in the H-*ras* gene in arthritic synovium could not be verified later by the same group [10], and mutations in WISP3 were found at similar levels in patients with RA and in those with OA [11].

These examples suggest that the detection of nuclear mutations might depend on the patient groups, the inflammatory disease activity and the detection methods used. Another possible explanation for the greater damage of mtDNA in patients with RA might be limitations of DNA repair in mitochondria. It is feasible that increased DNA damage through ROS in RA can be compensated for in the nucleus by the upregulation of repair mechanisms, whereas in the mitochondria no such adjustment can take place. One study that analyzed the expression of mismatch repair enzymes in RA found upregulation of an enzyme responsible for the repair of large insertion/deletion mispairings and down-regulation of an enzyme mainly needed for single-base mispairings. The authors suggest that this could be a mechanism to shift protection from changes in single base pairs in favor of protection from major damage to DNA [12].

In assessing the expressed mutational burden – that is, mutations that will change mtND1 protein subunits – Da Sylva and colleagues found it to be higher in RA tissue than in OA tissue. This could mean that the changed protein actually contributes to the activated phenotype of synoviocytes in RA [13]. MtND1 is a subunit of complex I of the respiratory chain located at the inner mitochondrial membrane. Impairment of complex I leads to an increased production of superoxide [14]. As a scavenger system, manganese superoxide dismutase (MnSOD) catalyzes the reaction of superoxide to hydrogen peroxide. Most interestingly, MnSOD production can be stimulated by cytokines such as tumor necrosis factor-α. The resulting hydrogen peroxide might contribute to the elevated levels of matrix metalloproteinase 1 (MMP1) in RA through the upregulation of gene expression and activation of proenzymes [15].

Da Sylva and colleagues propose another mechanism for how somatic mtDNA mutations might contribute to the pathogenesis of RA. Using major histocompatibility complex (MHC) epitope prediction algorithms, the authors searched for possible epitope regions that were affected by the mutations. They found five mutated peptides in patients with RA that would potentially be presented by MHC II, but none in patients with OA. Again, this difference could indicate a characteristic feature of RA synoviocytes. The altered peptides might be recognized as non-self after presentation and lead to the initiation of an inflammatory response. However, neither this hypothesis nor the complex I impairment theory can explain how these mutational changes could possibly provide a survival advantage for the RA synoviocytes.

Conclusion

The detection of increased somatic mtDNA mutations in RA tissue is clearly intriguing and raises many questions that have yet to be analyzed. One question to be solved is whether these mutations are homoplasmic (that is, the mutation is found in all mitochondria of a cell) or heteroplasmic (that is, a cell can have a mixture of normal and mutated mtDNA copies). If they are heteroplasmic, it is questionable whether they actually affect mitochondrial function, because the normal mtDNA copies would rescue the cell from the loss of any mitochondrial gene product. If mutated peptides are presented and recognized as non-self, heteroplasmic mutations could substantially contribute to the pathogenesis of disease, but the initial question about the triggering factor of RA still remains unanswered. Do mtDNA mutations initiate the autoimmune reaction in RA, or are they a consequence of inflammatory damage to the cell? In future, in addition to further analysis of mitochondrial mutations, it would be worth looking at the functionality and the gene expression pattern of mitochondria to obtain a more complete picture of the role of mitochondria in health and disease.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Da Sylva TR, Connor A, Mburu Y, Keystone E, Wu GE: **Somatic mutations in the mitochondria of rheumatoid arthritis synoviocytes.** *Arthritis Res Ther* 2005, **7:**R844-R851.
2. DiMauro S, Schon EA: **Mitochondrial DNA mutations in human disease.** *Am J Med Genet* 2001, **106:**18-26.
3. Carew JS, Huang P: **Mitochondrial defects in cancer.** *Mol Cancer* 2002, **1:**9.
4. Hayakawa M, Hattori K, Sugiyama S, Ozawa T: **Age-associated oxygen damage and mutations in mitochondrial DNA in human hearts.** *Biochem Biophys Res Commun* 1992, **189:**979-985.
5. Corral-Debrinski M, Horton T, Lott MT, Shoffner JM, McKee AC, Beal MF, Graham BH, Wallace DC: **Marked changes in mitochondrial DNA deletion levels in Alzheimer brains.** *Genomics* 1994, **23:**471-476.
6. Shigenaga MK, Hagen TM, Ames BN: **Oxidative damage and mitochondrial decay in aging.** *Proc Natl Acad Sci USA* 1994, **91:**10771-10778.
7. Hitchon CA, El-Gabalawy HS: **Oxidation in rheumatoid arthritis.** *Arthritis Res Ther* 2004, **6:**265-278.
8. Yamanishi Y, Boyle DL, Rosengren S, Green DR, Zvaifler NJ, Firestein GS: **Regional analysis of p53 mutations in rheumatoid arthritis synovium.** *Proc Natl Acad Sci USA* 2002, **99:**10025-10030.
9. Kullmann F, Judex M, Neudecker I, Lechner S, Justen HP, Green DR, Wessinghage D, Firestein GS, Gay S, Scholmerich J, *et al.*: **Analysis of the p53 tumor suppressor gene in rheumatoid arthritis synovial fibroblasts.** *Arthritis Rheum* 1999, **42:**1594-1600.
10. Roivainen A, Zhu F, Sipola E, Yli-Jama T, Toivanen P: **Failure to verify H-ras mutations in arthritic synovium: comment on the article by Roivainen et al.** *Arthritis Rheum* 2001, **44:**2705.
11. Cheon H, Boyle DL, Firestein GS: **Wnt1 inducible signaling pathway protein-3 regulation and microsatellite structure in arthritis.** *J Rheumatol* 2004, **31:**2106-2114.
12. Lee SH, Chang DK, Goel A, Boland CR, Bugbee W, Boyle DL, Firestein GS: **Microsatellite instability and suppressed DNA repair enzyme expression in rheumatoid arthritis.** *J Immunol* 2003, **170:**2214-2220.
13. Ospelt C, Neidhart M, Gay RE, Gay S: **Synovial activation in rheumatoid arthritis.** *Front Biosci* 2004, **9:**2323-2334.
14. Pitkanen S, Robinson BH: **Mitochondrial complex I deficiency leads to increased production of superoxide radicals and induction of superoxide dismutase.** *J Clin Invest* 1996, **98:**345-351.
15. Nelson KK, Melendez JA: **Mitochondrial redox control of matrix metalloproteinases.** *Free Radic Biol Med* 2004, **37:**768-784.