HHS Public Access

Author manuscript

Free Radic Biol Med. Author manuscript; available in PMC 2015 April 29.

Published in final edited form as:

Free Radic Biol Med. 2011 May 15; 50(10): 1213–1214. doi:10.1016/j.freeradbiomed.2011.02.015.

Diabetic Neutrophil Mitochondrial Dysfunction: an Inflammatory Situation?

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Despite longstanding research into mechanisms of diabetes pathogenesis, detailed molecular understanding of immune cell dysfunction remains largely unknown. Classification of diabetes mellitus is typically divided into two categories: type 1 diabetes (**I**nsulin **D**ependent **D**iabetes **M**ellitus- IDDM) that encompasses autoimmune attack against pancreatic insulin producing beta cells thus requiring insulin therapy, and type 2 diabetes (**N**on-**I**nsulin **D**ependent **D**iabetes **M**ellitus- NIDDM) which encompasses a complex set of pathological features including peripheral tissue insulin resistance, impaired regulation of hepatic glucose production, and declining ß-cell function often leading to ß-cell failure. Importantly, type 2 diabetes is intimately linked to obesity due to the newly appreciated relationship between adipose tissue and immune cells which interact to elicit numerous pathophysiological responses such as, insulin receptor desensitization, elevated cytokine production, and dysfunctional glucose metabolism, all known to play an important role in the development and progression of type 2 diabetes [1, 2]. However, the molecular mechanisms involved in immune cell dysfunction during type 2 diabetes remain poorly understood. In this issue of Free Radical Biology and Medicine, a study by Hernadez-Mijares and colleagues examines the phenotype of type 2 diabetic polymorphonuclear leukocytes (PMN's) with respect to reactive oxygen species (ROS) generation and mitochondrial function revealing a novel and potentially important link between PMN mitochondrial dysfunction and redox imbalance during type 2 diabetes.

It is widely accepted that oxidative stress is an important pathophysiological mediator of diabetes development and progression along with associated complications [3]. Given the strong link between diabetes and obesity it stands to reason that increased caloric intake exceeding energy expenditure can lead to mitochondrial electron transport uncoupling permitting the formation of ROS, particularly superoxide anion and hydrogen peroxide (H_2O_2). ROS are known mediators of oxidative damage to cells that contribute to alterations of insulin/insulin receptor substrate signaling pathways leading to insulin resistance and inflammatory settings [4]. While ROS may be a common pathogenic factor for beta and endothelial cell dysfunction during type 2 diabetes, little specific clinical information exists regarding this relationship with circulating PMN's in type 2 diabetic patients. In the paper by Hernadez-Mijares et al, diabetic PMN's had reduced oxygen consumption that was associated with a clear increase in ROS formation. These data indicate that type 2 diabetic leukocytes have defective mitochondrial respiration contributing to intracellular oxidant

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formation. The authors also found that these diabetic PMN's contained decreased reduced glutathione and increased GSSG/GSH ratios highlighting redox imbalance.

Current experimental and clinical evidence indicates that chronic inflammatory responses are involved in development of type 2 diabetes wherein monocyte/macrophage activation in adipose tissue contributes in maintaining a pro-inflammatory response [5-8]. It has also been suggested that PMN's manifest increased respiratory burst upon stimulation and that this leukocyte type is important for oxidative stress and inflammation during diabetes [9, 10]. The study by Hernadez-Mijares and colleagues confirms these hypotheses as plasma TNF-α and IL-6 was significantly increased in type 2 diabetic patients. Importantly, increased inflammatory cytokine levels were associated with PMN oxidative stress and mitochondrial dysfunction highlighting immune cell activation concomitant with metabolic disease. However, it is not clear whether increased cytokine levels are linked or influenced by diabetic PMN's, which require further investigation.

Mitochondrial dysfunction in multiple tissues is known to play a role in diabetic pathophysiology and associated complications [11-14]. Specifically, mitochondrial dependent ROS formation may emanate from different sources including complex I and III. The authors' present data demonstrating that diabetic PMN's display a loss of mitochondrial membrane potential coupled with decreased complex I activity. These data together with measurements of ROS are novel and associated with distinct diabetic clinical parameters. First, these data represent significant changes in ROS production from a well controlled cohort of diabetic subjects that have not achieved ideal control of their disease according to the American Diabetes Association (ADA) recommended treatment guidelines of hemoglobin A1c (HbA1c) levels of ≤6.0%. The mean HbA1c in this study was 7.2 ±1.6 which is indicative of poor glycemic control and an index of insulin resistance (HOMA-IR) was also similarly increased. Second, diabetic patients also displayed dyslipidemia as well as elevated high sensitivity C reactive protein levels which are indicators of existing cardiovascular disease [15, 16]. Together, these data demonstrate that PMN mitochondrial dysfunction and redox imbalance are clearly associated with poorly controlled type 2 diabetic patients.

Oxidative stress activates numerous inflammatory pathways such as increased adhesion molecule, interleukin, and other cytokine expression (e.g. TNF-α and IFN-γ) as well as activation of immune signaling responses including phospholipase activity, MAP kinase, and STAT and TLR signaling pathways [17]. Furthermore, excess glucose and free fatty acids cumulatively affect inflammatory responses through oxidative stress which can be ameliorated by antioxidant treatment [18]. Given these facts, several questions arise from the current findings that could have significant impact on our understanding and eventual management of redox influenced inflammation during type 2 diabetes. Firstly, how dependent is type 2 diabetic PMN ROS production on mitochondrial dysfunction? An equally plausible source of ROS in PMN's is from NADPH oxidase (NOX) enzymes which have been implicated in priming of diabetic neutrophil oxidative burst involving premature p47phox subunit cell membrane translocation [19]. Additional studies examining NOX expression or activity versus mitochondrial dysfunction will provide important clinical information regarding sources of ROS during type 2 diabetes. Secondly, are diabetic PMN's

with altered redox status and mitochondrial dysfunction more sensitive to activation stimuli or more aggressive in their activation response? Hand and colleagues have reported that type 2 diabetic PMN's display more robust respiratory burst activation, yet it is not known whether other neutrophil functions would respond similarly [9]. Thirdly, to what extent do diabetic PMN's with mitochondrial dysfunction sustain chronic inflammatory responses including TNF-α, IL-6, and adipokine levels? Given the increasingly clear relationship between these cytokines [20], it is important to understand whether expression of these inflammatory cytokines is linked to neutrophil mitochondrial dysfunction and ROS production. Lastly, are these metabolic features of diabetic neutrophils a harbinger of eventual leukocyte dysfunction and death? Answers to these questions will provide essential information regarding the importance of neutrophil mitochondrial dysfunction during type 2 diabetic pathophysiological responses.

A significant strength of the current study lies in the fact that this clinical study was performed using a large cohort of type 2 diabetic subjects. Previous studies examining diabetic leukocyte responses performed studies with smaller cohorts (n=16-70), which provides limited conclusions and can skew experimental outcomes. This current study examined a much larger population of type 2 diabetics (n=182) and both the control and diabetic cohorts were well controlled with respect to anthropomorphic characteristics of type 2 diabetes with the exception being waist circumference, which one would expect to be larger in diabetic subjects. Additional clinical and metabolic characteristics also complete the clinical picture of the diabetic subjects who manifest PMN associated redox imbalance coupled with mitochondrial dysfunction. These details enable accurate comparison and understanding with that of previous studies while also providing a useful benchmark for future comparisons. In summary, given the growing interest in mitochondrial based antioxidant therapies [21, 22], this study and accompanying data help provide a foundation for further investigation into whether mitochondrial targeted therapy could be beneficial for immune dysfunction during type 2 diabetes.

Acknowledgments

C.G.K is the recipient of and American Diabetes Association basic science grant 1-10-BS-84 and NIH grant HL80482 and S.C.B. is funded by a fellowship from the Malcom Feist Cardiovascular Research Endowment, LSU Health Sciences Center-Shreveport.

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