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Parkin in the regulation of fat uptake and mitochondrial biology emerging links in the pathophysiology of Parkinson's Disease

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Abstract

Purpose of review—Perturbations in fatty acid levels and in regulatory proteins linked to fat and mitochondrial homeostasis are associated with modifying the risk of Parkinson Disease (PD). Findings, that are not surprising, based on the high fat content of the brain, the myriad of neurological functions dependent on polyunsaturated fatty acids and the role of mitochondria in energy supply and stress amelioration. Nevertheless, dissecting out the molecular links between lipid biology, mitochondrial regulation and PD is complicated by the divergent etiologies underpinning PD pathophysiology. Here, we summarize aspects of fatty acid biology relevant to PD; the known links between the modulation of fat and PD; and introduce mechanisms whereby the E3-ubiquitin ligase, Parkin know to be mutated as a genetic predisposing factor in PD, modulates fat uptake and mitochondrial control.

Recent Findings—Prior evidence supports that Parkin, under mitochondrial stress conditions, plays a pivotal role in the mitophagy mitochondrial housekeeping program. Recent evidence now demonstrates a broader role of Parkin in controlling fat uptake and mitochondrial regulatory programs.

Summary—The identification that Parkin has a multifunctional role in modulating cellular fatty acid uptake and mitochondrial biology further strengthens the pathophysiologic link between fat metabolism, mitochondria, and Parkinson Disease.

Keywords

Parkin; CD36; fat uptake; PGC-1 α

Introduction

The objective of this review is to highlight evidence supporting the concept that dysfunction in the regulation in lipid biology and mitochondrial homeostasis may be operational in the development of Parkinson's disease (PD). As background, PD is caused by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), a region in the midbrain

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Conflict of Interest

No conflicts of interest to report.

important for modulating motor control. The disease is largely sporadic and degenerative in nature, although underlying genetic predisposing factors are being identified. Autosomal recessive and dominant genetic defects account for approximately 2% of sporadic onset PD (presenting at $\approx$ 70 years of age) and for $\approx$ 50% of patients that present with early onset PD (EOPD), presenting prior to the age of 40 years (reviewed [1]). A common pathological feature of sporadic and alpha-synuclein mutation associated PD is the presence of abnormal cytoplasmic inclusions, called Lewy bodies. The relevance of lipid biology in Lewy body associated PD will be briefly expanded upon in this review.

Another subset of EOPD patients, with autosomal recessive loss-of-function mutation/s in *PARK2*, a gene encoding the Parkin protein, is linked to disruption in mitochondrial homeostasis with increased susceptibility to cellular redox stress [1]. Here, the pathophysiology appears to be independent of Lewy body cytopathies [2]. Data linking *PARK2* mutations with lipid homeostasis and mitochondrial regulatory programs are the major new findings discussed in this review. Although additional genetic defects associate with PD, these are not described here as the role of lipid perturbations in their pathophysiology has not been ascertained.

Prior to reviewing the potential role of lipid metabolism in PD, it is interesting to note that a recent meta-analysis of gene-discovery studies suggest that metabolic programs controlled by the transcriptional coactivator peroxisome proliferator activated receptor gamma co-activator 1 alpha (PGC-1 α) are blunted early on in the development of PD [3]. Although not directly explored in that meta-analysis [3], PGC-1 α is a pivotal transcriptional mediator of lipogenesis, fat oxidation and mitochondrial homeostasis [4, 5].

Fatty acid metabolism in the brain and links to PD risk

As the brain is highly enriched in fatty acids and cholesterol, it is not surprising that perturbations in lipid levels is associated with the development of a multitude of developmental and degenerative neurological diseases (reviewed [6]). Lipids, of which about 1/3 is made up of long chain polyunsaturated fatty acids (LCPUFA), constitute > 50% of the adult brain dry weight. The role of LCPUFA in neuronal homeostasis has been reviewed [7]), and only aspects implicated in the pathophysiology of PD are addressed here. In brief, neuronal LCPUFA levels are determined, in large part, via dietary intake, are found to be important in brain development, and diminish in the aging brain. LCPUFA are essential for the brain due to their requirement for *de novo* neuronal biosynthesis of saturated and monounsaturated fatty acids. LCPUFA also play important roles in neuronal membrane fluidity, in cell signaling via phospholipase mediated generation of eicosanoid signaling intermediates and as potential anti-oxidant buffers [7]. Also, the phospholipid and glycerophospholipid content of mitochondria, organelles implicated in the pathophysiology of numerous mutations associated with EOPD, are instrumental in maintaining mitochondrial integrity and function [8].

The mechanisms of LCPUFA uptake or transport across the blood brain barrier has not been fully characterized, although intramembranous fatty acid transport proteins (FATP) and intracellular fatty acid binding proteins have been implicated in this process [9]. Recent data

show that FATP4, FATP5 and the fatty acid translocase/CD36 are the predominant transporters of LCPUFA across the blood brain barrier [10]. The redundancy in these transporters may explain, in part, the subtle brain phenotype following the genetic ablation of distinct brain enriched fatty acid transporters, as demonstrated in the CD36 knockout mice [11]. In that study, the loss of CD36 did not disrupt LCPUFA levels, but resulted in reduced brain monounsaturated fatty acid levels [11].

Turning to PD itself, emerging data illustrate potential complexity in the interplay between lipid homeostasis and the pathophysiology of PD. On the one hand, epidemiologic data suggest that lower circulating levels of both cholesterol and fatty acids increase the risk of PD [12–14] and that high dietary intake of omega-3 LCPUFA decreased PD risk [15]. On the other hand, elevated PUFA levels promote the formation of insoluble α -synuclein aggregates, an integral component of Lewy inclusion bodies [16] and elevated PUFA levels have been found in association with Lewy body formations in brain biopsies from PD subjects [17].

The role of Parkin mutations in increasing PD susceptibility

Parkin is an E3-ubiquitin ligase, which has been identified to mediate classical as well as non-classical ubiquitin linkages to facilitate proteasome-dependent and independent effects [18–21]. Parkin is predominantly localized in the cytoplasm, with evidence of nuclear effects [22], and localization to the outer mitochondrial membrane in response to mitochondrial ‘stress’ [23, 24]. Numerous Parkin substrates have been identified in these distinct subcellular locations [25, 26]. The role of Parkin in the modulation of these substrates continues to be explored although our understanding of their links to the pathophysiology of PD needs further clarification. Additionally, experimental in-vivo models suggest that Parkin mutations and the genetic deletion of Parkin function to enhance susceptibility to the development of PD, rather than being primarily causative [27–30].

To date, the most prevalent hypothesis as to the mechanism underpinning Parkin mediated control of susceptibility to PD is attributed to the role of Parkin in controlling the mitochondrial housekeeping program of mitophagy (reviewed [31]). Here, Parkin is shown to localize to mitochondria during the initiation of mitophagy in response to ‘mitochondrial-stress’ conditions. However, as additional substrates of Parkin are being identified, implications for a broader role of Parkin in modulating PD susceptibility are being uncovered. Recent studies, showing roles of Parkin in the regulation of fat uptake and in an additional mitochondrial regulatory program, are described below.

Parkin is lipid responsive and enhances stability of the fatty acid translocase CD36

It had previously been recognized that Parkin knockout mice displayed slower weight gain in the months to years prior to evidence of neurological or mitochondrial deficits [32]. To directly address this biology, wildtype and Parkin knockout mice were challenged with a high-fat diet [33]. Parkin knockout mice were found to be resistant to weight gain, to hepatosteatosis and to insulin resistance. This phenotype was not due to alterations in

appetite, activity or global mitochondrial function. In wildtype mice the high-fat diet resulted in marked induction of Parkin levels in multiple tissues and Parkin was found to play a pivotal role in facilitating fat uptake by enhancing the stability of the fatty acid translocase CD36 [33]. This increased stability of CD36 appeared to result from Parkin mediated monoubiquitination of this transport protein. In parallel with these findings, transformed cells from patients with Parkin mutations similarly showed diminished fat uptake and Parkin knockout mouse embryonic fibroblasts resisted fat accumulation during differentiation into adipocytes [33]. Although fat uptake in the brain was not directly assessed in this study, Parkin and CD36 levels increased in parallel in wildtype mice brain in response to high-fat feeding. The link between fat uptake and PD in this model has not been delineated, although it would be intriguing to explore, especially since epidemiologic evidence suggests increased PD susceptibility in individuals with low circulating levels of fatty acids [13].

Parkin modulates brain PGC-1 α levels

Recently PARIS, a member of the family of Kruppel-associated box zinc-finger proteins - a major transcriptional repressor of PGC-1 α , was identified as a Parkin substrate [34]. Here, Parkin ubiquitinated and targeted PARIS for proteosomal degradation with the resultant induction of PGC-1 α levels. In mice, the acute conditional KO of Parkin in the SNc led to progressive loss of dopamine neurons in parallel with increased PARIS and diminished PGC-1 α levels. These alterations in PARIS and PGC-1 α levels were similarly found in human brain tissue from patients with sporadic PD compared with age-matched controls. Interestingly the reduction in PGC-1 α levels in these subjects with sporadic PD, reconcile with the previous meta-analysis described in the introduction of this review [3]. However, an unresolved issue here, is why sporadic PD subjects have similar PGC-1 α levels to those found in Parkin knockout mice? This paradox is further complicated by the findings in a recent study assessing PGC-1 α levels in primary skin fibroblasts from an EOPD family with Parkin mutations compared to controls. Here, levels of PGC-1 α were elevated, rather than reduced, albeit in association with mitochondrial dysfunction [35]. In this study, the higher levels of PGC-1 α did not transactivate known peroxisome-proliferator-activated-receptor target genes, questioning whether despite higher levels, the activity of PGC-1 α was nevertheless impaired. An additional obvious difference between the sporadic and familial PD subjects were the different tissue types assayed. Nevertheless, these findings regarding the alteration of a pivotal regulatory protein controlling mitochondrial homeostasis is additional evidence supporting that mitochondrial dysfunction may play a role in the development of or susceptibility to PD.

Conclusion

Whether the pathophysiology of sporadic degenerative PD overlaps with *PARK2* mutation associated increasing susceptibility to EOPD has not been completely established. From a clinical and pathologic perspective, clear differences do exist, including the lower incidence of Lewy bodies and dementia and the markedly earlier age of onset in the *PARK2* mutation associated EOPD. Nevertheless, similarities are being uncovered with respect to the role of perturbations in the control of lipid biology and the regulation of mitochondrial homeostasis

in modifying risk for the development of PD. Additional aspects of lipid biology may also be operational in this pathophysiology, although these require additional investigation [26]. Taken together, the fact that regulatory programs modulating fat and mitochondrial homeostasis are emerging as candidate programs in modulating PD disease susceptibility is advancing our understanding of this disease process. In addition, these findings may provoke further research into dietary interventions and into metabolic and mitochondrial modulators in delaying the onset of, or diminishing the risk of PD.

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References

1. Obeso JA, Rodriguez-Oroz MC, Goetz CG, et al. Missing pieces in the Parkinson's disease puzzle. *Nat Med.* 2010; 16:653–661. [PubMed: 20495568]
2. Ahlskog JE. Parkin and PINK1 parkinsonism may represent nigral mitochondrial cytopathies distinct from Lewy body Parkinson's disease. *Parkinsonism Relat Disord.* 2009; 15:721–727. [PubMed: 19815446]
- 3*. Zheng B, Liao Z, Locascio JJ, et al. PGC-1 α , a potential therapeutic target for early intervention in Parkinson's disease. *Sci Transl Med.* 2010; 2:52ra73. This meta-analysis links the downregulation of PGC-1 α to the risk of developing PD.
4. Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α): transcriptional coactivator and metabolic regulator. *Endocr Rev.* 2003; 24:78–90. [PubMed: 12588810]
5. Summermatter S, Baum O, Santos G, et al. Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) promotes skeletal muscle lipid refueling in vivo by activating de novo lipogenesis and the pentose phosphate pathway. *J Biol Chem.* 2010; 285:32793–32800. [PubMed: 20716531]
6. Bazan NG, Molina MF, Gordon WC. Docosahexaenoic Acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. *Annu Rev Nutr.* 2011; 31:321–351. [PubMed: 21756134]
7. Lauritzen L, Hansen HS, Jorgensen MH, Michaelsen KF. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res.* 2001; 40:1–94. [PubMed: 11137568]
8. Houtkooper RH, Vaz FM. Cardiolipin, the heart of mitochondrial metabolism. *Cell Mol Life Sci.* 2008; 65:2493–2506. [PubMed: 18425414]
9. Owada Y. Fatty acid binding protein: localization and functional significance in the brain. *Tohoku J Exp Med.* 2008; 214:213–220. [PubMed: 18323691]
10. Mitchell RW, On NH, Del Bigio MR, et al. Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells. *J Neurochem.* 2011; 117:735–746. [PubMed: 21395585]
11. Song BJ, Elbert A, Rahman T, et al. Genetic ablation of CD36 does not alter mouse brain polyunsaturated fatty acid concentrations. *Lipids.* 2010; 45:291–299. [PubMed: 20306148]
12. Huang X, Abbott RD, Petrovitch H, et al. Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study. *Mov Disord.* 2008; 23:1013–1018. [PubMed: 18381649]
13. de Lau LM, Bornebroek M, Witteman JC, et al. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology.* 2005; 64:2040–2045. [PubMed: 15985568]
14. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum cholesterol levels and the risk of Parkinson's disease. *Am J Epidemiol.* 2006; 164:998–1002. [PubMed: 16905642]

15. Bousquet M, Calon F, Cicchetti F. Impact of omega-3 fatty acids in Parkinson's disease. *Ageing Res Rev.* 2011; 10:453–463. [PubMed: 21414422]
16. Assayag K, Yakunin E, Loeb V, et al. Polyunsaturated fatty acids induce alpha-synuclein-related pathogenic changes in neuronal cells. *Am J Pathol.* 2007; 171:2000–2011. [PubMed: 18055555]
17. Sharon R, Bar-Joseph I, Mirick GE, et al. Altered fatty acid composition of dopaminergic neurons expressing alpha-synuclein and human brains with alpha-synucleinopathies. *J Biol Chem.* 2003; 278:49874–49881. [PubMed: 14507911]
18. Lim KL, Chew KC, Tan JM, et al. Parkin mediates nonclassical, proteasomal-independent ubiquitination of synphilin-1: implications for Lewy body formation. *J Neurosci.* 2005; 25:2002–2009. [PubMed: 15728840]
19. Fallon L, Belanger CM, Corera AT, et al. A regulated interaction with the UIM protein Eps15 implicates parkin in EGF receptor trafficking and PI(3)K-Akt signalling. *Nat Cell Biol.* 2006; 8:834–842. [PubMed: 16862145]
20. Xiong H, Wang D, Chen L, et al. Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation. *J Clin Invest.* 2009; 119:650–660. [PubMed: 19229105]
21. Moore DJ, West AB, Dikeman DA, et al. Parkin mediates the degradation-independent ubiquitination of Hsp70. *J Neurochem.* 2008; 105:1806–1819. [PubMed: 18248624]
22. da Costa CA, Sunyach C, Giaime E, et al. Transcriptional repression of p53 by parkin and impairment by mutations associated with autosomal recessive juvenile Parkinson's disease. *Nat Cell Biol.* 2009; 11:1370–1375. [PubMed: 19801972]
23. Narendera D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J Cell Biol.* 2008; 183:795–803. [PubMed: 19029340]
24. Geisler S, Holmstrom KM, Skujat D, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol.* 2010; 12:119–131. [PubMed: 20098416]
25. Li H, Guo M. Protein degradation in Parkinson disease revisited: it's complex. *J Clin Invest.* 2009; 119:442–445. [PubMed: 19306499]
26. Abumrad NA, Moore DJ. Parkin reinvents itself to regulate fatty acid metabolism by tagging CD36. *J Clin Invest.* 2011; 121:3389–3392. [PubMed: 21865651]
27. Pesah Y, Pham T, Burgess H, et al. Drosophila parkin mutants have decreased mass and cell size and increased sensitivity to oxygen radical stress. *Development.* 2004; 131:2183–2194. [PubMed: 15073152]
28. Goldberg MS, Fleming SM, Palacino JJ, et al. Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. *J Biol Chem.* 2003; 278:43628–43635. [PubMed: 12930822]
29. Perez FA, Palmiter RD. Parkin-deficient mice are not a robust model of parkinsonism. *Proc Natl Acad Sci U S A.* 2005; 102:2174–2179. [PubMed: 15684050]
30. Kitada T, Tong Y, Gautier CA, Shen J. Absence of nigral degeneration in aged parkin/DJ-1/PINK1 triple knockout mice. *J Neurochem.* 2009; 111:696–702. [PubMed: 19694908]
31. Youle RJ, Narendera DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol.* 2011; 12:9–14. [PubMed: 21179058]
32. Palacino JJ, Sagi D, Goldberg MS, et al. Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J Biol Chem.* 2004; 279:18614–18622. [PubMed: 14985362]
- 33*. Kim KY, Stevens MV, Akter MH, et al. Parkin is a lipid-responsive regulator of fat uptake in mice and mutant human cells. *J Clin Invest.* 2011; 121:3701–3712. This article shows that Parkin plays a pivotal role in enhancing fat uptake, in part, by increasing the protein half-life of the fatty acid translocase CD36, in multiple tissue types and demonstrates that cells from patients with Parkin mutations have impaired fat uptake. [PubMed: 21865652]
- 34*. Shin JH, Ko HS, Kang H, et al. PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. *Cell.* 2011; 144:689–702. This article shows that Parkin can indirectly regulate a master regulator of mitochondrial biogenesis, i.e. PGC-1α by modulating the stability of PARIS, a transcriptional repressor of PGC-1α. [PubMed: 21376232]
- 35*. Pacelli C, De Rasmio D, Signorile A, et al. Mitochondrial defect and PGC-1alpha dysfunction in parkin-associated familial Parkinson's disease. *Biochim Biophys Acta.* 2011; 1812:1041–1053.

This article links perturbations in mitochondrial function and PGC-1 α dysfunction in primary skin fibroblasts from patients with PD and mutations in Parkin. [PubMed: 21215313]

Key points

- Long chain polyunsaturated fatty acids are essential ‘building blocks’ for neuronal function and homeostasis.
- Perturbations in fatty acid levels and mitochondrial homeostasis regulatory programs modulate the risk of developing Parkinson’s Disease (PD)
- Mutations in *PARK2* associate with increased susceptibility to early onset PD
- Disruption of the *PARK2* encoded protein Parkin, disrupts fat uptake and mitochondrial homeostatic programs
- The mechanistic interplay between these metabolic programs may be integral to both sporadic degenerative and hereditary early onset PD