This table documents apparent plagiarism in:

> Warda, J, and M. Han. 2008. Mitochondria, the missing link between body and soul: Proteomic prospective evidence. Proteomics, Epub ahead of print.

Passages from Warda and Han are shown on the left, and passages from these sources are shown on the right:

> Butterfield, D.A., M. Perluigi, and R. Sultana. 2006. Oxidative stress in Alzheimer's disease brain: New insights from redox proteomics. European Journal of Pharmacology 545: 39-50.
>
> Reddy, P.H. 2006. Mitochondrial oxidative damage in aging and Alzheimer's disease: implications for mitochondrially targeted antioxidant therapeutics. 2006. Journal of Biomedicine and Biotechnology, article 31372
>
> John, G.B., Y. Shang, L. Li, C. Renken, C. A. Mannella, J. M.L. Selker, L. Rangell, M. J. Bennett, and J. Zha. 2005. The mitochondrial inner membrane protein mitofilin D controls cristae morphology. Molecular Biology of the Cell 16: 1543-1554.
>
> McDonald, T., S. Sheng, B. Stanley, D. Chen, Y. Ko, R. N. Cole, P. Pedersen, and J. E. Van Eyk. 2006. Expanding the subproteome of the inner mitochondria using protein separation technologies: One- and two-dimensional liquid chromatography and two-dimensional gel electrophoresis. Molecular and Cellular Proteomics 5:2392-2411
>
> Mitochondrial Research and Innovation Group, University of Rochester Medical Center: http://www.urmc.edu/mrig/
>
> Finck, B.N., and D.P. Kelly. 2007. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) regulatory cascade in cardiac physiology and disease. Circulation 115: 2540-2548.
>
> Modica-Napolitano, J.S., and K.K. Singh. 2004. Mitochondrial dysfunction in cancer. Mitochondrion 4: 755-762.

In the comment thread at http://scienceblogs.com/pharyngula/2008/02/a_baffling_failure_of_peer_rev.php, commenter "Sili" first suggested that the style of the Warda and Han paper suggested it might be plagiarized; Ian York ("Ian") first noticed plagiarism of McDonald et al.; "RobertC" first noticed plagiarism of John et al.; and Lars Juhl Jensen first noticed the plagiarism of Finck and Kelly and the MRIG web page.

John H. McDonald
Department of Biological Sciences
University of Delaware
mcdonald@udel.edu
February 10, 2008

Warda and Han 2008	Butterfield et al. 2006
Oxidative stress is caused by an imbalance between the pro-oxidant and antioxidant systems, which may cause reversible and/or irreversible modifications on sensitive proteins leading to structural, functional, and stability modulations.	Oxidative stress is caused by an imbalance in the prooxidant and antioxidant systems. Oxidative stress may cause reversible and/or irreversible modifications on sensitive proteins leading to structural, functional and stability modulations.
Oxidative damage of proteins is one of the modifications leading to a severe failure of biological functions and cell death.	Oxidative damage of proteins is one of the modifications leading to a severe failure of biological functions and cell death.
Mitochondrial-born free radicals may directly oxidize amino acid residue sidechains (mostly histidine, arginine, and lysine residues) or cause damage of proteins by an adduction of products of glycoxidation and/or lipid peroxidation.	Free radicals may directly oxidize amino acid residue side-chains (mostly hystidine, arginine and lysine residues) and also lead to damage of proteins by an adduction of products of glycoxidation and/or lipid peroxidation.
Protein modifications such as carbonylation, nitration, and protein-protein cross-linking are generally associated with loss of function and may lead to either the unfolding and degradation of the damaged proteins or aggregation leading to accumulation as cytoplasmic inclusions, as observed in agerelated neurodegenerative disorders.	Protein modifications such as carbonylation, nitration, and protein-protein cross-linking are generally associated with loss of function and may lead to either the unfolding and degradation of the damaged proteins or aggregation leading to accumulation as cytoplasmic inclusions, as observed in age-related neurodegenerative disorders
Therefore, accumulation of oxidatively modified proteins disrupts cellular functions either by a loss of catalytic ability or by an interruption of regulatory pathways	Therefore, accumulation of oxidatively modified proteins disrupts cellular functions either by a loss of catalitic ability or by an interruption of regulatory pathways
In addition to a variety of new approaches, proteomics still relies heavily on 2-DE as the underlying separation technology. This technique uses the power of both IEF and SDS-PAGE to separate proteins firstly by their pI and then by their relative mobility.	In addition to a variety of new approaches, proteomics still relies heavily on twodimensional electrophoresis as the underlying separation technology. This technique uses the power of both isoelectric focusing and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) to separate proteins firstly by their isoelectric point and then by their relative mobility
The expression profile, on the other hand, can be traced by labeling a mixture of two samples with different isotopes that bind to specific amino acid side-chains. The resulting isotopic labeled sample is further analyzed by MS. This technique is referred to as isotopically coded affinity tags (ICAT)	Alternatively, expression profiling can also be obtained by labeling a mixture of two samples with different isotopes that bind to specific amino acid side-chains. The resulting isotopic labeling is further analyzed by a mass spectrometer. This technique is referred as isotopically coded affinity tags (ICAT)

The gel-separated proteins are digested into peptides by specific proteases, and an eluted peptide mixture is acquired.	First, the gel-separated proteins are digested into peptides by specific proteases, and an eluted peptide mixture is acquired.
Database search programs can create theoretical PMFs for all the proteins in the database, and compare them with those obtained experimentally. ESI yields partial amino acid sequences from the peptides (sequence tags). Database searches are then performed using both molecular weight and sequence information. PMF is usually obtained with MALDI-TOF, and sequence tags by nano-ESI MS/MS. The sensitivity of protein identification by MS is in the femtomole range. The identification of a protein from its peptide sequence derived from the mass spectrum has been facilitated by the development of proteomics databases. The first major protein database was Swiss-Prot, which allows protein identification by using online freely accessible computer algorithms. These search engines provide a theoretical protease digestion of the proteins contained in the database. Comparison of the resulting theoretical peptide masses to the experimental masses obtained from the in-gel digested proteins leads to protein identification. Several factors have to be considered to obtain correct protein identification, such as the protein size and the probability of a single peptide occurring in the whole database. The search engines produce a probability score for each entry, which is calculated by a mathematical algorithm specific for each search engine. Any hit with a score higher than that of statistical significance from the search engine is considered statistically significant and has an excellent chance of being the protein cut from a given spot. In addition, the molecular weight and the pI of the protein are calculated based on the position in the 2-D map to avoid any false identification.	Database search programs can create theoretical PMFs for all the proteins in the database, and compare them to those obtained experimentally. ESI yields partial amino acid sequences from the peptides (sequence tags). Database searches are then performed using both molecular weight and sequence information. PMF is usually obtained with MALDI-TOF, and sequence tags by nano-ESI tandem mass spectrometry (MS/MS). The sensitivity of protein identification by MS is in the femtomole range. The identification of a protein from its peptide sequence derived from the mass spectrum has been facilitated by the development of proteomics databases. The first major protein database was Swiss-Prot, which allows protein identification by using computer algorithms freely accessible online. These search engines provide a theoretical protease digestion of the proteins contained in the database. Comparison of the resulting theoretical peptide masses to the experimental masses obtained from the ingel digested proteins leads to protein identification. Several factors have to be considered to obtain correct protein identification, such as the protein size and the probability of a single peptide to occur in the whole database. The search engines produce a probability score for each entry, which is calculated by a mathematical algorithm that is specific for each search engine. Any hit with a score higher then that for statistical significance from the search engine is considered statistically significant and has an excellent chance to be the protein cut from a given spot. In addition, the molecular weight and the pI of the protein are calculated based on the position in the 2-dimensional map to avoid any false identification.

Warda and Han 2008	Reddy 2006
ROS generation has been shown to increase in mitochondria under conditions of excess electrons (e.g., increased caloric intake) or as a result of several cellular insults, including ultraviolet irradiation, redox-cycling of quinones, the metabolism of xenobiotics , aging, environmental mitochondrial toxins, and mutant toxic proteins (e.g., Ab in AD, mutant huntingtin in Huntington's disease, alpha-synuclein in PD, mutant SOD1 in amyotrophic lateral sclerosis)	The generation of free radicals can occur via several cellular insults, including ultraviolet irradiation, redox-cycling of quinones, the metabolism of xenobiotics, aging, environmental mitochondrial toxins, and mutant toxic proteins (eg, A[beta] in AD, mutant huntingtin in Huntington's disease, alpha-synuclein in Parkinson's disease, mutant SOD1 in amyotrophic lateral sclerosis)

The chronic exposure of ROS to cells can result in oxidative damage to mitochondrial and cellular proteins, lipids, and nucleic acids, and acute exposure to ROS can inactivate the TCA cycle aconitase and the iron-sulfur centers of ETC at complexes 1, 2, and 3, resulting in a shutdown of mitochondrial energy production	The chronic exposure of ROS to cells can result in oxidative damage to mitochondrial and cellular proteins, lipids, and nucleic acids, and acute exposure to ROS can inactivate the TCA-cycle aconitase and the iron-sulfur centers of ETC at complexes 1, 2, and 3, resulting in a shutdown of mitochondrial energy production.
Compared to other organs, the brain has been found to be more vulnerable to oxidative stress due to its high lipid content, with more liability to lipid in a relatively high-oxygen metabolic environment, and low level of antioxidant defenses	Compared to other organs, the brain has been found to be more vulnerable to oxidative stress due to its high lipid content, its relatively high oxygen metabolism, and its low level of antioxidant defenses
Soluble or insoluble forms of Ab have been suggested to impair ATP production by generating defects in mitochondrial energy metabolism and oxidative stress, which suggests that oxidative stress is a key event in AD pathogenesis and other kinds of dementia.	Soluble or insoluble forms of A[beta] have been suggested to impair ATP production by generating defects in mitochondrial energy metabolism and oxidative stress. Taken together, these results suggest that oxidative stress is a key event in AD pathogenesis.

However, until recently, a major limitation in developing antioxidant therapies has been the inability to enhance antioxidant levels in mitochondria. Consequently, new versions of mitochondria-targeted antioxidants have been developed, which preferentially enter the mitochondria at several hundred-fold more than natural antioxidants where they rapidly neutralize free radicals and decrease mitochondrial toxicity. To make a breakthrough, however, further research is needed to determine whether these mitochondria-targeted antioxidants can be used in mouse models of aging and in age-related neurodegenerative diseases such as AD, PD, and Huntington's disease	However, until recently, a major limitation in developing antioxidant therapies for AD patients has been the inability to enhance antioxidant levels in mitochondria. There has been a breakthrough in the mitochondrial targeting of antioxidants. Mitochondrially targeted antioxidants have been developed, which preferentially enter the mitochondria--at several hundred-fold more than they enter natural antioxidants--where they rapidly neutralize free radicals and decrease mitochondrial toxicity. However, further research is needed to determine whether these mitochondrially targeted antioxidants can be used in mouse models of aging and in age-related neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's.
Warda and Han 2008	**John et al. 2005**
Although the molecular basis of cristae morphogenesis is not completely understood, there is increasing evidence that the mitochondrial fission and fusion machinery plays an important role in this process. OPA1/Mgm1, a large dynamin-like GTPase, is located in the intermembrane space, where its down-regulation results in altered cristae architecture and dissipation of the mitochondrial membrane potential structure	Although the molecular basis for cristae morphogenesis is still unknown, there is increasing evidence that the mitochondrial fission and fusion machinery plays an important role in this process. OPA1/Mgm1, a large dynamin-like GTPase, is located in the intermembrane space, the same submitochondrial compartment where mitofilin resides.

Logically, there is a connection between the disrupted mitochondrial morphology and the progression of neurodegenerative diseases, since comparative proteomic analysis of the cerebral cortex of a seizure-sensitive strain of gerbil and its seizure-resistant counterpart revealed a marked difference in the pI of mitofilin between the two strains . Another supportive study on cortical brain samples of fetal Down syndrome showed a double-fold reduction of mitofilin, highlighting its contribution as a mitochondrial protein in the development of this syndrome	Comparative proteomic analysis of the cerebral cortex of a seizuresensitive strain of gerbil and its seizure-resistant (SR) counterpart revealed that gerbil mitofilin showed consistent differences in their isoelectric point between the two strains (Omori et al., 2002). Sequence analysis of mitofilin cDNAs showed several mutations in the SR strains, including one that resides within a conserved region immediately carboxyl terminal of the membrane-anchoring domain. A recent study in cortical brain samples of fetal Down syndrome showed a double-fold reduction of mitofilin, highlighting its importance for normal mitochondrial function (Myung et al., 2003).
Warda and Han 2008	**McDonald et al. 2006**
Nevertheless, due to the large number of unique protein species along with the difference in their relative abundance, there is no single proteomics technology yet that has the full analytical capacity or sensitivity to realize the goal of complete mitochondrial proteome coverage.	Due to the large number of unique protein species produced coupled with differences in their relative abundance, there is as of yet no single proteomics technology that has the analytical capacity or sensitivity to realize the goal of complete proteome coverage.
The 2-DLC technique traditionally couples a charge-based method (e.g., IEF or strong cation exchange) as a first dimension with RP-HPLC as the second dimension, thereby increasing the extent of protein fractionation compared with 1-DLC.	2-DLC traditionally couples a chargebased method (e.g. isoelectric focusing or strong cation exchange) as a first dimension with RP-HPLC as the second dimension thereby increasing the extent of protein fractionation compared with 1-DLC.

Although intact mitochondria have been studied using different proteomics technologies and the isolation protocol is well established the obtained data comprise only part of the estimated 697-4532 total mitochondrial proteins. However, because these estimations can have a false discovery rate of up to 68%, the absolute number of mitochondrial proteins is not currently known. A problem with the existing mitochondrial databases derived from proteomics analysis is the bias toward proteins localized to the matrix and outer membrane and the lack of IMM-associated proteins. To increase the coverage of the IMM subproteome, McDonald et al. used an enriched IMM preparation and demonstrated that there are novel proteins within this subproteome. Using the same well characterized IMM preparation tested, there was minimal overlapping of observed proteins when using three different separation technologies (2-DE, 1-DLC, and 2-DLC), thereby expanding proteome coverage.	Although intact mitochondria have been studied using different proteomics technologies, these databases comprise only part of the estimated 697- 4532 total mitochondrial proteins. However, because these estimations can have a false discovery rate of up to 68% , the absolute number of mitochondrial proteins is not currently known. A problem with the existing mitochondrial databases derived from proteomics analysis has been the bias toward proteins localized to the matrix and outer membrane and the lack of IMM-associated proteins. To increase the coverage of the IMM subproteome, Da Cruz et al. used an enriched IMM preparation and demonstrated that there are novel proteins within this subproteome. Using the same well characterized IMM preparation we tested the hypothesis that there would be a minimal overlap of observed proteins when using three different separation technologies (2-DE, 1-DLC, and 2-DLC) thereby expanding proteome coverage.

Currently the database of McDonald and coworkers contains 286 proteins not in the former database and 134 proteins not observed in any of these extensive databases. This difference is likely due to both the enrichment of the IMM proteins prior to analysis and the increased resolving power of separating proteins based on a variety of physical characteristics. The majority of these proteins were observed only using 1-DLC, suggesting the promising use of this method for the future discovery of novel proteins in a subproteome.	Our database contains 286 proteins (82% of combined database) not in this database and 134 proteins not observed in any of these extensive databases (39% of the combined protein database). This difference is likely due to both the enrichment of the IMM proteins prior to analysis and the increased resolving power of separating proteins based on a variety of physical characteristics. The majority of these proteins were observed only using 1-DLC (96 proteins; 72%) suggesting that this is a useful technology to use for the discovery of novel proteins in a subproteome.

Warda and Han	Finck and Kelly
Emerging evidence supports the notion that derangements in mitochondrial energy metabolism contribute to cardiac dysfunction. For example, human mitochondrial DNA mutations resulting in global impairment in mitochondrial respiratory function cause hypertrophic or dilated cardiomyopathy and cardiac conduction defects. Mutations in nuclear genes encoding mitochondrial fatty acid oxidation enzymes may also manifest as cardiomyopathy. Interestingly, cardiomyopathies resulting from inborn errors in mitochondrial fatty acid oxidation enzymes are often provoked by physiological or pathophysiological conditions that increase dependence on fat oxidation for myocardial ATP production such as prolonged exercise or fasting associated with infectious illness. A causal relationship between mitochondrial dysfunction and cardiomyopathy is also evidenced by several genetically engineered mouse models. Targeted deletion of the adenine nucleotide translocator 1, which transports mitochondrially generated ATP to the cytosol, leads to mitochondrial dysfunction and cardiomyopathy. Mice with cardiac-specific deletion of the transcription factor of activated mitochondria, which controls transcription and replication of the mitochondrial genome, also exhibit marked impairments in mitochondrial metabolism, severe cardiomyopathy, and premature mortality. Cardiomyopathy and/or conduction defects are also observed in several mouse models with targeted deletion of specific fatty acid oxidation enzymes.	However, emerging evidence, including observations of the phenotypic expression of genetic defects in humans and animal models, supports the notion that derangements in mitochondrial energy metabolism contribute to cardiac dysfunction. For example, human mitochondrial DNA mutations resulting in global impairment in mitochondrial respiratory function cause hypertrophic or dilated cardiomyopathy and cardiac conduction defects. Mutations in nuclear genes encoding mitochondrial fatty acid oxydation enzymes may also manifest as cardiomyopathy. Interestingly, cardiomyopathies resulting from inborn errors in mitochondrial fatty acid oxydation enzymes are often provoked by physiological or pathophysiological conditions that increase dependence on fat oxidation for myocardial ATP production such as prolonged exercise or fasting associated with infectious illness. A causal relationship between mitochondrial dysfunction and cardiomyopathy also is evidenced by several genetically engineered mouse models. Targeted deletion of the adenine nucleotide translocator 1, which transports mitochondrially generated ATP to the cytosol, leads to mitochondrial dysfunction and cardiomyopathy. Mice with cardiac-specific deletion of transcription factor of activated mitochondria, which controls transcription and replication of the mitochondrial genome, also exhibit marked impairments in mitochondrial metabolism, severe cardiomyopathy, and premature mortality. Cardiomyopathy and/or conduction defects also are observed in several mouse models with targeted deletion of specific FAO enzymes.
Warda and Han	**MRIG**
Mitochondria are the gatekeepers of the life and death of most cells in the body and regulate signaling, metabolism, and energy production needed for cellular function.	Mitochondria are the gatekeepers of the life and death of most cells that regulate signaling, metabolism, and energy production needed for cellular function.

Recent scientific studies show that mitochondrial dysfunction is more commonplace for the development of many pathological events than previously thought. Mitochondrial dysfunction is now implicated in a wide range of human diseases, including aging, diabetes, atherosclerosis, heart failure, myocardial infarction, stroke and other ischemic- reperfusion injuries, neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD), cancer, HIV, sepsis, and trauma with multiorgan dysfunction or failure. Some rare mitochondrial diseases (e.g., MELAS, Kearns-Sayre) are associated with an altered mitochondrial genome and/or proteome. Mitochondrial abnormality is generally prominent in sites with high-energy dependency. More recently, the so-called OXPHOS diseases that reflect a limited capacity to produce the energy needed to respond to normal stress conditions have been described.	Recent scientific studies show that mitochondrial dysfunction is more commonplace than previously thought and that substantial mitochondrial involvement is present in many acute and chronic diseases. Mitochondrial dysfunction is now implicated in a range of human diseases, including aging, diabetes, atherosclerosis, heart failure, myocardial infarction, stroke and other ischemic-reperfusion injuries, neurodegenerative diseases including Alzhiemer's and Parkinson's diseases; cancer, HIV; sepsis and trauma with multiorgan dysfunction or failure. Some rare mitochondria diseases (e.g., MELAS, Kearns-Sayre) are associated with large deletions in the mitochondrial genome. More recently, the so-called OXPHOS diseases that reflect a limited capacity to produce the energy needed to respond to normal stress conditions, were associated with genetically determined deficiencies in mitochondrial energy production
Warda and Han	**Modica-Napolitano et al.**
With an estimated 1000 different mitochondrial proteins, advances in proteomic technologies have made the quantitative analysis of protein expression in mitochondria possible. A mitochondrial proteomic database has recently been established by the National Institutes of Standards and Technology. Research efforts to obtain mitochondrial protein profiles in normal and cancer cells will undoubtedly lead to identification of markers for clinical detection of cancer, and contribute to an understanding of how differential protein expression might influence the development of the disease	It is estimated that 1000 different proteins comprise mitochondria. Advances in proteomic technologies have made possible the quantitative analysis of protein expression in mitochondria, and a mitochondrial proteomic database has recently been established by the National Institutes of Standards and Technology. Research efforts to obtain mitochondrial protein profiles in normal and cancer cells will undoubtedly lead to identification of markers for clinical detection of cancer, and contribute to an understanding of how differential protein expression might influence the development of the disease.