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Review

Proteomics in animal models of Alzheimer's and Parkinson's diseases

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ABSTRACT

The risk of developing neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) increases with age. AD and PD are the two most common neurodegenerative diseases that currently affect millions of persons within the United States population. While many clues about the mechanisms of these disorders have been uncovered, to date, the molecular mechanisms associated with the cause of these diseases are not completely understood. Furthermore, there are no available cures or preventive treatments for either disorder. Animal models of AD and PD, though not perfect, offer a means to gain knowledge of the basic biochemistry associated with these disorders and with drug efficacy. The field of proteomics which focuses on identifying the dynamic nature of the protein content expressed within a particular cell, tissue, or organism, has provided many insights into these disturbing disorders. Proteomic studies have revealed many pathways that are associated with disease pathogenesis and that may lead to the development of potential therapeutic targets. This review provides a discussion of key findings from AD and PD proteomics-based studies in various animal models of disease.

1. Introduction

1.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder that currently plagues five million Americans. AD can be broadly classified into either familial or sporadic forms of the disease. Familial cases result from genetic mutations in *amyloid precursor protein* (APP) and proteins involved in APP processing, including *presenilin 1* (PS1) and *presenilin 2* (PS2) (Rocchi et al., 2003; Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). However, the vast majority (>90%) of AD cases are of the sporadic variety. A well-established genetic risk factor for sporadic AD is *apolipoprotein E* (ApoE), specifically its ApoE4 isoform. ApoE4 has been the subject of extensive research because individuals that are homozygous for the ApoE4 allele have a high incidence of developing sporadic AD (Corder et al., 1993; Strittmatter and Roses, 1996). Clinical AD diagnosis occurs when multiple symptoms including memory impairment, aphasia, apraxia, agnosia, and general loss of executive functions, are manifested in the individual and collectively contribute to dementia not due to other causes (Association, 2000). It is interesting to note that these symptoms also arise in the reverse order of which they are acquired throughout childhood development (Reisberg et al., 1986).

On a molecular level AD is characterized by the accumulation of senile plaques (SP), which are predominately composed of the short amyloid β-peptide (Aβ), and neurofibrillary tangles (NFT), which are composed largely of hyperphosphorylated tau protein. The 40 and 42 amino acid peptides of Aβ are prevalent in SP of AD patients. Both SPs and NFTs are formed in the hippocampus and neocortical regions of the brain. Molecular confirmation of the clinical diagnosis of AD is made post-mortem based upon criteria such as the number of senile plaques and neurofibrillary tangles (Mirra et al., 1991) and by Braak-stage scoring (Braak and Braak, 1991).

SPs and NFTs, together with synapse loss, are the classical pathological hallmarks of AD. The exact mechanisms accounting for these pathological hallmarks and their contribution to the clinical symptoms associated with the disease are not yet fully understood. Using the knowledge of genetic mutations that result in familial AD and the association of sporadic AD with the ApoE4 allele (see Table 1), several rodent models have been developed to aid in the elucidation of AD pathogenesis.

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Table 1
Genetic mutations in Alzheimer's disease (AD) and Parkinson's disease (PD)

Gene/protein	Pathology	Function	Form	References
APP	Senile plaques	Unknown	Familial AD	Goate et al. (1991)
PS1	Senile plaques	Notch signaling	Familial AD	Sherrington et al. (1995)
PS2	Senile plaques	Notch signaling	Familial AD	Levy-Lahad et al. (1995)
ApoE	Senile plaques and neurofibrillary tangles	Cholesterol regulation and triglyceride metabolism	Familial and sporadic AD	Corder et al. (1993) and Strittmatter and Roses (1996)
α-Synuclein	Lewy bodies	Synaptic vesicle processing	Familial and sporadic PD	Polymeropoulos et al. (1997)
DJ-1	Unknown	Cellular stress response	Familial PD	Kruger et al. (1998) and Zarranz et al. (2004)
LRRK2	Lewy bodies	Mitochondrial-associated protein kinase	Familial and sporadic PD	Zimprich et al. (2004) and Paisan-Ruiz et al. (2004)
Parkin	Lewy bodies, rarely	Ubiquitination of proteins	Familial PD	Kitada et al. (1998)
PINK-1	Unknown	Mitochondrial kinase	Familial PD	Valente et al. (2004)
UCH-L1	Lewy bodies	De-ubiquitination of proteins	Familial and sporadic PD	Leroy et al. (1998)

1.2. Parkinson's disease

Parkinson's disease (PD) follows AD as the second most common age-related neurodegenerative disorder amongst the elderly, occurring in 1–2% of the population over the age of 60 years (de Rijk et al., 2000; Lang and Lozano, 1998; Martin, 1999; Nutt and Wooten, 2005). Disruptions to the central motor system in PD patients result in symptoms such as bradykinesia, resting tremors, postural instability, and muscular rigidity (Lotharius and Brundin, 2002; Moore et al., 2005). Thus, unlike AD patients, PD patients have normal access to learning and memory brain functions, however, PD patients have severe physical impairments. Pathologically, PD is similar to other tauopathies and neurodegenerative disorders, in which protein aggregates are associated with disease pathogenesis. Specifically, Lewy-body (LB) inclusions found in the substania nigra (SN) of PD patients consist of aggregates of α-synuclein protein. In addition to LBs, the SN also exhibits substantial dopaminergic loss such that the disease clinically manifests when approximately 70% neuronal death has occurred in the SN and striatum brain regions (Fearnley and Lees, 1991; Lees, 1992). Because dopamine is the primary neurotransmitter involved in motor functions, its loss directly impacts physical movements and contributes to the clinical symptoms.

More than 90% of PD cases are sporadic and associated with unknown causes, while the remaining 10% of cases represent familial inherited forms of the disease resulting from genetic mutations to genes listed in Table 1. These genes are *parkin*, *ubiquitin carboxy-terminal hydrolase L1* (UCH-L1), *DJ-1*, *α-synuclein*, *PTEN-induced putative kinase 1* (PINK-1) and *leucine rich repeat kinase* (LRRK2) (Bonifati et al., 2003; Farrer et al., 2005; Kitada et al., 1998; Leroy et al., 1998; Lesage et al., 2005; Polymeropoulos et al., 1997; Recchia et al., 2004; Valente et al., 2004; von Coelln et al., 2004; Paisan-Ruiz et al., 2004; Savitt et al., 2006). The most common mutations in the α-synuclein protein associated with PD are A30P, A53T, and E46K (Kruger et al., 1998; Spira et al., 2001; Zarranz et al., 2004). In addition to being present in LBs, α-synuclein is believed to be involved in synaptic vesicle formation (Abeliovich et al., 2000). Parkin and UCH-L1 are proteins involved in ubiquination and de-ubiquination, respectively, of misfolded or damaged proteins that become targets for proteasome degradation (Moore et al., 2005; Zhang et al., 2000), although UCH-L1 also has synaptic functions associated with memory (Gong et al., 2006). The functions of DJ-1 are still not clear, although this protein is believed to be involved in cellular stress responses by acting as an antioxidant, redox-sensitive chaperone, and protease (Moore et al., 2005). PINK-1 is a mitochondrial protein kinase, and its mutations may contribute to mitochondrial dysfunction in PD (Valente et al., 2004). Lastly, the LRRK2 protein, which is also associated with mitochondria, has been found to bind to parkin and is believed to be involved in membrane and protein trafficking (Savitt et al., 2006).

Key factors believed to contribute to the development of PD are oxidative stress, mitochondrial dysfunction, proteasome dysfunction, inflammation, protein aggregation and exposure to various environmental toxins (Dawson and Dawson, 2002, 2003; Hunot and Hirsch, 2003; Paolini et al., 2004; Savitt et al., 2006; Vila et al., 2000). Because the exact mechanisms governing dopamine neuron loss are not fully understood, proteomics studies in PD model systems may provide valuable insight to disease pathogenesis. These animal models have been established based on genetic mutations of PD and PD induction by exposure to toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or rotenone. Current treatment for PD involves L-DOPA administration and MAO inhibitors, which at best reduce associated disease symptoms (Savitt et al., 2006).

To-date, there are no cures or preventive therapeutic targets available for AD or PD. Thereby, novel strategies and clues that assist in drug development for aid in the prevention and cure of these diseases are necessary. A brief summary of proteomic methods and a discussion of key findings from proteomics studies of various AD and PD animal models is provided in this review.

2. Proteomics methods

The field of proteomics involves the determination of the protein identities of a cell, tissue, or organism under a given set of conditions. Primarily, proteomic techniques are used to examine differences in protein expression in a normal versus diseased state (e.g., control vs. AD), although they are also used to determine the structures and functions of proteins. The most traditional and widely used proteomic method is two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) (Rabilloud, 2002). In the first dimension of this approach, proteins are separated on an immobilized pH gradient strip with isoelectric focusing and migrate to the point on the strip at which their net charge is zero (i.e., isoelectric point). In the second dimension, charge-separated proteins are exposed to sodium dodecyl sulfate (SDS) PAGE and are separated according to their molecular migration distance through the gel—a separation that is approximately proportional to the molecular weight of the protein (Klose and Kobalz, 1995).

A typical high-resolution gel can contain hundreds to thousands of protein spots in which spot intensities can be used to calculate differences in expression between various samples. Another method for gel quantitation is differential gel electrophoresis (DIGE), in which different fluorophores (e.g., Cy2, Cy3 and Cy5) are used to derivatize individual samples. Derivatized samples are then combined into a single mixture that is separated with 2D-PAGE, and the gels are scanned at excitation and emission

wavelengths corresponding to the individual fluorophores (Tonge et al., 2001). Quantitation of protein expression differences from multiple gel replicates of control and experimental samples is performed with sophisticated image analysis software (e.g., PDQuest, BioRad). Limitations of 2D-PAGE include a limited protein pI range (i.e., pH 3–10), poor solubilization of highly acidic, basic proteins and membrane-associated proteins, and poor detection of low-abundance proteins.

The protein map obtained from a 2D-PAGE gel can also be used to identify post-translational modifications such as glycosylation, phosphorylation, and/or carbonylation. The identification of carbonylated proteins is one aspect of the field of redox proteomics (Butterfield, 2004). In this instance, carbonylated proteins can be derivatized with 2,4-dinitrophenylhydrazine (DNPH) prior to 2D-PAGE separation. After separation, proteins in gels are transferred onto a nitrocellulose or polyvinylidene fluoride membrane and probed with an anti-DNP antibody for immunoreactivity. The level of carbonylation of individual proteins in 2D Oxyblots is normalized to their total protein content in 2D gels and the specific carbonylation levels compared between control and diseased samples.

Individual protein spots of interest (e.g., up-regulated in disease, increased carbonylation) from 2D gels or 2D Oxyblots are excised, digested with trypsin, and the resultant peptides are analyzed by matrix assisted laser desportion ionization (MALDI)-MS or electrospray ionization (ESI)-MS to generate a peptide fingerprint. The list of peptide masses is then submitted to a database search engine, such as MASCOT, and searched against a species-specific database for protein identification. MASCOT is a probability-based scoring algorithm in which a returned protein hit with a score greater than the defined cutoff, has a 1 in 20 chance of being a random identification ($p < 0.05$) (Perkins et al., 1999). An overview of the 2D-PAGE approach is shown in Fig. 1.

Non-gel proteomic approaches generally involve the separation of proteins or peptides (resulting from enzymatic digestion with trypsin) with high-performance liquid chromatography (HPLC). Multiple dimensions of LC based on different separation principles (e.g., strong cation exchange, reversed-phase chromatography) can be coupled to increase overall protein resolution and peak capacity prior to MS and tandem MS (MS/MS) detection. The most noted of these approaches is multidimensional protein identification (MUDPIT) technology, which is capable of identifying low-abundance proteins (Wolters et al., 2001). A drawback of MUDPIT is the extensive data collection and analysis necessary for protein identification (e.g., terabytes of storage are often necessary). Quantitation of proteins with LC–MS/MS methods can be performed by the incorporation of isotopic labels at different stages of sample preparation. For example, in the isotopically coded affinity tags (ICAT) method, amino acids in individual samples are derivatized with a light or heavy label after protein extraction before tryptic digestion (Smolka et al., 2001). The relative intensities of light and heavy labeled peptides (and/or proteins) in the ICAT generated mass spectra can be used to examine relative amounts of up- or down-regulation of proteins in the mixture. A drawback of ICAT is that cysteine residues must be present and reactive in a protein in order for it to be detected.

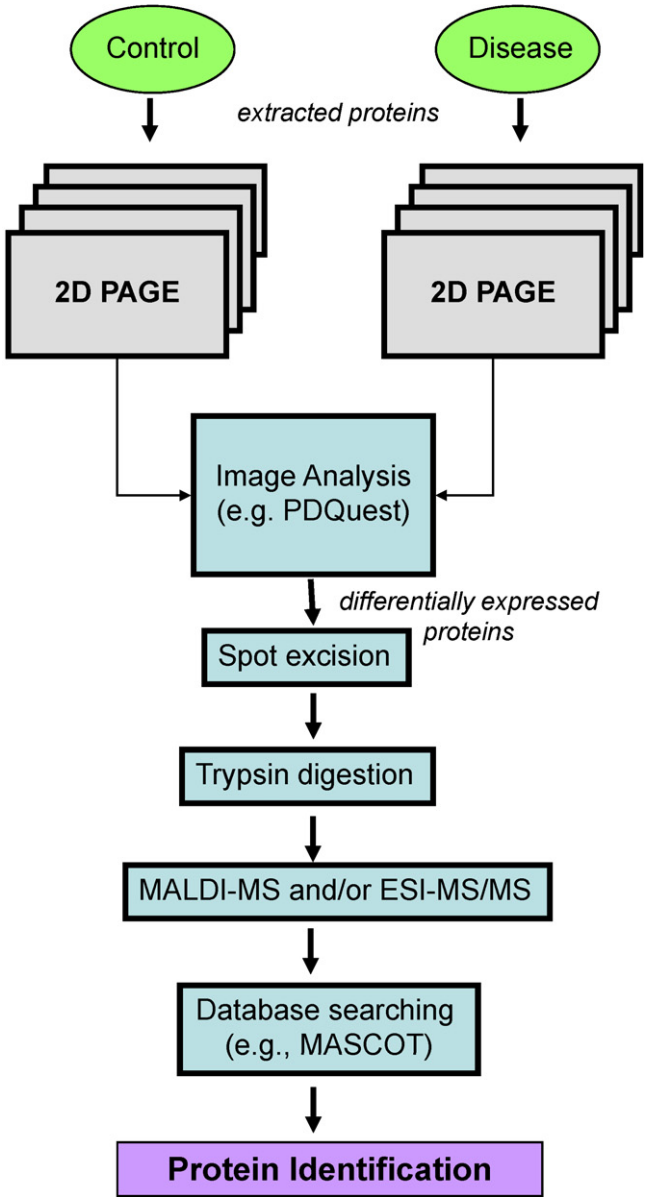

Fig. 1. Schematic diagram of 2D-PAGE proteomics analysis in control and diseases tissues.

3. Proteomics findings from animal models of Alzheimer's disease

3.1. Amyloid precursor protein models: Swedish double mutant-based mouse models

The APP gene is located on chromosome 21 and genetic mutations that occur in APP in familial AD have been well characterized. To-date, there are 18 missense mutations reported, which occur in amyloid-beta (Aβ) peptide encoded exon sequences 16 or 17 of the APP gene (Papassotiropoulos et al., 2006). Approximately 40 mouse models have been raised with both single and multiple combinations of these genetic alterations, with the most commonly used being the Hsiao Tg-2576 mouse (Hsiao et al., 1996), the Swedish double mutant (K670M/N671L) and the London mutant (V717I) (http://www.alzforum.org/res/com/tra/app/appsw.asp). For the purpose of this review only models used in proteomics studies will be covered.

The APP Swedish (APPSw) transgenic mutant experiences amyloidosis in the second year of life, with Aβ (1-40) levels as high as 200 ng mg^{-1} of tissue in the hippocampus and neocortex occurring at 24 months of age (http://www.alzforum.org/res/com/tra/app/appsw.asp). Proteomics studies of APPSw mice show differential expression of several proteins with varying physiological functions. Pyruvate kinase (PK), aconitase, α-enolase, glial

fibrillary acidic protein (GFAP), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), dihydropyrimidase-like 2 (DRP2), similar to zinc finger 1111 protein, and dynamin-1 have shown increased levels (Shin et al., 2004). Conversely, proteasome complex activator subunit 2, malate dehydrogenase, γ-enolase, and ATP synthase α chain have decreased levels in APPSw mutants (Shin et al., 2004). The functions of these proteins encompass a wide range of physiological roles, including metabolism (e.g., PK, GAPDH, and malate dehydrogenase) the ubiquitin/proteasome system, cellular transport (e.g., dynamin), synaptic and axonal integrity (e.g., DRP2), and inflammatory markers (e.g., GFAP). Of the aforementioned proteins, GAPDH, DRP2, ATP synthase α chain, similar to zinc finger 1111, and dynamin-1 have also been shown to be differentially expressed in human AD brain (Butterfield et al., 2007) and thus may be key pathways important for AD pathogenesis.

Proteomics studies in the Swedish/London (Swe/Lon) combination mutant mice have revealed eight proteins with increased levels compared to age-matched wild-type controls (Sizova et al., 2007) that overlap with human AD (Castegna et al., 2002a,b; Schonberger et al., 2001; Tsuji et al., 2002). These proteins are GFAP, ApoE precursor, peroxiredoxin 6 (Prdx6), DRP2, synaptotagamin I, *N*-ethylmaleimide sensitive fusion protein, serum albumin precursor, and PK. Like APPSw mutants, the Swe/Lon mice also express changes in metabolic, inflammatory marker, and synaptic and axonal integrity proteins relative to controls. Prdx6 and ApoE are also up-regulated in this AD model. Prdx6 is an antioxidant enzyme that is critical for clearance of hydrogen peroxide, a reactive oxygen species (Sarafian et al., 1999). ApoE allele type has a link to AD, and cholesterol metabolism is altered in AD (Casserly and Topol, 2004). It is important to note that in this particular mouse model neuronal loss is limited even though plaque deposition begins at 6 months of age (Sizova et al., 2007). Up-regulation of these proteins supports the notion that oxidative stress and disruption to metabolic processes occur in AD brain.

3.2. Presenilin 1, presenilin 2, and APP/PS mouse models

Mutations in the presenilins, PS1 and PS2, account for the majority of familial AD cases (Papassotiropoulos et al., 2006). It is widely accepted that the presenilins are a part of the γ-secretase complex (Scheuner et al., 1996) and mutations in the transmembrane domain lead to aberrant APP processing. PS1 and PS2 are highly homologous proteins; however, PS2 warrants its own classification because it has been traced to a single German family (Bird et al., 1988). PS1 and PS2 mouse models experience varying degrees of altered PS1 and PS2 expression; however, none of the models develops AD pathology at a quicker rate than the wild-type counterpart. Therefore, models with mutations in both APP and PS1 and/or PS2 were developed. It should be noted that proteomic studies of PS1 or PS2 models are limited (Wood et al., 2005).

The coupling of APP and PS mutations allow for reduced phenotypic variance of APP mutants and more rapid senile plaque deposition. APP/PS mice overcome the shortcomings of single gene mutations of APP or PS models of AD because they experience cognitive defects and senile plaque deposition. While, proteomics studies also are limited in this model, APP/PS models may be useful in applications testing efficacy of therapeutic approaches. Proteomics analysis of oxidatively modified APP/PS-1 mice as a function of age has recently been completed in our laboratory and the results will be published soon.

3.3. Human P301L and GSKβ tau mouse models

The mouse models discussed above have been associated with mutations in APP and PS, which are related to SP formation. None of these models have hyperphosphorylated tau and NFTs present, in spite of the importance of NFTs as pathological hallmarks of AD. To date, proteomics studies have been conducted for only 2 of 26 tau mutant/transgenic mouse models (http://www.alzforum.org/res/com/tra/tau/default.asp). One of the models expresses the longest mutant human tau isoform P301L, while the other has a constitutively active glycogen synthase kinase β protein present (David et al., 2006; Tilleman et al., 2002).

A proteomics study conducted by David et al. used P301L tau (P301) mice that were injected with Aβ (1-42) into the amygdala (David et al., 2006). As a control, the reverse sequence of Aβ (e.g., 42-1) was used. The researchers observed a wide range of differentially expressed proteins in this AD model. Up-regulated proteins include: actin, carbonic anhydrase II, isocitrate dehydrogenase (ICDH) NADH cytoplasm, DRP2, proteasome subunit α-3, transferrin, phosphoglycerate mutase 1, synapsin-2, stress protein 70 (grp75), and DRP5. Proteins that were down-regulated include: Prdx5, Prdx6, tubulin α-4 chain, ribose-phosphate pyrophosphate kinase II, NADH ubiquinone oxidoreductase B15 subunit, and NADH dehydrogenase. Differentially expressed proteins identified in this model were numerous and vary in function; in addition, there is overlap with proteins identified in other AD models. For example, DRP2 is important for synaptic/axonal maintenance and is affected in AD (Castegna et al., 2002b) and the aforementioned transgenic models.

Tilleman et al. conducted proteomics experiments on an aberrant GSKβ protein that abnormally phosphorylates tau, leading to the development of NFTs (Tilleman et al., 2002). The study identified a number of proteins with varying expression and functionalities that were also present in aforementioned models (e.g., DRP2, creatine kinase BB, heat shock protein 90, α-enolase, isocitrate dehydrogenase, succinate dehydrogenase, and glutathione-*s*-transferase).

3.4. ApoE4 mouse model

The ApoE4 allele is a well-established risk factor for sporadic AD (Papassotiropoulos et al., 2006). ApoE is important in the regulation of cholesterol and triglyceride metabolism (Breslow et al., 1982) and has three major isoforms: ApoE2, ApoE3, and ApoE4. The only differences present in the isoforms occur in the amino acid residues at positions 112 and 158. Specifically, ApoE2 has a cysteine at both positions, ApoE3 has a cysteine residue at 112 and an arginine at 158, and ApoE4 has two arginine residues at both positions (Osorio et al., 2007).

Osorio et al. conducted a study using ApoE3 and ApoE4 targeted replacement mice. In this study, the endogenous mouse ApoE was replaced by either human ApoE3 (control) or ApoE4 (Osorio et al., 2007). The only protein that was found to be differentially expressed in ApoE4 mice hippocampus relative to controls was the mitochondrial protein mortalin, also known as mtHSP70 and GRP75. The mortalin-c isoform was shown to have a 14-fold increase in expression in ApoE4 mouse, while the mortalin-d isoform was shown to have a 3.4-fold increase. Both mortalin isoforms were also found to be differentially phosphorylated and mortalin-d was identified as differently expressed in human AD hippocampus (Osorio et al., 2007). Mortalin plays a role in diverse processes, including cell survival, stress response, mitochondrial biogenesis, intracellular trafficking, and cell differentiation (Kaul et al., 2002; Wadhwa et al., 2005). The authors hypothesize that mortalin plays a protective role in a yet to be defined mechanism and may be useful as a biomarker for AD.

3.5. Senescence-accelerated prone mouse model

The senescence-accelerated prone mouse (SAMP8) mouse strain has a shorter lifespan and experiences problems with

learning and memory in an age-dependent manner compared to wild-type mice (Butterfield and Poon, 2005). SAMP8 mice experience impaired immunity and have Aβ deposition at an advanced rate (Flood and Morley, 1998). Since the single greatest risk factor for sporadic AD is age, studying the SAMP8 mouse provides a useful platform for studying the effects of aging. Redox proteomics studies have been conducted in SAMP8 mice using APP-directed antisense oligonucleotide (AO) and α-lipoic acid (LA) as treatments to decrease Aβ (1-42) levels (Poon et al., 2004b, 2005b). Aβ (1-42) is believed to be the most toxic form of Aβ in human AD (Butterfield et al., 2007).

LA is a potent endogenous molecule that induces antioxidant proteins that have the capacity to scavenge reactive oxygen species (ROS), chelate metals, and recycle other endogenous enzymes (Kagan et al., 1992; Ou et al., 1995; Sen et al., 1997). SAMP8 mice given subcutaneous injection of LA (100 mg/kg dose) had lower levels of carbonyls and performed better in cognitive tests (Poon et al., 2005b). A proteomics study of brain proteins found neurofilament triplet L protein, mitochondrial creatine kinase, and α-enolase to have increased expression. Neurofilament triplet L (NF-L) is a component of neurofilaments (NFT), which are responsible for axonal structural integrity (Brady, 1993; Hoffman et al., 1987). NF-L protein levels were found to be lower in AD brains relative to age-matched controls, thus suggesting that NF-L protein is important for proper brain activity (Bajo et al., 2001) and that LA may be helpful in maintaining axonal integrity. Mitochondrial creatine kinase (mCK) and its cytosolic counterpart are implicated in regulating ATP concentration in cerebral gray matter (Kekelidze et al., 2001). Cytosolic creatine kinase (cCK) has been previously shown to be oxidized in brains of aged SAMP8 mice (Poon et al., 2004a). The up-regulation of mCK by LA treatment may compensate for aberrant cCK, in order to maintain normal neuronal ATP concentrations. α-Enolase has also been shown to be oxidized in aged SAMP8 brain (Poon et al., 2004a). LA treatment reduces the level of α-enolase oxidation and increases its expression in SAMP8 mouse brain; this suggests that altered glucose metabolism, characteristic of the SAMP8 mouse model, is improved with LA treatment (Ikegami et al., 1992; Poon et al., 2005b).

Redox proteomics showed that lactate dehydrogenase, DRP2, and α-enolase were significantly less carbonylated (Poon et al., 2005b) in LA-treated SAMP8 mice. Redox proteomics on the AO-treated mice showed that aldolase 3 (Aldo3), Coronin 1a (Coro1a), and Prdx2 were significantly less carbonylated (Poon et al., 2005a). Both AO and LA treatments resulted in changes to protein expression and levels of carbonyl modification. In addition to being a glycolytic enzyme, Aldo3 interacts with DRP2 during times of oxidative stress, aiding in the guidance of synaptic vesicles (Bulliard et al., 1997). Coro1a is important for cytoskeletal integrity and was shown to be impaired in Down's syndrome, a disorder characterized by an extra copy of the APP bearing chromosome 21 (de Hostos et al., 1991). Less oxidative modification of these proteins from AO treatment may provide some protection for neurotransmission through restoration of cytoskeletal repair, antioxidant capability, and increased metabolism and may be associated with improved learning and memory in SAMP8 mice treated with LA or AO (Farr et al., 2003; Morley et al., 2002).

3.6. Aβ-injected rat models

Aβ (1-42) has been proposed to play a critical role in oxidative stress observed in AD (Butterfield et al., 2001). To test this hypothesis, Aβ (1-42) was injected into rat nucleus basalis magnocellularis (NBM) and compared to saline injected controls for an *in vivo* redox proteomics study (Boyd-Kimball et al., 2005). Glutamine synthetase (GS) and tubulin chain 15/α were found to be oxidized in the cortex, 14-3-3ζ and HSP60 were oxidized in the NBM, and 14-3-3ζ, β-synuclein, pyruvate dehydrogenase, GAPDH, and phosphoglycerate mutase-1 were oxidized in the hippocampus. Metabolic enzymes, chaperones, GS, tubulin chain 15/α, and 14-3-3ζ were perturbed in this model. GS catalyzes the conversion of glutamate to glutamine, preventing the build-up of the potentially excitotoxic amino acid glutamate and keeping ammonia levels in balance (Casamenti et al., 1999). Tubulin chain 15/α is part of the microtubule assembly core and 14-3-3ζ has multiple roles, including protein trafficking and metabolism (Dougherty and Morrison, 2004). *In vivo* Aβ (1-42) affects in GS are similar to changes observed in AD (Castegna et al., 2002a) which support the notion that Aβ (1-42) plays a key role in the oxidative stress present in AD brain. It is noteworthy that although Aβ (1-42) was injected in the NBM, oxidative modification of hippocampal and cortical proteins was observed. This observation may relate to cholinergic innervation of the outer molecular layer of the hippocampus in the NBM. The NBM is extensively affected in AD as is the hippocampus.

3.7. Transgenic rats expressing human mutant APP model

A proteomics study of transgenic rats expressing Swedish mutant human APP found 12 proteins to be differentially expressed in hippocampal CA1 region pyramidal cells (Wilson et al., 2005). The transgenic rats were developed to express the Swedish mutant of APP at levels slightly higher than basal endogenous rat APP levels (Wilson et al., 2005). Proteins identified as up-regulated were adenine phosphoribosyltransferase, annexin V, peroxiredoxin 2A, peroxiredoxin 2B, phosphoglycerate mutase, and phosphoglycerate mutase B. Down-regulated proteins included ATP synthase subunit D, tubulin β chain A, tubulin β chain B, heat shock protein 70, NEDD-4, and vasopressin activated calcium mobilizing receptor (CUL5). NEDD4 is a protein involved in neddylation, a process that stabilizes/destabilizes cullin proteins. Cullin proteins have been shown to promote E3 ubiquitin ligase activity *in vitro* (Wu et al., 2005) and therefore are indirectly involved in the ubiquitin/proteasome pathway. CUL5 is a cullin protein stabilized by neddylation, such that the observed decreased expression of NEDD-4 and CUL5 is consistent with the biological functions of these proteins.

3.8. Caenorhabditis elegans expressing human Aβ (1-42) model

C. elegans expressing human Aβ (1-42) is a non-mammalian model used to test the *in vivo* effects of Aβ (1-42). In a redox proteomics study, 16 proteins were found to be oxidatively modified in this model (Boyd-Kimball et al., 2006). Interestingly even in this non-mammalian model, the oxidatively modified proteins are associated with similar pathways as in the mammalian models including energy metabolism, antioxidant defense, and cytoskeletal structural integrity.

4. Proteomic findings from animal models of Parkinson's disease

4.1. Parkin knock-out and A30P transgenic mouse models

Proteomic findings from animal models of PD have recently provided insights into several pathways that may be related to disease pathogenesis. Models that are designed to mimic human familial PD include *parkin* knock-out (KO) and A30P α-synuclein transgenic mice. Utilizing DIGE, Periquet et al. identified a total of 87 proteins that are differentially expressed in *parkin* KO mice

relative to controls (Periquet et al., 2005). These proteins were associated with pathways involving energy metabolism, ubiquitin/proteasome degradation, detoxification, stress-related chaperones, and synaptic scaffolding. Interestingly, several of these pathways have also been implicated in proteomic studies of AD as discussed above.

Our laboratory has used redox proteomics to determine proteins that undergo oxidative modification in the brains of A30P α-synuclein transgenic mice relative to controls (Poon et al., 2005c). In these studies, lactate dehydrogenase 2, carbonic anhydrase 2, and α-enolase had significantly higher levels of carbonylation in A30P mice relative to controls. Oxidative modification of proteins has been shown to lead to loss of function (Butterfield, 2004; Butterfield et al., 1997; Hensley et al., 1995; Lauderback et al., 2001). The activities of these three proteins were shown to be significantly lower in the A30P mice than in controls, highlighting the importance of oxidative stress in PD.

4.2. MPTP-treated mouse models

One of the commonly used mouse models of PD is MPTP-treated rodents, which results in mitochondrial toxicity through inhibition of Complex I (Heikkila and Sonsalla, 1987; Ogawa et al., 1987). Jin et al. used ICAT proteomics to identify 110 mitochondrial-isolated proteins that were differentially expressed in SN from MPTP- and probenecid-treated animals relative to controls (Jin et al., 2005). Probenecid reduces clearance of MPTP and its metabolites. Of these proteins, particular attention was focused on DJ-1, whose significant increase in expression in PD mice, was validated by Western blot analysis. In addition, immunohistochemical studies revealed that DJ-1 is localized in granular inclusions in dopaminergic neurons with the α-synuclein protein (Jin et al., 2005). While the function of DJ-1 is still not clear, this protein may be involved in mitochondrial function (Dawson and Dawson, 2003). This observation is particularly noteworthy since PD mitochondrial function is altered (Jin et al., 2005).

The MPTP-treated mouse also has decreased expression of Purkinje cell protein 4 (PEP-19), as assessed by nanoflow LC–ESI-MS (Skold et al., 2006). PEP-19 was found to be localized to the striatum from imaging MALDI-MS analyses (Skold et al., 2006). PEP-19 is a calmodulin-binding protein that is involved in neuronal signal transduction through Ca^{2+}-independent mechanisms (Putkey et al., 2003). In other proteomic studies of MPTP-induced parkinsonism changes in the expression levels of over 400 microglial-associated proteins have been identified in a variety of mouse strains stimulated with lipopolysaccharide (McLaughlin et al., 2006). Due to the large number of proteins that were identified in these studies, the authors limited their preliminary validation of proteomics results to inducible nitric oxide synthase (iNOS). Elevation of the iNOS protein in the lipopolysaccharide-treated strains studied (i.e., C57BL6 and SWR/J) relative to controls provided consistent evidence that iNOS is increased during inflammatory processes (McLaughlin et al., 2006).

A more recent proteomic study of the MPTP-treated mouse model focused on kinetic proteome changes in the ventral midbrains of a wild-type mice strain (i.e., C57BL/6) and a transgenic mice strain that overexpresses L1 cell adhesion molecule (L1cam) in astrocytes (Diedrich et al., 2008). L1cam has been shown to counteract dopaminergic loss resulting from MPTP treatment by enhancing neurite growth and survival in dopaminergic neurons (Diedrich et al., 2008). Traditional MPTP methods to induce PD only result in a 4 day period of reduced locomotor activity, these proteomic studies focused on changes that occur at acute (i.e., 1 day post-injection) and recovery (i.e., 7 days post-injection) phases after MPTP injection. Overall, MPTP treatment in both wild-type mice and L1cam transgenic mice resulted in alterations to proteins involved in mitochondrial dysfunction, glycolysis, neurogenesis and the cytoskeleton and ubiquitin pathways (Diedrich et al., 2008). These altered pathways are consistent with those aforementioned in AD and/or PD animal models.

Our laboratory has used the MPTP-treated mouse model to examine drug treatments that cross the blood–brain barrier and that may reduce dopamine loss (Chinta et al., 2006). In particular *in vivo* (and *in vitro*) treatment with the glutathione precursor, γ-glutamylcysteinyl ethyl ester (GCEE), was shown to reduce dopamine-associated striatal neuron loss in MPTP-treated mice (Chinta et al., 2006). Although proteomic studies have not been performed to-date, studies of this nature are in progress and are expected to provide insight into approaches which might reduce dopamine loss in PD.

4.3. "Hemiparkinsonian" rat model

The most common rat model of PD is the "hemiparkinsonian rat", which develops PD pathology by intracerebral injection of 6-hydroxydopamine, a neurotoxin that causes dopaminergic loss in the SN. Proteomic studies by De Iuliis et al. identified increased levels of α-enolase and β-actin in hemiparkinsonian rats relative to controls within the SN and striatum brain regions (De Iuliis et al., 2005). These two proteins have previously been implicated in AD where they were found to be oxidatively modified (Butterfield et al., 2006; Reed et al., 2008). α-Enolase is a metabolic enzyme involved in glycolysis, while β-actin is a structural cytoskeletal protein. It is possible that in addition to increase of these two proteins in PD, oxidation levels may also change.

Proteomic studies can also be used to identify proteins that change in expression after treatment of subjects with potential drug candidate compounds. For example, Valastro et al. treated hemiparkinsonian rats with L-DOPA or bromocriptine, a dopamine receptor agonist, and assessed the corresponding protein changes relative to controls (Valastro et al., 2007). Overall, striatal proteins from animals treated with either L-DOPA or bromocriptine that were changed were primarily involved in energy metabolism, structural synaptic plasticity, oxidative stress, and protein degradation (Valastro et al., 2007). These observations support the possibility that oxidative stress and impairments in the proteasome are key to PD pathogenesis. Subsequent detailed analysis identified five proteins with significant changes in L-DOPA-induced dyskinesia (LID)-associated animals; αβ-crystallin, a heat shock protein, and guandiacetate methyltransferase, a protein involved in creatine synthesis, were down-regulated in LID rats relative to non-dyskinetic and bromocriptine-treated rats (Valastro et al., 2007). γ-Enolase, a glycolytic enzyme, proteasome α-2 subunit, and vinculin, a protein involved in endothelial adherent junctions, were up-regulated in LID rats (Valastro et al., 2007). These findings provide insights into pathways that have not previously been associated with motor activity and may be useful in the development of new therapies for PD.

4.4. Axotomized rat models

Axotomy of the medial forebrain has been used to induce PD in rats (Venero et al., 1997), resulting in an ~50% loss of dopaminergic neurons. 2D-PAGE MALDI-MS analyses identified increased expression in haptoglobin and transthyretin proteins and decreased ApoE in the cerebrospinal fluid (CSF) of axotomized rats (Rite et al., 2007). Haptoglobin is a hemoglobin-binding protein that also has antioxidant, antibacterial, and acute-phase response activity. Transthyretin, a thyroxine hormone-delivering

protein, while shown to increase in this PD model (Rite et al., 2007) and in aging, was decreased in AD (Serot et al., 1997). ApoE is a major protein found in CSF and astrocytes in brain that is involved in lipid metabolism. Decreases in ApoE, as revealed by this PD proteomic study, suggest the possible role of ApoE in other neurodegenerative diseases in addition to AD.

4.5. *In vitro* dopamine quinone-treated mitochondria isolated from rat brain model

Dopamine oxidation products, such as dopamine quinone, cause mitochondrial dysfunction in rat brain or liver and are associated with dopaminergic neuronal loss (Berman and Hastings, 1999); thus, this system provides another model with which to investigate PD pathogenesis. Recently, Van Laar et al. utilized 2D-DIGE proteomics to identify altered proteins isolated from rat brain mitochondria following *in vitro* treatment with dopamine quinone (Van Laar et al., 2008). Proteins that exhibited greater than 50% reduced expression levels in dopamine quinone-treated mitochondria relative to controls, in both a Cys- and Lys-CyDye DIGE labeling scheme, include mitochondrial creatine kinase (MtCK), mitofilin, fumarylacetoacetate hydrolase domain containing 2A, voltage-dependent anion channel 2, and glycerol-3-phosphate dehydrogenase (Van Laar et al., 2008). Western blot analysis validated the changes associated with MtCK and mitofilin in dopamine quinone-treated mitochondria. Reductions in the levels of other proteins included mortalin, the 75-kDa subunit of NADH dehydrogenase, and superoxide dismutase 2 (Van Laar et al., 2008). These proteins are involved in various mitochondrial functions including structural integrity, energy metabolism, antioxidant defense, and cellular transport. These perturbations to the mitochondria are consistent with other reports presented in this review and support the possibility that mitochondrial dysfunction is a key contributor to PD pathogenesis.

4.6. A30P and A53T α-synuclein transgenic Drosophila models

Drosophila melanogaster has recently been exploited in proteomics as a useful model for PD. In particular, *Drosophila* expressing the human A30P mutant α-synuclein have provided further evidence that mitochondrial- and cytoskeletal-related pathways are important in PD pathogenesis (Xun et al., 2007b). Of 1727 proteins that were identified across different disease stages (i.e., presymptomatic, early, and advanced stages), altered expression levels of 49 proteins were observed in an A30P transgenic α-synuclein *Drosophila* model (Xun et al., 2007b). Changes unique to presymptomatic and early disease stages in PD *Drosophila* were primarily associated with the cytoskeleton and mitochondria. Additional evidence for perturbations to these pathways was obtained in proteomic studies that sampled seven ages spanning the entire lifespan of PD *Drosophila* (Xun et al., 2007a). Xun et al. also examined protein changes in the A53T *Drosophila* PD model that are specific to the presymptomatic stage (Xun et al., 2008). The expression levels of 24 proteins changed in A53T transgenic α-synuclein *Drosophila* and represented proteins with a variety of biological functions. Proteins such as heat shock protein 70 cognate 3, Mn superoxide dismutase and ATP-synthase were up-regulated in A53T *Drosophila* (Xun et al., 2008), supporting the possibility that oxidative stress, mitochondrial, energy metabolism and protein folding/degradation pathways are important in PD pathogenesis.

4.7. Wild-type α-synuclein transgenic C. elegans models

The importance of actin (or cytoskeletal-associated proteins) as a target in PD pathogenesis from the models discussed above was recently demonstrated by proteomic studies of *C. elegans* that overexpressed wild-type human α-synuclein protein (Ichibangase et al., 2008). In these studies employing fluorogenic derivatization LC–MS/MS, five proteins including, actin, ribosomal protein large subunit (rpl) 13, rpl 23, rpl 30, and rpl 43 had decreased expression in PD worms (Ichibangase et al., 2008). Moreover these findings support the utility of various animal models of PD and their ability to provide clues to commonality of molecular pathways across a variety of models of disease etiology.

5. Conclusions

There are several commonalities from the proteomic studies of models of AD and PD discussed in this review. Primarily, it important to note that proteomics can provide insightful and powerful information that can be used to further exploit specific pathways. For example, proteomics studies have identified a number of common proteins and/or functional categories that change in AD and/or PD model systems (Table 2). Table 2 provides a more comprehensive view of key biological pathways altered in AD

Table 2
Compilation of key biological pathways and proteins that are altered in animal models of Alzheimer's and Parkinson's diseases determined by proteomics[a]

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Amino acid synthesis				
D-3-Phosphoglycerate dehydrogenase	GSKβ	Tilleman et al. (2002)	–	–
Aspartate aminotransferase	–	–	MPTP mice	Diedrich et al. (2008)
Dimethylarginine dimethylaminohydrolase 1	–	–	MPTP mice	Diedrich et al. (2008)
Glutamate oxaloacetate transaminase 2	–	–	A30P *Drosophila*	Xun et al. (2007a)
Glutamine synthetase	**Aβ (1-42)-injected rat, GSKβ**	**Boyd-Kimball et al. (2005) and Tilleman et al. (2002)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005), Jin et al. (2005) and Diedrich et al. (2008)**
Henna	–	–	A30P *Drosophila*	Xun et al. (2007a)
Serine racemase	–	–	*parkin* KO mice	Periquet et al. (2005)
Blood pH regulation				
Carbonic anhydrase II	**P301L tau**	**David et al. (2006)**	**A30P α-synuclein mice, parkin KO mice**	**Poon et al. (2005c) and Periquet et al. (2005)**
Cellular transport				
ADP, ATP carrier protein	–	–	MPTP mice	Jin et al. (2005)
ATPase, H^+ transporting, V1 subunit 5	–	–	MPTP mice	Diedrich et al. (2008)
Calcium ATPase at 60A	–	–	A30P *Drosophila*	Xun et al. (2007a)
Complexin 1	**GSKβ**	**Tilleman et al. (2002)**	**MPTP mice**	**Diedrich et al. (2008)**

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Complexin 2	–	–	MPTP mice	Jin et al. (2005) and Diedrich et al. (2008)
Dynamin-1	**APP/Sw**	**Shin et al. (2004)**	**parkin KO mice**	**Periquet et al. (2005)**
Ferritin heavy chain	–	–	MPTP mice	Diedrich et al. (2008)
Ferritin 1 heavy chain homologue	–	–	A30P *Drosophila*	Xun et al. (2007a)
G protein β-subunit 13F	–	–	A30P *Drosophila*	Xun et al. (2007a)
Globin 1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Larval serum protein 2b	–	–	A30P *Drosophila*	Xun et al. (2007a)
Na^+/K^+ transporting ATPase α-1 chain	–	–	MPTP mice	Jin et al. (2005)
Na^+/K^+ transporting ATPase α-2 chain	–	–	MPTP mice	Jin et al. (2005)
Na^+/K^+ transporting ATPase α-3 chain	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Jin et al. (2005)
Neutral amino acid transporter A	–	–	MPTP mice	Jin et al. (2005)
Phosphate carrier protein	–	–	MPTP mice	Jin et al. (2005)
Rho GDP-dissociation inhibitor 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	–	–	MPTP mice	Jin et al. (2005)
Septin 2 or 6 homologue	–	–	*parkin* KO mice	Periquet et al. (2005)
Septin 5	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Diedrich et al. (2008)
Septin 7	–	–	*parkin* KO mice	Periquet et al. (2005)
Septin 11	–	–	MPTP mice	Diedrich et al. (2008)
Septin-like protein KIAA0202	–	–	*parkin* KO mice	Periquet et al. (2005)
Serum albumin precursor	Swe/Lon	Sizova et al. (2007)	–	–
Sorting nexin 5	–	–	*parkin* KO mice	Periquet et al. (2005)
Transferrin	P301L tau	David et al. (2006)	–	–
Vesicular fusion protein	GSKβ	Tilleman et al. (2002)	–	–
Cytoskeletal structural integrity				
14-3-3ε	–	–	MPTP mice	Jin et al. (2005)
14-3-3γ	–	–	MPTP mice	Diedrich et al. (2008)
14-3-3ζ	**Aβ (1-42)-injected rat**	**Boyd-Kimball et al. (2005)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005)** and **Jin et al. (2005)**
α-Internexin	**GSKβ**	**Tilleman et al. (2002)**	**MPTP mice**	**Diedrich et al. (2008)**
β-Actin	**P301L tau**	**David et al. (2006)**	**Hemiparkinsonian rat, α-synuclein C. elegans, parkin KO mice, MPTP mice**	**De Iuliis et al. (2005), Ichibangase et al. (2008), Periquet et al. (2005)** and **Diedrich et al. (2008)**
Actin-related protein 2/3 complex, subunit 5-lik	–	–	MPTP mice	Diedrich et al. (2008)
Adenyl cyclase-associated protein 1	–	–	*parkin* KO mice	Periquet et al. (2005)
ARP2/3 complex 20-kDa subunit	–	–	*parkin* KO mice	Periquet et al. (2005)
Capping protein of actin filament	–	–	MPTP mice	Diedrich et al. (2008)
Cofilin	–	–	MPTP mice	Jin et al. (2005) and Diedrich et al. (2008)
Fascin	GSKβ	Tilleman et al. (2002)	–	–
Glial fibrillary acidic protein	APP/Sw, Swe/Lon	Shin et al. (2004) and Sizova et al. (2007)	–	–
Histone H4 replacement	–	–	A30P *Drosophila*	Xun et al. (2007a)
Kinesin heavy chain	–	–	A30P *Drosophila*	Xun et al. (2007a)
Microtubule associated protein 2	–	–	MPTP mice	Jin et al. (2005)
Muscle LIM protein at 60A	–	–	A53T *Drosphila*	Xun et al. (2008)
Muscle specific protein 300b	–	–	A30P *Drosophila*	Xun et al. (2007a)
Myosin alkali light chain 1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Paramyosin	–	–	A53T *Drosphila*	Xun et al. (2008)
Profilin	SAMP8	Poon et al. (2005a)	–	–
Profilin II splice isoform IIB	–	–	MPTP mice	Diedrich et al. (2008)
Similar to ARP1 actin-related protein 1	–	–	MPTP mice	Jin et al. (2005)
Similar to myosin Vb	–	–	MPTP mice	Jin et al. (2005)
Spectrin α-chain	–	–	*parkin* KO mice	Periquet et al. (2005)
Spectrin β-chain	–	–	MPTP mice	Jin et al. (2005)
Stathmin 1	–	–	MPTP mice	Diedrich et al. (2008)
Transketolase	–	–	MPTP mice	Diedrich et al. (2008)
Troponin C	–	–	A30P *Drosophila*	Xun et al. (2007a)
Troponin T	–	–	A53T *Drosphila*	Xun et al. (2008)
Tubulin chain 15/α	Aβ (1-42)-injected rat	Boyd-Kimball et al. (2005)	–	–
Tubulin α-1 chain	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Tubulin α-1a chain	–	–	MPTP mice	Diedrich et al. (2008)
Tubulin α-2 chain	–	–	MPTP mice	Diedrich et al. (2008)
Tubulin α-4 chain	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Jin et al. (2005)** and **Diedrich et al. (2008)**
Tubulin β chain 1	GSKβ	Tilleman et al. (2002)	–	–
Tubulin β chain A	**Swedish human mutant transgenic rat**	**Wilson et al. (2005)**	**MPTP mice**	**Diedrich et al. (2008)**
Tubulin β chain B	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Tubulin β-4	–	–	MPTP mice	Diedrich et al. (2008)
Tubulin polymerization-promoting protein	–	–	MPTP mice	Diedrich et al. (2008)
Upheld	–	–	A53T *Drosphila*	Xun et al. (2008)
Vinculin	–	–	L-DOPA mice	Valastro et al. (2007)
Energy metabolism				
α-Enolase	**APP/Sw**, **GSKβ**, **SAMP8**	**Shin et al. (2004)**, **Tilleman et al. (2002)** and **Poon et al. (2005b)**	**A30P α-synuclein mice; hermiparkinsonian rat**, **MPTP mice**	**Poon et al. (2005c)**, **De Iuliis et al. (2005)** and **Diedrich et al. (2008)**
γ-Enolase	**APP/Sw**	**Shin et al. (2004)**	**parkin KO mice**, **MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Aconitase	**APP/Sw**	**Shin et al. (2004)**	**parkin KO mice**, **MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Aconitate hydratase			MPTP mice	Diedrich et al. (2008)
Aldolase 3	SAMP8	Poon et al. (2005a)	–	–
Aldose reductase	GSKβ	Tilleman et al. (2002)	–	–
ATP synthase subunit D	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
ATP synthase α chain	**APP/Sw**	**Shin et al. (2004)**	**In vitro dopamine quinone-treated rats**, **parkin KO mice**, **A30P Drosophila**, **MPTP mice**	**Van Laar et al. (2008)**, **Periquet et al. (2005)**, **Xun et al. (2007a)** and **Diedrich et al. (2008)**
ATP synthase α chain, mitochondrial	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
ATP synthase β chain, mitochondrial	–	–	*parkin* KO mice, A53T *Drosophila*, A30P *Drosophila*	Periquet et al. (2005), Xun et al. (2008) and Xun et al. (2007a)
ATP synthase γ chain, mitochondrial	–	–	MPTP mice, A30P *Drosophila*	Jin et al. (2005) and Xun et al. (2007a)
ATP α	–	–	A30P *Drosophila*	Xun et al. (2007a)
Citrate synthase	–	–	*parkin* KO mice	Periquet et al. (2005)
Creatine kinase β chain	**GSKβ**	**Tilleman et al. (2002)**	**MPTP mice**	**Jin et al. (2005)**
Creatine kinase	–	–	MPTP mice	Diedrich et al. (2008)
Cytochrome *c*, oxidase	–	–	MPTP mice	Jin et al. (2005)
Cytochrome *c*, oxidase subunit 5A	–	–	MPTP mice	Diedrich et al. (2008)
Cytochrome *c*, oxidase subunit 6B1	–	–	MPTP mice	Diedrich et al. (2008)
Cytochrome *c*1	–	–	MPTP mice	Jin et al. (2005)
Cytochrome P450 reductase	–	–	A53T *Drosphila*	Xun et al. (2008)
Dihydrolipoadmide dehydrogenase	–	–	*parkin* KO mice	Periquet et al. (2005)
Fructose-bisphosphate aldolase	–	–	MPTP mice	Diedrich et al. (2008)
Fructose-bisphosphate aldolase A	–	–	MPTP mice	Diedrich et al. (2008)
Fructose-bisphosphate aldolase C	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Jin et al. (2005) and Diedrich et al. (2008)
Glyceraldehyde-3-phosphate dehydrogenase	**APP/Sw**, **Aβ (1-42)-injected rat**	**Shin et al. (2004)** and **Boyd-Kimball et al. (2005)**	**parkin KO mice**, **MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Glycerol-3-phosphate dehydrogenase	–	–	L-DOPA mice, A53T *Drosophila*, MPTP mice	Valastro et al. (2007), Xun et al. (2008) and Jin et al. (2005)
GTP:AMP phosphtransferase mitochondrial	–	–	*parkin* KO mice	Periquet et al. (2005)
Hexokinase	–	–	MPTP mice	Jin et al. (2005)
Isocitrate dehydrogenase NADH cytoplasm	P301L tau, GSKβ	David et al. (2006) and Tilleman et al. (2002)	–	–
Lactate dehydrogenase	**SAMP8**	**Poon et al. (2005b)**	**parkin KO mice**, **A53T Drosphila**	**Periquet et al. (2005)** and **Xun et al. (2008)**
Malate dehydrogenase	**APP/Sw**	**Shin et al. (2004)**	**parkin KO mice**	**Periquet et al. (2005)**
Mitochondrial creatine kinase	SAMP8	Poon et al. (2005b)	–	–
NADH dehydrogenase	P301L tau	David et al. (2006)	–	–
NADH dehydrogenase 1 α subcomplex 8	–	–	MPTP mice	Jin et al. (2005)
NADH dehydrogenase, 75-kDa subunit	–	–	*In vitro* dopamine quinone-treated rats	Van Laar et al. (2008)
NADH dehydrogenase Fe–S protein 8	–	–	MPTP mice	Diedrich et al. (2008)
NADH ubiquinone oxidoreductase 23-kDa subunit	GSKβ	Tilleman et al. (2002)	–	–
NADH ubiquinone oxidoreductase 24-kDa subunit	GSKβ	Tilleman et al. (2002)	–	–
NADH ubiquinone oxidoreductase 39-kDa subunit	–	–	MPTP mice	Jin et al. (2005)
NADH ubiquinone oxidoreductase 49-kDa subunit	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice**	**Periquet et al. (2005)**
NADH ubiquinone oxidoreductase 51-kDa subunit	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
NADH ubiquinone oxidoreductase 75-kDa subunit	–	–	MPTP mice	Jin et al. (2005)
NADH ubiquinone oxidoreductase B15 subunit	P301L tau	David et al. (2006)		
Phosphofructokinase	–	–	A30P *Drosophila*, MPTP mice	Xun et al. (2007a) and Diedrich et al. (2008)
Phosphoglucomutase	GSKβ	Tilleman et al. (2002)	–	–
Phosphoglycerate kinase 1	–	–	*parkin* KO mice	Periquet et al. (2005)

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Phosphoglycerate mutase 1	**P301L tau, Aβ (1-42)-injected rat, Swedish mutant human transgenic rat**	**David et al. (2006), Boyd-Kimball et al. (2005) and Wilson et al. (2005)**	**In vitro dopamine quinone-treated rats, MPTP mice**	**Van Laar et al. (2008) and Diedrich et al. (2008)**
Phosphoglycerate mutase B	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Phospoglycerate kinase 1	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
Pyruvate dehydrogenase	**Aβ (1-42)-injected rat**	**Boyd-Kimball et al. (2005)**	**A30P α-synuclein mice**	**Poon et al. (2005c)**
Pyruvate dehydrogenase E1 component α subunit	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Jin et al. (2005) and Diedrich et al. (2008)
Pyruvate dehydrogenase E1 component β subunit	–	–	*parkin* KO mice	Periquet et al. (2005)
Pyruvate kinase	**APP/Sw, Swe/Lon**	**Shin et al. (2004)** and **Sizova et al. (2007)**	**parkin KO mice, A30P Drosophila, MPTP mice**	**Periquet et al. (2005), Xun et al. (2007a)** and **Diedrich et al. (2008)**
Pyruvate kinase 3	–	–	MPTP mice	Jin et al. (2005)
Succinate dehydrogenase	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Triosephosphate isomerase	–	–	MPTP mice	Jin et al. (2005)
Vacuolar ATP synthase subunit G1	–	–	MPTP mice	Jin et al. (2005)
Vacuolar ATP synthase subunit β-brain isoform	GSKβ	Tilleman et al. (2002)	–	–
Vacuolar H^+ ATPase E1	–	–	MPTP mice	Diedrich et al. (2008)
Energy metabolism/mitochondrial function				
Acetyl-CoA acetyltransferase	–	–	*parkin* KO mice	Periquet et al. (2005)
Acetyl-CoA acetyltransferase, mitochondrial	–	–	*parkin* KO mice	Periquet et al. (2005)
Mitochondrial import inner membrange translocase subunit TIM13 A	–	–	MPTP mice	Jin et al. (2005)
Succinyl-CoA ligase β-chain, mitochondrial	–	–	*parkin* KO mice	Periquet et al. (2005)
Ubiquinol-cytochrone *c* reductase complex 11-kDa protein, mitochondrial precursor	–	–	MPTP mice	Jin et al. (2005)
Ubiquinol-cytochrone *c* reductase complex core protein 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Ubiquinol-cytochrone *c* reductase complex core protein 2	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Diedrich et al. (2008)
Ubiquitin thiolesterase L1	–	–	MPTP mice	Diedrich et al. (2008)
Inflammation/immune response				
CD166 antigen precursor	–	–	MPTP mice	Jin et al. (2005)
Complement c1 q	Swe/Lon	Sizova et al. (2007)	–	–
Inducible nitric oxide synthase	–	–	MPTP mice	McLaughlin et al. (2006)
Low-affinity immunoglobulin ε FC receptor	–	–	*parkin* KO mice	Periquet et al. (2005)
Macrophage migration inhibitory factor	–	–	MPTP mice	Jin et al. (2005)
Lipid metabolism				
ACAT	Swe/Lon	Sizova et al. (2007)	–	–
Acyl carrier protein, mitochondrial precursor	–	–	MPTP mice	Jin et al. (2005)
Acyl-CoA dehydrogenase, very long chain specific	–	–	*parkin* KO mice	Periquet et al. (2005)
Acyl-CoA oxidase 2, peroxisomal	–	–	*parkin* KO mice	Periquet et al. (2005)
Acyl-CoA thioester hydrolase	–	–	*parkin* KO mice	Periquet et al. (2005)
Acyl-protein thioesterase 2	–	–	MPTP mice	Jin et al. (2005)
Annexin 5	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
ApoE precursor	**Swe/Lon**	**Sizova et al. (2007)**	**Axotomized rats**	**Rite et al. (2007)**
Lysophospholipase 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Phosphatidylethanolamine-binding protein	–	–	MPTP mice	Diedrich et al. (2008)
Propionyl CoA carboxylase α-chain	–	–	*parkin* KO mice	Periquet et al. (2005)
Yippee interacting protein 2	–	–	A30P *Drosophila*	Xun et al. (2007a)
Mitochondrial function				
Atp5b protein	–	–	MPTP mice	Diedrich et al. (2008)
Dihydrolipoyl dehydrogenase, mitochondrial	–	–	MPTP mice	Jin et al. (2005)
DJ-1	–	–	MPTP mice	Jin et al. (2005)
Mitochondrial matrix protein P1 precursor	GSKβ	Tilleman et al. (2002)	–	–
Mitochondrial precursor proteins import receptor	–	–	MPTP mice	Jin et al. (2005)
Mitofilin	–	–	*In vitro* dopamine quinone-treated rats	Van Laar et al. (2008)
Voltage-dependent anion channel 2	–	–	*In vitro* dopamine quinone-treated rats, MPTP mice	Van Laar et al. (2008), Jin et al. (2005) and Diedrich et al. (2008)
Voltage-dependent anion-selective channel protein 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Neurotransmission related				
4-Aminobutyrate aminotransferase, mitochondrial	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Comatose	–	–	A30P *Drosophila*	Xun et al. (2007a)
Excitatory amino acid transporter 2	–	–	MPTP mice	Jin et al. (2005)
Gamma-aminobutyric acid	–	–	MPTP mice	Jin et al. (2005)
n-Synaptobrevin	–	–	A30P *Drosophila*	Xun et al. (2007a)
Ras opposite	–	–	A30P *Drosophila*	Xun et al. (2007a)
Sodium- and chloride-dependent GABA transporter 3 homolog	–	–	MPTP mice	Jin et al. (2005)
Tyrosine 3-hydroxylase	–	–	*parkin* KO mice	Periquet et al. (2005)
Oxidative stress/antioxidant defense				
Antioxidant protein 2	GSKβ	Tilleman et al. (2002)	–	–
Carbonyl reductase 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Glutathione-*s*-transferase	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice**	**Periquet et al. (2005)**
Glutathione-*s*-transferase Mu 3	–	–	MPTP mice	Jin et al. (2005)
Glyoxalase 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Haptoglobin	–	–	Axotomized rats	Rite et al. (2007)
Peroxidase			MPTP mice	Diedrich et al. (2008)
Peroxiredoxin 1			MPTP mice	Diedrich et al. (2008)
Peroxiredoxin 2	**SAMP8**	**Poon et al. (2005a)**	**MPTP mice**	**Diedrich et al. (2008)**
Peroxiredoxin 2A	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Peroxiredoxin 2B	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Peroxiredoxin 3			MPTP mice	Diedrich et al. (2008)
Peroxiredoxin 5	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Diedrich et al. (2008)**
Peroxiredoxin 6	**Swe/Lon**	**Sizova et al. (2007)**	**MPTP mice**	**Diedrich et al. (2008)**
PHGPx	–	–	A30P *Drosophila*	Xun et al. (2007a)
Superoxide dismutase 1 (Cu–Zn)	–	–	MPTP mice	Diedrich et al. (2008)
Superoxide dismutase 2 (Mn)	–	–	*In vitro* dopamine quinone-treated rats, A53T *Drosphila*	Van Laar et al. (2008), Xun et al. (2008)
Thioredoxin reductase	–	–	*parkin* KO mice	Periquet et al. (2005)
Thioredoxin-like protein 2	–	–	MPTP mice	Jin et al. (2005)
Protein biosynthesis				
40S ribosomal protein SA	–	–	MPTP mice	Diedrich et al. (2008)
Ribosomal protein S12	–	–	MPTP mice	Diedrich et al. (2008)
Ribobsomal protein S17	–	–	A30P *Drosophila*	Xun et al. (2007a)
Ribosomal protein large subunits 13, 23, 30, and 43	–	–	α-Synuclein *C. elegans*	Ichibangase et al. (2008)
Ribosomal protein S3A	–	–	A30P *Drosophila*	Xun et al. (2007a)
Ribosomal protein small subunit 8	–	–	A53T *Drosophila*	Xun et al. (2008)
Ribosomal proteins large subunits 6, 14, and 23A	–	–	A53T *Drosophila*	Xun et al. (2008)
Similar to 60S ribosomal protein L18a	–	–	MPTP mice	Jin et al. (2005)
Stab	–	–	A30P *Drosophila*	Xun et al. (2007a)
Threonyl tRNA synthetase	–	–	*parkin* KO mice	Periquet et al. (2005)
Tyrosyl tTNA synthetase	–	–	*parkin* KO mice	Periquet et al. (2005)
RNA processing/transcription related				
ATP-dependent RNA helicase DDX19, dead box protein	–	–	*parkin* KO mice	Periquet et al. (2005)
Elongation factor 1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Elongation factor 1 R48D	–	–	A30P *Drosophila*	Xun et al. (2007a)
Elongation factor 2	–	–	MPTP mice	Jin et al. (2005)
Poly(rC)binding protein	–	–	*parkin* KO mice	Periquet et al. (2005)
Probable ATP-dependent RNA helicase p47	–	–	*parkin* KO mice	Periquet et al. (2005)
Similar to transcription elongation factor B polypeptide 3	–	–	MPTP mice	Jin et al. (2005)
Transcriptional associated protein purine-rich single stranded DNA binding protein α	GSKβ	Tilleman et al. (2002)	–	–
Zinc finger protein TZF-L	–	–	MPTP mice	Jin et al. (2005)
Signal transduction				
2′,3′-Cyclic nucleotide 3′-phosphodiesterase	–	–	MPTP mice	Jin et al. (2005)
Calbindin	–	–	A30P *Drosophila*	Xun et al. (2007a)
Calcium/calmodulin-dependent 3′,5′-cyclic nucleotide phosphodiesterase	–	–	MPTP mice	Jin et al. (2005)
Calcium/calmodulin-dependent protein kinase type II β chain	–	–	MPTP mice	Jin et al. (2005)
Calretinin	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
CaMK-II alpha subunit	Swe/Lon	Sizova et al. (2007)	–	–
CaMK-II of P11798 calcium/calmodulin dependent kinase type II α chain	–	–	MPTP mice	Jin et al. (2005)
cAMP/cGMP diesterase	–	–	MPTP mice	Jin et al. (2005)
Clathrin coat assembly protein AP50	–	–	MPTP mice	Jin et al. (2005)

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Dual specificity mitogen-actived protein kinase kinase 1	GSKβ	Tilleman et al. (2002)	–	–
G protein, γ 2 subunit	–	–	MPTP mice	Jin et al. (2005)
G protein, γ 12 subunit	–	–	MPTP mice	Jin et al. (2005)
MAGUK p55 subfamily member 2	–	–	*parkin* KO mice	Periquet et al. (2005)
MAGUK p55 subfamily member 3	–	–	*parkin* KO mice	Periquet et al. (2005)
MAGUK p55 subfamily member 6	–	–	*parkin* KO mice	Periquet et al. (2005)
Mitogen-activated protein kinase 1	GSKβ	Tilleman et al. (2002)	–	–
Peptidylprolyl *cis–trans* isomerase	–	–	MPTP mice	Diedrich et al. (2008)
Phosphatidyl inotisol transferase α isoform	GSKβ	Tilleman et al. (2002)	–	–
Protein kinase C and casine kinase substrate in neurons protein 1	–	–	MPTP mice	Jin et al. (2005)
Protein kinase C, γ type	–	–	MPTP mice	Jin et al. (2005)
Protein phosphatase 2 regulatory subunit	–	–	MPTP mice	Jin et al. (2005)
Protein TYPROTEIN tyrosine kinase 9-like	–	–	MPTP mice	Jin et al. (2005)
Protein tyrosine phosphatase, non-receptor type 1-1	–	–	*parkin* KO mice	Periquet et al. (2005)
Proto-oncogene C-*crk*	–	–	*parkin* KO mice	Periquet et al. (2005)
Purkinje cell protein 4	–	–	MPTP mice	Skold et al. (2006)
Ras-related C3 botulinum toxin substrate 1	–	–	NADH ubiquinone oxidoreductase 49-kDa subunit	
Receptor of activated protein kinase C1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Ser/Thr protein phosphatase 1 catalytic γ subunit	GSKβ	Tilleman et al. (2002)	–	–
Ser/Thr protein phosphatase 2B catalytic subunit, α isoform	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice**	**Periquet et al. (2005)**
Ser/Thr protein phosphatase PP1-β catalytic subunit	–	–	*parkin* KO mice	Periquet et al. (2005)
Ser/Thr protein phosphatase PP1-γ catalytic subunit	–	–	MPTP mice	Jin et al. (2005)
Similar to peptidyl-prolyl *cis–trans* isomerase	–	–	MPTP mice	Jin et al. (2005)
Sumo-1 activating enzyme subunit 2	–	–	*parkin* KO mice	Periquet et al. (2005)
β-Adrenergic receptor kinase 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Stress-related proteins/chaperones				
αβ-crystallin	–	–	L-DOPA mice	Valastro et al. (2007)
Aconitate hydratase, mitochondrial	–	–	*parkin* KO mice	Periquet et al. (2005)
Calnexin 99A	–	–	A53T *Drosphila*	Xun et al. (2008)
Glucose-regulated protein 78 kDa	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
Heat shock 70-related protein APG-1	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005) and Diedrich et al. (2008)
Heat shock cognate 71 kDa protein	–	–	*parkin* KO mice	Periquet et al. (2005)
Heat shock cognate 73	–	–	MPTP mice	Jin et al. (2005)
Heat shock protein 1			MPTP mice	Diedrich et al. (2008)
Heat shock protein 60	**Aβ (1-42)-injected rat**	**Boyd-Kimball et al. (2005)**	**MPTP mice**	**Diedrich et al. (2008)**
Heat shock protein 70	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Heat shock protein 90b	GSKβ	Tilleman et al. (2002)	–	–
Heat shock protein cognate 3	–	–	A53T *Drosphila*	Xun et al. (2008)
Heat shock-related 70-kDa protein 2	–	–	*parkin* KO mice	Periquet et al. (2005)
Mortalin (mtHSP70, GRP75)	**ApoE4**	**Osorio et al. (2007)**	**In vitro dopamine quinone-treated rats**	**Van Laar et al. (2008)**
Rtn11			A53T *Drosphila*	Xun et al. (2008)
Stress protein 70	**P301L tau**	**David et al. (2006)**	**parkin KO mice**	**Periquet et al. (2005)**
T-complex protein 1 ε subunit	**GSKβ**	**Tilleman et al. (2002)**	**MPTP mice**	**Jin et al. (2005)**
T-complex protein 1 θ and β subunits	GSKβ	Tilleman et al. (2002)	–	–
T-complex protein 1, α-subunit B	–	–	*parkin* KO mice	Periquet et al. (2005)
Transgelin-3	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Diedrich et al. (2008)**
Transthyretin	–	–	Axotomized rat	Rite et al. (2007)
Synaptic/axonal integrity				
Clipin E/coronin 6 type C	–	–	MPTP mice	Jin et al. (2005)
Coronin 1a	SAMP8	Poon et al. (2005a)	–	–
Coronin like protein P57 fragment	**GSKβ**	**Tilleman et al. (2002)**	**MPTP mice**	**Jin et al. (2005)**
Dihydropyrimidase-like 2	**APP/Sw, Swe/Lon, P301L tau, GSKβ, SAMP8**	**Shin et al. (2004), Sizova et al. (2007), David et al. (2006), Tilleman et al. (2002)** and **Poon et al. (2005b)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005)** and **Diedrich et al. (2008)**
Dihydropyrimidase-like 5	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Jin et al. (2005) and Diedrich et al. (2008)**
Micotubule-associated protein 1B			MPTP mice	Diedrich et al. (2008)
Myelin basic protein	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Jin et al. (2005)**
N-Ethylmaleimide sensitive fusion protein	**Swe/Lon**	**Sizova et al. (2007)**	**parkin KO mice**	**Periquet et al. (2005)**
Neurofascin precursor	–	–	MPTP mice	Jin et al. (2005)
Neurofilament triplet L protein	**SAMP8, GSKβ**	**Poon et al. (2005b)** and **Tilleman et al. (2002)**	**MPTP mice**	**Diedrich et al. (2008)**
Neurofilament M			MPTP mice	Diedrich et al. (2008)

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Stoned	–	–	A30P *Drosophila*	Xun et al. (2007a)
Synapsin-2	**P301L tau**	**David et al. (2006)**	**MPTP mice**	**Diedrich et al. (2008)**
Synaptonal associated protein	GSKβ	Tilleman et al. (2002)	–	–
Synaptophysin	–	–	MPTP mice	Jin et al. (2005)
Synaptotagamin I	Swe/Lon	Sizova et al. (2007)		
Syntaxin 1B	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Diedrich et al. (2008)
Syntaxin-binding protein 1	–	–	*parkin* KO mice, MPTP mice	Periquet et al. (2005), Jin et al. (2005)
Ubiquitin/proteaosome degradation			–	–
26S protease regulatory subunit 4	–	–	MPTP mice	Jin et al. (2005)
α-Synuclein			MPTP mice	Diedrich et al. (2008)
Deubiquitinating enzyme OTUB1	–	–	*parkin* KO mice	Periquet et al. (2005)
NEDD-4	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Proteasome complex activator subunit 2	APP/Sw	Shin et al. (2004)	–	–
Proteasome subunit α-2	–	–	L-DOPA mice	Valastro et al. (2007)
Proteasome subunit α-3	P301L tau	David et al. (2006)	–	–
Proteasome subunit β type 5	–	–	*parkin* KO mice	Periquet et al. (2005)
Ubiquitin activating enzyme 1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Ubiquitin carboxyterminal hydrolase L1	–	–	*parkin* KO mice	Periquet et al. (2005)
Ubiquitin-like protein Nedd8			MPTP mice	Diedrich et al. (2008)
Vasopressin activated calcium mobilizing receptor (CUL5)	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Others				
3-Oxoacid CoA transferase 1	–	–	MPTP mice	Diedrich et al. (2008)
11 days embryo cDNA	–	–	MPTP mice	Jin et al. (2005)
α-1-Antitrypsin 1–5	–	–	MPTP mice	Diedrich et al. (2008)
β-Synuclein	**Aβ (1–42)-injected rat**	**Boyd-Kimball et al. (2005)**	**MPTP mice**	**Diedrich et al. (2008)**
ADAM22	–	–	MPTP mice	Jin et al. (2005)
ADAM23	–	–	MPTP mice	Jin et al. (2005)
Adapter-related protein complex 2 α1 subunit	–	–	–	–
Adenine phosphoribosyltransferase	Swedish human mutant transgenic rat	Wilson et al. (2005)	–	–
Adenosine	–	–	A30P *Drosophila*	Xun et al. (2007a)
Adenosylhomocysteinase at 13	–	–	A30P *Drosophila*	Xun et al. (2007a)
Adenylosuccinate synthetase	–	–	MPTP mice	Jin et al. (2005)
Adenyl cyclase-associated protein 1	–	–	MPTP mice	Diedrich et al. (2008)
ADP-ribosylarigine hydrolase	–	–	*parkin* KO mice	Periquet et al. (2005)
Alpha adducing	–	–	MPTP mice	Jin et al. (2005)
Amyloid β A4 protein precursor	–	–	MPTP mice	Jin et al. (2005)
Astrocytic phosphoprotein PEA-15	–	–	MPTP mice	Diedrich et al. (2008)
Bent	–	–	A30P *Drosophila*	Xun et al. (2007a)
Chaoptic	–	–	A53T *Drosphila*, A30P *Drosophila*	Xun et al. (2008) and Xun et al. (2007a)
Cheerio	–	–	A30P *Drosophila*	Xun et al. (2007a)
Chickadee	–	–	A30P *Drosophila*	Xun et al. (2007a)
Claudin-11	–	–	MPTP mice	Jin et al. (2005)
Cleavage and polyadenylation specificity factor, 100-kDa subunit	–	–	MPTP mice	Jin et al. (2005)
D-Dopachrome tautomerase	–	–	MPTP mice	Jin et al. (2005)
Diphenol oxidase 2	–	–	A30P *Drosophila*	Xun et al. (2007a)
Discs large homolog 1	–	–	MPTP mice	Jin et al. (2005)
DnaJ homolog subfamily A member 2	–	–	MPTP mice	Jin et al. (2005)
Failed axon connections	–	–	A53T *Drosophila*	Xun et al. (2008)
Fat body protein 1	–	–	A53T *Drosophila*, A30P *Drosophila*	Xun et al. (2008) and Xun et al. (2007a)
Fatty acid binding protein			MPTP mice	Diedrich et al. (2008)
Frizzled 7 precursor	–	–	MPTP mice	Jin et al. (2005)
Glutactin	–	–	A30P *Drosophila*	Xun et al. (2007a)
Growth factor receptor bound protein 2	–	–	MPTP mice	Diedrich et al. (2008)
Guanine nucleotide-binding protein β-subunit 1	–	–	MPTP mice	Diedrich et al. (2008)
Hemoglobin α	GSKβ	Tilleman et al. (2002)	–	–
Heparin sulfate *N*-deacetylase/*N*-sulfotransferase	–	–	MPTP mice	Jin et al. (2005)
HLA-B-asssociated transcript 1a	–	–	MPTP mice	Jin et al. (2005)
Hypothetical serine-rich containing protein	–	–	MPTP mice	Jin et al. (2005)
Hypoxanthine guanine phosphoribosyl transferase	GSKβ	Tilleman et al. (2002)	–	–
Karst	–	–	A53T *Drosophila*	Xun et al. (2008)
Lactoylglutathione lyase	–	–	MPTP mice	Jin et al. (2005)
MKIAA0968 protein, splice isoform α	–	–	MPTP mice	Jin et al. (2005)
Methylcrotonyl-CoA carboxlase β-chain	–	–	MPTP mice	Diedrich et al. (2008)
Nectin-like protein 1	–	–	MPTP mice	Jin et al. (2005)
Nucleoside diphosphate kinase A	GSKβ	Tilleman et al. (2002)	–	–

Table 2 (*Continued*)

Biological function/protein(s)	AD		PD	
	Model(s)	References	Model(s)	References
Nucleoside diphosphate kinase 2	–	–	MPTP mice	Diedrich et al. (2008)
Odorant binding protein 44a	–	–	A30P *Drosophila*	Xun et al. (2007a)
Odorant binding protein 99	–	–	A53T *Drosophila*	Xun et al. (2008)
Peanut-like protein	GSKβ	Tilleman et al. (2002)	–	–
Protein CGI-51 homolog	–	–	MPTP mice	Jin et al. (2005)
Pugilista	–	–	A30P *Drosophila*	Xun et al. (2007a)
Punch	–	–	A30P *Drosophila*	Xun et al. (2007a)
Purple	–	–	A30P *Drosophila*	Xun et al. (2007a)
Q8R3V5 SH3 domain GRB2-like protein B2	–	–	MPTP mice	Jin et al. (2005)
Retinal degeneration A	–	–	A53T *Drosphila*	Xun et al. (2008)
Retinin	–	–	A53T *Drosophila*, A30P *Drosophila*	Xun et al. (2008) and Xun et al. (2007a)
Ribose-phosphate pyrophosokinase 1	–	–	*parkin* KO mice	Periquet et al. (2005)
Rpt1	–	–	A30P *Drosophila*	Xun et al. (2007a)
Serine (or cysteine) proteinase inhibitor, clade A, member 1e			MPTP mice	Diedrich et al. (2008)
Serum albumin	**GSKβ**	**Tilleman et al. (2002)**	**parkin KO mice, MPTP mice**	**Periquet et al. (2005) and Diedrich et al. (2008)**
Similar to CGI-49	–	–	MPTP mice	Jin et al. (2005)
Small nuclear ribonucleoprotein polypeptide F	–	–	MPTP mice	Diedrich et al. (2008)
Spermidine synthase	–	–	*parkin* KO mice	Periquet et al. (2005)
Splice isoform 1 of P60202 myelin proteolipid protein	–	–	MPTP mice	Jin et al. (2005)
Splice isoform 3 of Q9EPR4 solute carrier family 23, member 2	–	–	MPTP mice	Jin et al. (2005)
TER94	–	–	A30P *Drosophila*	Xun et al. (2007a)
Transformation sensitive protein IEF SSP 3521	GSKβ	Tilleman et al. (2002)	–	–
Trehalose-6-phosphate synthase 1b	–	–	A30P *Drosophila*	Xun et al. (2007a)
Tropomyosin	–	–	A30P *Drosophila*	Xun et al. (2007a)
Uncharacterized hematopoietic stem/progenitor cells protein MDS029 homolog	–	–	MPTP mice	Jin et al. (2005)
Walrus	–	–	A30P *Drosophila*	Xun et al. (2007a)
Valosin-containing protein	–	–	MPTP mice	Diedrich et al. (2008)

[a] It should be noted that proteins listed in this table were grouped according to the text and tables found within the corresponding references (including Zabel et al., 2008). Bolded proteins were identified in proteomics studies of both AD and PD models. Refer to references for a complete list of proteins identified in individual studies.

and PD that extends upon a recent review by Zabel et al. that compared protein expression overlap in AD, PD, Huntington's disease, and amyotrophic lateral sclerosis (Zabel et al., 2008). Thus, these results have revealed specific pathways relevant to neurodegeneration and that should be further investigated to fully understand their role in human disease pathogenesis. A recurring theme of synaptic/axonal maintenance, metabolic, chaperone, and antioxidant protein variability occurs in the AD models described in this review. Similarly, metabolic, transport, stress response, synaptic integrity, and ubiquitin/proteasome pathways consistently were perturbed in PD models at the protein level.

Overall, these findings are consistent with hypotheses that mechanisms for energy production, protection from oxidative damage and improper protein clearance, and synapse integrity are disrupted and contribute to AD and PD pathogenesis. Animal models that take advantage of known genetic mutations in both familial and sporadic forms of AD and PD have shed light on important physiological processes that may be implicated in disease pathogenesis. Additional studies of this nature, that utilize proteomics as a tool to understand disease etiology, will help in the development of treatments to slow or prevent these devasting neurodegenerative disorders.

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