Published in final edited form as:

Diabetes Metab Res Rev. 2016 October ; 32(7): 672–674. doi:10.1002/dmrr.2833.

Commentary: Mitochondrial DNA damage and loss in diabetes

Robert Gilkerson^{1,2,*}

¹Departments of Biology, The University of Texas Rio Grande Valley, Edinburg, TX, USA

²Clinical Laboratory Sciences, The University of Texas Rio Grande Valley, Edinburg, TX, USA

Abstract

This commentary discusses damage and loss of mitochondrial DNA (mtDNA) in type 2 diabetes mellitus from both the clinical and experimental perspectives. Increasingly, an array of studies in experimental models and patients suggests that the cellular stresses of insulin resistance in type 2 diabetes damage mtDNA, leading to loss of mitochondrial genetic content. As such, mtDNA is emerging as both a valuable monitoring tool and translational preventive target for metabolic disease.

Unlike nuclear DNA, mitochondrial DNA (mtDNA) typically exists in ~1000 copies per cell; however, this extranuclear DNA is particularly susceptible to damage and loss of genetic material in response to cellular stresses. Clinical and experimental model studies indicate that damage and loss of mtDNA are emerging as a molecular signature of metabolic diseases such as type 2 diabetes mellitus and obesity. The cellular stresses of diabetes appear to have major impact on the macromolecular organization of mtDNA within a range of tissues and cell types, causing defects in mtDNA maintenance, rather than somatic mutations in the mitochondrial genome. As such, mtDNA content may be a key tool in monitoring cellular damage in diabetes and related metabolic diseases, as well as a provocative translational target. In this issue, Zhou *et al.* examine mtDNA content in peripheral blood and its correlation with glucose, insulin, and β -cell function in a large clinical cohort, providing new insight into loss of mtDNA as a mechanism of diabetes at a population level.

Decreased mitochondrial function and gene expression have been widely shown in patients with type 2 diabetes, suggesting that mitochondrial dysfunction plays a role (whether causative, contributory, or collateral) in insulin resistance. Pathogenic mutations of mtDNA cause insulin resistance and maternally inherited diabetes [1,2], indicating that mtDNA-derived mitochondrial dysfunction may in fact be causative for T2DM, while decreased expression of nuclear and mtDNA-encoded genes [3] and diminished bioenergetic function [4] appear frequently in non-familial clinical studies. Recently, Stephens *et al.* found that mtDNA content is decreased in ‘exercise resistant’ diabetic patients: individuals with T2DM who failed to respond to exercise intervention. These non-responders ($n = 9$ patients) showed a dramatic decrease in mtDNA content in skeletal muscle relative to control exercise

*Correspondence to: Robert Gilkerson, The University of Texas Rio Grande Valley, 1201 West University Drive, Edinburg, TX 78539-2999, USA. robert.gilkerson@utrgv.edu.

Conflict of interest

The author has nothing to disclose.

responder, along with parallel decreases in metabolic gene expression, with diminished oxidative capacity in these individuals [5]. Prior to that, Hsieh *et al.* (2011) found that mtDNA was decreased in muscle, but actually increased in leukocytes of type 2 diabetic patients relative to non-diabetic controls [6]. These studies provided an exciting clinical exploration of diabetic impacts on mitochondrial content and function, albeit in limited sample size. Gianotti *et al.* (2008) found that decreased mtDNA content was correlated with insulin resistance in a relatively large cohort ($n = 175$) of adolescents [7]. In this issue, Zhou *et al.* explicitly examine mtDNA content and plasma glucose in a large cohort of control ($n = 200$), pre-diabetic ($n = 197$), and diabetic patients ($n = 159$). They find that decreased mtDNA content is strongly associated with lowered glucose-stimulated insulin secretion. Thus, loss of mtDNA content is linked with hyperglycemia and increased oxidative stress. Collectively, these studies, capped by the large-cohort findings of Zhou *et al.*, provide a critical clinical viewpoint of mtDNA damage, indicating that mtDNA is damaged and lost in a variety of tissues and cell types as a contributing mechanism of type 2 diabetes.

To explore the biology behind this emerging genetic defect, a range of whole-organism and cell-based models provide insight. A range of experimental findings indicate that diabetes-associated cell stresses including cytokines, inflammation, and oxidative insults cause loss of mtDNA content, rather than base-change mutations of mtDNA. These diabetic insults appear to disrupt the macromolecular packaging of mtDNA by its associated proteins, thus leading to loss of mitochondrial genetic material. Within the organelle, mtDNA associates with a variety of interacting proteins that help package, replicate, and transcribe the mitochondrial genome to integrate mtDNA into mitochondrial bioenergetic and signalling capabilities. Typically, one or two copies of mtDNA are packaged with their interacting factors into DNA–protein assemblies called nucleoids [8]. Nucleoid packaging ensures that mtDNA genetic content is efficiently distributed throughout the mitochondrial network of human cells. Transcription factor A, mitochondrial (TFAM) is the major mtDNA-binding factor responsible for this packaging function. TFAM, an HMG-box DNA binding protein, efficiently binds and compacts mtDNA [9,10], while additional nucleoid-associated proteins interact either directly or indirectly to mtDNA to contribute to replication and transcription, as well as holding the nucleoid in place via tethering interactions with the mitochondrial inner membrane [11]. In addition to mtDNA packaging and replication/transcription functions, a number of factors with key cellular signalling roles associate with the mitochondrial nucleoid, providing integration of mtDNA into both bioenergetics and crucial cell signalling pathways such as apoptosis and autophagy. As the principal mtDNA packaging and transcription factor, TFAM plays a key role in governing mtDNA copy number and maintenance. A growing body of evidence suggests that the inflammatory cytokines and oxidative insults intrinsic to insulin resistance disrupt the stability of mtDNA nucleoid packaging, resulting in the loss of mtDNA found in the clinical cohorts discussed above.

Hotamisligil *et al.* first demonstrated cytokine-mediated inflammation as a key mechanism of insulin resistance [12]. Subsequent research has extensively demonstrated that cytokine-mediated inflammation and oxidative stress is a major mechanism of insulin resistance associated with diabetes mellitus and obesity [13–15]. These cellular stressors appear to target mtDNA as a prime target. Shokolenko *et al.* showed that oxidative insults cause rapid

degradation of mtDNA, with strand breakage much more frequent than base-change mutation [16], while cytokines such as tumour necrosis factor- α (TNF- α) cause similar rapid loss of mtDNA content in a variety of cellular contexts [17,18], and appears to require the TNF- α -associated Toll-like receptors [19]. These findings are echoed by organismal studies that reveal loss of mtDNA content in models of metabolic disease [20] and heart failure [21], and are consistent with age-related loss of mtDNA in pancreatic islets [22] and the clinical analyses described above. While diabetic decreases in mitochondrial content and function have been demonstrated in a variety of clinical and experimental settings, it remains unclear whether mitochondrial dysfunction is causative, contributory, or collateral in regard to the development of insulin resistance. While type 2 diabetic patients were shown to have decreased mitochondrial content and function [4], and patients with inherited mtDNA mutation present with insulin resistance and maternally inherited diabetes mellitus [1], subsequent murine studies suggest that loss of mitochondrial function is not causative for insulin resistance [23,24].

Collectively, these clinical and experimental findings suggest that the cellular stresses intrinsic to diabetes cause damage and destabilization of mtDNA, resulting in loss of mtDNA content. Taken together, then, a collective model is emerging: the cytokine-mediated inflammatory and oxidative insults that drive insulin resistance and diabetic pathology have serious, direct impacts on the stability and maintenance of mtDNA within a wide range of cell and tissue contexts. These studies provoke a range of both basic and clinical questions, motivating exploration of the mechanistic steps in mtDNA destabilization at the macromolecular level, as well as the clinical dynamics of mtDNA loss in different cell and tissue types in diabetic patients. Moreover, these findings indicate that stabilization of mtDNA represents a new preventive translational axis for strategies to protect mtDNA from these cellular stresses. For example, over expression of the mtDNA-packaging TFAM protein protects against diabetic neuropathy in a mouse model [25]. As such, damage and loss of mtDNA content represent an emerging mechanism of diabetic pathology with opportunity for improved diagnosis, prevention, and improved patient outcomes in type 2 diabetes mellitus and related conditions.

Acknowledgments

Supported by 1SC3GM116669-01 from the National Institute of General Medical Sciences (NIH) and Diabetes Action Research and Education Foundation Grant 409 to RG.

References

1. Lindroos MM, Borra R, Mononen N, et al. Mitochondrial diabetes is associated with insulin resistance in subcutaneous adipose tissue but not with increased liver fat content. *J Inherit Metab Dis*. 2011; 34(6):1205–1212. [PubMed: 21556834]
2. Kadowaki T, Kadowaki H, Mori Y, et al. A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. *N Engl J Med*. 1994; 330(14):962–968. [PubMed: 8121460]
3. Mootha VK, Lindgren CM, Eriksson KF, et al. PGC-1 α -responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet*. 2003; 34(3):267–273. [PubMed: 12808457]

4. Ritov VB, Menshikova EV, Azuma K, et al. Deficiency of electron transport chain in human skeletal muscle mitochondria in type 2 diabetes mellitus and obesity. *Am J Physiol Endocrinol Metab.* 2010; 298(1):E49–E58. [PubMed: 19887598]
5. Stephens NA, Xie H, Johannsen NM, et al. A transcriptional signature of “exercise resistance” in skeletal muscle of individuals with type 2 diabetes mellitus. *Metabolism.* 2015; 64(9):999–1004. [PubMed: 26163877]
6. Hsieh CJ, Weng SW, Liou CW, et al. Tissue-specific differences in mitochondrial DNA content in type 2 diabetes. *Diabetes Res Clin Pract.* 2011; 92(1):106–110. [PubMed: 21281975]
7. Gianotti TF, Sookoian S, Dieuzeide G, et al. A decreased mitochondrial DNA content is related to insulin resistance in adolescents. *Obesity.* 2008; 16(7):1591–1595. [PubMed: 18451773]
8. Kopeck BG, Shtengel G, Xu CS, Clayton DA, Hess HF. Correlative 3D superresolution fluorescence and electron microscopy reveal the relationship of mitochondrial nucleoids to membranes. *Proc Natl Acad Sci U S A.* 2012; 109(16):6136–6141. [PubMed: 22474357]
9. Kaufman BA, Durisic N, Mativetsky JM, et al. The mitochondrial transcription factor TFAM coordinates the assembly of multiple DNA molecules into nucleoid-like structures. *Mol Biol Cell.* 2007; 18(9):3225–3236. [PubMed: 17581862]
10. Kanki T, Ohgaki K, Gaspari M, et al. Architectural role of mitochondrial transcription factor A in maintenance of human mitochondrial DNA. *Mol Cell Biol.* 2004; 24(22):9823–9834. [PubMed: 15509786]
11. Bogenhagen DF, Rousseau D, Burke S. The layered structure of human mitochondrial DNA nucleoids. *J Biol Chem.* 2008; 283(6):3665–3675. [PubMed: 18063578]
12. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science.* 1993; 259(5091):87–91. [PubMed: 7678183]
13. Feinstein R, Kanety H, Papa MZ, Lunenfeld B, Karasik A. Tumor necrosis factor- α suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates. *J Biol Chem.* 1993; 268(35):26055–8. [PubMed: 8253716]
14. Lee YS, Li P, Huh JY, et al. Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. *Diabetes.* 2011; 60(10):2474–2483. [PubMed: 21911747]
15. Nguyen MT, Satoh H, Favelyukis S, et al. JNK and tumor necrosis factor- α mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes. *J Biol Chem.* 2005; 280(42):35361–35371. [PubMed: 16085647]
16. Shokolenko I, Venediktova N, Bochkareva A, Wilson GL, Alexeyev MF. Oxidative stress induces degradation of mitochondrial DNA. *Nucleic Acids Res.* 2009; 37(8):2539–2548. [PubMed: 19264794]
17. Suematsu N, Tsutsui H, Wen J, et al. Oxidative stress mediates tumor necrosis factor- α -induced mitochondrial DNA damage and dysfunction in cardiac myocytes. *Circulation.* 2003; 107(10):1418–1423. [PubMed: 12642364]
18. Vadrot N, Ghanem S, Braut F, et al. Mitochondrial DNA maintenance is regulated in human hepatoma cells by glycogen synthase kinase 3 β and p53 in response to tumor necrosis factor α . *PLoS One.* 2012; 7(7):e40879
19. Suliman HB, Welty-Wolf KE, Carraway MS, et al. Toll-like receptor 4 mediates mitochondrial DNA damage and biogenic responses after heat-inactivated *E. coli*. *FASEB J.* 2005; 19(11):1531–1533. [PubMed: 15994412]
20. Liu J, Lloyd SG. High-fat, low-carbohydrate diet alters myocardial oxidative stress and impairs recovery of cardiac function after ischemia and reperfusion in obese rats. *Nutr Res.* 2013; 33(4):311–321. [PubMed: 23602249]
21. Ide T, Tsutsui H, Hayashidani S, et al. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts after myocardial infarction. *Circ Res.* 2001; 88(5):529–535. [PubMed: 11249877]
22. Cree LM, Patel SK, Pyle A, et al. Age-related decline in mitochondrial DNA copy number in isolated human pancreatic islets. *Diabetologia.* 2008; 51(8):1440–1443. [PubMed: 18528676]

23. Pospisilik JA, Knauf C, Joza N, et al. Targeted deletion of AIF decreases mitochondrial oxidative phosphorylation and protects from obesity and diabetes. *Cell*. 2007; 131(3):476–491. [PubMed: 17981116]
24. Holloszy JO. “Deficiency” of mitochondria in muscle does not cause insulin resistance. *Diabetes*. 2013; 62(4):1036–1040. [PubMed: 23520283]
25. Chandrasekaran K, Anjaneyulu M, Inoue T, et al. Mitochondrial transcription factor A regulation of mitochondrial degeneration in experimental diabetic neuropathy. *Am J Physiol Endocrinol Metab*. 2015; 309(2):E132–E141. [PubMed: 25944881]