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Validity of the MPTP-treated mouse as a model for Parkinson's disease

Cornelius J.H.M. Klemann, M.Sc. [1], Gerard J.M. Martens, Ph.D. [1], Geert Poelmans, M.D., Ph.D. [1,2,3] *, Jasper E. Visser, M.D., Ph.D. [1,4,5] *

[1] Department of Molecular Animal Physiology, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

[2] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[3] Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands

[4] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[5] Department of Neurology, Amphia Hospital, Breda, The Netherlands

* Equal contribution

Corresponding author: Jasper E. Visser, MD PhD
Department of Neurology
Radboud University Medical Center
P.O.Box 9101
6500 HB Nijmegen, The Netherlands
Telephone: +31 (0)24 361 66 00
Fax: +31 (0)24 354 11 22
Email: jasper.visser@radboudumc.nl

FIGURE DESCRIPTIONS

Parkinson's disease (PD) as well as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment result in the degeneration of dopaminergic neurons in the substantia nigra (SN), leading to a decrease of dopamine (DA) release to the striatum. Below, the molecular landscapes of biological processes shared between PD and MPTP treatment in the substantia nigra (SN) (Figures 1a and 1b) and striatum (Figure 2) are described in full detail, and the current knowledge about the functions and interactions of all landscape proteins is presented. In these descriptions, proteins that appear in **bold** are dysregulated in both human PD and the MPTP mouse model. Underlined proteins are associated with PD through either expression or genetic data from PD patients, and familial PD proteins are double underlined.

Detailed description of the biological processes depicted in Figure 1A. Molecular landscape of interacting proteins, encoded by the mRNAs that are differentially expressed in the SN of *both* human PD patients and MPTP-treated mice, located primarily in the (pre) synapse and axon of the DA neuron.

DA synthesis

TH catalyzes the rate-limiting step in DA synthesis, i.e. the conversion of the amino acid L-tyrosine into L-3,4-dihydroxyphenylalanine (L-DOPA)[1,2]. **TH** expression is increased by the receptor tyrosine-protein kinase **RET**[3] and **SLC6A3**[4]. **TH** is activated by the adaptor protein **YWHAZ**[5,6] and the cyclin-dependent kinase **CDK5**[7], and DA itself inhibits **TH** activity in a negative feedback loop[8,9]. **YWHAZ** also binds to the kinases **MARK2**[10], involved in microtubule regulation[11], and **PDXK**[12], required for the synthesis of pyridoxal-5-phosphate (PLP) from vitamin B6[11]. PLP, in turn, is an essential cofactor for the conversion of L-DOPA into DA by dopa decarboxylase[13].

(DA) release

Soluble NSF Attachment Protein Receptor (SNARE) proteins form a complex that is required for synaptic vesicle docking and subsequently the release of their contents (e.g., DA) into the synaptic cleft[11]. **SNAP25** and **VAMP2**, core components of the SNARE complex, physically interact with each other[14] and form a complex together with **STXBP1**[15], a protein that is also involved in synaptic vesicle fusion and docking[11]. **STXBP1** binds to **CDK5**[16], a protein involved in cytoskeleton regulation, synapse plasticity, exocytosis and endocytosis (see more on **CDK5** below). The vesicle fusion ATPase **NSF** increases the dissociation of the SNARE complex (dissociation of **SNAP25** and **VAMP2**) and thereby enables the vesicle to fuse with the plasma membrane[17]. **NSF** binds to **YWHAZ**[18] and AKT1[19], and inhibits CASP3 activity[20].

The DA – acetylcholine (ACh) balance may be involved in PD pathology[21] and ACh regulates DA release[22]. The extracellular protein **ACHE** hydrolyzes ACh that is released into the synaptic cleft[11]. Although **ACHE** does not directly interact with other landscape proteins, its function may well be linked to PD since its activity is reduced in the cerebral cortex and the medial occipital cortex of PD patients[23]. Moreover, **ACHE** is inactivated by MPTP[24] and **ACHE** deficiency is neuroprotective in the MPTP mouse model[25].

DA reuptake

In response to an action potential, DA is released from vesicles in the synaptic cleft by exocytosis and reuptake of extracellular DA occurs by **SLC6A3** to terminate the signal[26,27]. **SLC6A3** binds to the familial PD proteins PARK2[28] and SNCA[29], which both enhance its activity. PARK2 and **RET** increase the expression of **SLC6A3**[30,28,3], while SNCA increases **SLC6A3** translocation to the plasma membrane[29]. In addition to increasing the expression of **TH**, **SLC6A3** activates AKT1[31] and both inhibits the activity[32] and decreases the expression of **CDK5**[33]. Cytoplasmic DA (either synthesized by **TH** or after reuptake by **SLC6A3**) is transported into cytoplasmic vesicles by SLC18A2[11]. These vesicles are subsequently translocated via axoplasmic transport to the synapse for exocytosis.

Recycling of membrane-bound synaptic components

To further control DA levels in the synaptic cleft, proteins including **SLC6A3**, DRD2 and the voltage-dependent calcium channel (VDCC) are endocytosed, transported to the endosome and either recycled back to the membrane or degraded. **ATP6V0D1** is a subunit of the proton V-ATPase and increases the acidity of the endosome[11], which is required for a normal endosomal function. DRD2 binds to **SLC6A3**[34] and increases its localization in the plasma membrane[35], and activates the transport activity of **SLC6A3**[36]. **SNAP25** is also involved in this process, by binding to **SLC6A3**[37] and VDCC[38,39]. Correct regulation of the recycling and degradation of DRD2 and **SLC6A3** is essential for normal neuronal DA signaling and deregulation of the proteins that regulate their endocytosis and/or expression at the plasma membrane can disturb this signaling. The G protein **GNAI2** regulates the expression of, binds to, and prevents the plasma membrane translocation of, DRD2[40]. **RGS4** binds to both DRD2[41] and **GNAI2**[42], and increases the GTPase activity of **GNAI2** (not shown)[43]. In turn, **GNAI2** increases the recruitment of **RGS4** to the plasma membrane (not shown) [44], where it binds – among others – to **LPAR1**[41]. The Rab GTPases **RAB4A**, **RAB6A**, **RAB11A** and **RAB14** are also involved in (vesicular) recycling and endosomal function; see the section '(Vesicle) trafficking and exocytosis' in the detailed description of figure 1b below for their functions within the landscape.

Cytoskeleton / cytoplasmic cascades

Recycling, trafficking and exocytosis require cytoskeletal regulation. A substantial number of landscape proteins control cytoskeleton dynamics, e.g., by regulating RAC1 activity. RAC1 is activated by **FRAT2**[45], **TNK2**[46], **FYN**[47], **DLK1**[48], **RET**[49,50], **LPAR1**[51], and **KIFAP3**[52], and inhibited by **CDK5**[53] and **CRMP1**[54]. Further, RAC1 binds to **RBM39**[55] and **RAP1GDS1**[56]. The latter also binds to **KIFAP3**[57] and regulates the GDP/GTP exchange of GTP-binding proteins such as RAC1[58]. RAC1 has multiple functions. First, it increases the expression of **CDH2**[59] and activates **MAPK8**[60], a serine/threonine-protein kinase that is involved in cell proliferation, differentiation, migration, transformation and programmed cell death (see also the section 'Mitochondrial function and apoptosis' in the description of figure 1b for the role of **MAPK8** in apoptosis)[11]. **MAPK8** binds to MAP3K7[61], CASP3[62], **mTORC1**[63] and **KLC1**[64]. Apart from RAC1 activation, **MAPK8** is also activated by **MAGED1**[65], **GNAI2**[66], **MAP2K4**[67], **RET**[49], **LPAR1**[68] and DA[69], and inhibited by AKT1[70]. **MAGED1** also binds to MAP3K7[71] and **ATXN10**[72], and activates CASP3[65]. **MAPK8** also activates CASP3[73,74] and **mTORC1**[63], and inhibits AKT1[75,76]. **MAP2K4** is an essential part of the MAP kinases signaling pathway and is bound to the phosphatase **DUSP19**[77], AKT1[70] and MAP3K7[78], whereas AKT1 inhibits[70] and MAP3K7 activates **MAP2K4**[79]. Multiple proteins in the

landscape regulate AKT1. AKT1 binds to **NSF** and **MAP2K4**, as mentioned above, as well as to **YWHAZ**[80] and **MARK2**[81], is activated by **SLC6A3** (see above), **YWHAZ**[82], **GNAI2**[83], **LPAR1**[68], **TNK2**[84] and **CDH2**[85], and inhibited by **MAPK8** (see above), **RGS4**[86] and **DLK1**[87]. Second, RAC1 increases the polymerization of globular actin(**ACTG1**)[88] to filament actin (F-actin)[11]. **ACTG1** binds to **CTBP2**[89], MAP3K7[90] and **NDRG1**[91] (see Figure 1b and its description for more **ACTG1** interactions). Moreover, **CDH2**[92], **GNAI2**[93] (not shown), **VSNL1**[94] and the **NMDAR**[95] bind to actin, and **CDK5** increases actin polymerization[53].

Microtubule-dependent trafficking

In addition to RAC1, **FYN** is a non-receptor tyrosine-protein kinase that is involved in cell growth and survival, cell adhesion, cytoskeletal remodeling and axon guidance[11]. **FYN** is activated by **L1CAM**[96] and is itself an activator of RAC1 (see above), **TNK2**[97] and CASP3[98]. **FYN** is cleaved by CASP3[99,100]and binds to **TNK2**[97], **GABRG2**[101] and MAPT[102]. Like **FYN, TNK2** is a non-receptor tyrosine-protein kinase and is involved in cell survival, proliferation and endocytosis[11], whereas **GABRG2** is a subunit of the GABA receptor and regulates neuronal inhibition[11]. Moreover, **FYN** phosphorylates MAPT[103,104], which is a susceptibility gene for idiopathic PD[105-109] that promotes assembly and stability of microtubules[11]. Microtubule-dependent trafficking is affected in PD and, among others, affects axonal transport of autophagosomes that contain damaged mitochondria and aggregated proteins, which can lead to SNCA accumulation and synaptic dysfunction[110,111]. In the landscape, MAPT binds to **MARK2**[112], **YWHAZ**[10], **KLC1**[113], **CDK5**[114], **STXBP1**[16] and **PPP2R2A**[115]. In addition, MAPT is phosphorylated by **CDK5**[116] and **FYN**[104], whereas **PPP2R2A** dephosphorylates MAPT[117]. Furthermore, **MARK2** phosphorylates both MAPT and **MAP4** which causes microtubule detachment and disassembly[11]. **CHP1** binds to microtubules and mediates the binding of the endoplasmic reticulum (ER) and the Golgi apparatus with microtubules (not shown)[11]. Other proteins in the landscape that bind microtubules are **MAPRE2** (not shown)[118], **NDRG1** (not shown)[119], **KLC1** (not shown)[11] and **MAP4** (not shown)[120]. **KLC1** is a kinesin that regulates microtubule-associated transport of organelles[11] and **MAP4** promotes the assembly of microtubules[121]. In addition, **MAPK8** is known to increase microtubular assembly[122,123].

Cell adhesion

The proteins **L1CAM**, **FYN**, **CDH2**, **CDH8** and **RET** regulate cell adhesion[11]. **L1CAM** regulates neuron-neuron adhesion and is found in axon terminals[11] and **FYN** regulates synapse formation[124]. The cadherins **CDH2** and **CDH8** are calcium-dependent adhesion molecules[11]. **CDH2** binds **KIFAP3**[125], **NMDAR**[95] and actin[92]. Cleavage of **RET** by caspases results in a fragment that functions as a cadherin accessory protein that potentiates cadherin-mediated cell aggregation[126].

Autophagy

As indicated above, microtubule-dependent trafficking is necessary for the transport of autophagosomes and degradation of their cargo. Autophagy dysregulation is also directly implicated in PD via the familial PD proteins[127]. In the landscape, **MAPK8**, **CDK5** and **AKT1S1** (**mTORC1**) regulate autophagy, e.g., **MAPK8** phosphorylates **BCL2**, which induces dissociation of **BCL2** from Beclin-1 and autophagy activation (not shown)[128]. In addition, **mTORC1** binds to[63], and is activated by, **MAPK8**[63], and has been shown to inhibit autophagy[129,130]. Furthermore, **mTORC1** binds to **PPP2R2A**[131], **YWHAZ**[12] and **RPL5**[132], whereas **YWHAZ** and **RPL5** also bind to each

other[12]. Lastly, the kinase **CDK5** has been shown to be required for autophagy in multiple PD models[133-135].

Calcium

Calcium channels regulate neuron excitability and release of neurotransmitters such as DA. In PD, nigral DA neurons show a dysregulation of calcium[136]. In the landscape, calcium is transported into the cell by the **NMDAR**[137] and the VDCC[138], and transported out of the cell by **SLC8A1**[139,140]. The **NMDAR** binds to **CDH2**[95]and the VDCC binds to **SLC8A1**[141,39], **TSPAN7**[142], **MAP4**[39], **MARK2**[39], **SLC4A3**[39], **CRMP1**[142], **PFKM**[39], **RAB14**[39] and, as already mentioned above, **SNAP25**[38,39]. These proteins have a wide range of functions. **SLC8A1** rapidly transports Ca2+ out of the cell to prevent overloading of intracellular stores[139]. **TSPAN7** is a surface glycoprotein that may have a role in neurite outgrowth[143]. **MAP4** and **MARK2** regulate microtubular dynamics (see above). **SLC4A3** is an anion exchanger that exchanges $HCO3^-$ for Cl^- and thereby regulates the intracellular pH[11]. Another protein in the PD landscape that regulates neuronal pH by transporting HCO3- into the cell is **SLC4A8**[11]. **CRMP1** regulates remodeling of the cytoskeleton[11]. **PFKM** binds to **YWHAZ**[18] and catalyzes the conversion of D-fructose 1,6-phosphate to D-fructose 1,6-biphosphate[11]. Binding of D-fructose 1,6-bisphosphate to soluble Fe2+ prevents its conversion to the insoluble Fe3+, an oxidation step that produces oxygen radicals. The availability of D-fructose 1,6-biphosphate may therefore affect iron content and oxygen radical levels[144] in the SN of PD patients. Lastly, **RAB14** and **SNAP25** are involved in intracellular trafficking (see above). Furthermore, VDCC function and thus calcium influx is inhibited by **CDK5**[145,146]. **LPAR1** increases calcium mobilization in the cytosol[147], whereas **RGS4** and **RGS7** both decrease mobilization of calcium[148,149]. In addition, **RAB4A** and **RAB11A** (not shown) increase the intracellular calcium concentration[150]. Calcium in turn activates **MAPK8**[151], **FYN**[96] and **VSNL1**[152,153], and inhibits **NSF**[154]. Moreover, calcium increases the expression of **NDRG1**[155] and binds to **VSNL1**[156], **CHP1** (not shown)[157], **CDH2**[11] and **CDH8**[11].

Familial PD proteins

The familial PD proteins have many interactions with components within the landscape. SNCA, the primary component of Lewy bodies in PD DA neurons, binds to **SLC6A3**[29], **TH**[158], **YWHAZ**[159], **MARK2**[159], **MAPK8**[160], **KLC1**[161], **MAP4**[159], **ATP6V0D1**[159], **FYN**[162,163], **STXBP1**[159], **SNAP25**[164] and **VAMP2**[165]. Further, SNCA activates **SLC6A3**[29], decreases **TH** expression (not shown)[166], inhibits **TH**[158,167] and **MAPK8**[168], and is inhibited itself by **FYN**[162]. Interestingly, SNARE (**SNAP25** and **VAMP2**) dysfunction results in mislocalization and accumulation of SNCA and could be an important pathomechanism of PD[169], which emphasizes the importance of the normal functioning of the SNARE complex. Furthermore, binding of PARK7 to **VAMP2**[170] and of LRRK2 to **NSF**[171] shows that other familial PD proteins also have a direct impact on SNARE complex function. LRRK2 also binds to **MAP2K4**[172], **GNAI2**[173] and **YWHAZ**[174], and activates AKT1[175]. PARK2, UCHL1, EIF4G1 and PINK1 are four other familial PD proteins that have interactions with proteins in the landscape, i.e., PARK2 binds to and is phosphorylated by **CDK5**[176], binds to **SLC6A3**[28] and **ACTG1**[177], inhibits **MAPK8**[178], and increases expression of **SLC6A3**[30]. UCHL1 binds to AKT1[19], SNCA[179], **RANBP9**[180], **mTORC1**[181] and **EIF1B**[72], while EIF4G1 binds to **YWHAZ**[182] and **MARK2** binds to[183], and activates, PINK1[183].

Detailed description of the biological processes depicted in Figure 1B. Molecular landscape of interacting proteins, encoded by the mRNAs that are differentially expressed in the SN of *both* human PD patients and MPTP-treated mice, located primarily in the cell body and axon of the DA neuron.

Transcriptional and translational regulation

Histone regulation. HDAC1 deacetylates core histones and thereby represses gene transcription[11]. HDAC1 expression is increased in the SN of PD patients[184] and is one of the central proteins in the landscape of SN mechanisms overlapping between PD and MPTP-treated mice. HDAC1 expression is increased by **SASH1**[185] and HDAC1 binds to **CDK5**[11], **DHX36**[186], **CCDC6**[187], PARK7[188], **MAPK8**[189], **PAPOLA**[190], the transcriptional regulators SIRT1[191], **GTF2I**[192], **DDX5**[193] and **NFKBIA**[194], and the transcription factors **SOX2**[195], **NR4A2**[196], **SATB1**[197] and NFKB[198]. HDAC1 itself activates AKT1[199], decreases the expression of BAX[200] and binds to the promoters of the genes encoding **SLC8A1**[201] and **TH**[196]. The HDAC1-associated transcriptional regulators SIRT1, **GTF2I**, **DDX5** and **NFKBIA** have multiple other landscape interactors. Variants in the SIRT1 gene promoter contribute to PD risk[202], and SIRT1 deacetylates HDAC1 and thereby increases its enzymatic activity (not shown)[191]. Further, SIRT1 binds to **USP22**[203,204], a histone deubiquitination protein that inhibits SIRT1 degradation[204] and, by removing ubiquitin from H2A and H2B, functions as a coactivator of histones[11]. Furthermore, SIRT1 binds to **SATB1**[205], **PAPOLA**[190], **GTF2I**[206], **MAPK8**[207] and the PD-associated[208]FOXO1[209]. SIRT1 inhibits FOXO1 (not shown)[210], whereas FOXO1 increases SIRT1 expression[211]. Further, **MAPK8** increases the degradation of SIRT1[212]. The familial protein PARK7 binds in the cytoplasm to **GTF2I** and thereby prevents its translocation to the nucleus in which **GTF2I**[213] is together with HDAC1 part of the deacetylation complex[11].In addition to binding to HDAC1, **DDX5** binds to **NDRG1**[91], AKT1[214] and **YWHAZ**[182]. Expression of NFKB is increased in the PD brain[215]. **NFKBIA** binds to NFKB and thereby prevents its activation and translocation to the nucleus[216]. **NFKBIA** degradation is increased by **RET**[217], **FYN**[218] and **MAPK8**[219], and inhibited by **BCL2**[220]. Increased degradation or inhibition of **NFKBIA** increases NFKB activation and translocation to the nucleus[216]. **NFKBIA** binds to **ACTG1**[90] and **PSMA1**[221], and activates **MAPK8**[222]. Further, **NFKBIA** increases the expression of the transcriptional repressor **MXD4**[223] and **RGS4**, a regulator of G proteins[224]. Furthermore, **NFKBIA** decreases the expression of the familial PD protein PARK7[223] and of adaptor protein **YWHAZ**[225]. Regulation of the expression by **NFKBIA** is probably an indirect effect of its inhibitory function on the NFKB complex. Like **NFKBIA,**NFKB binds also to **ACTG1**[90], **PSMB5**[90], **PAPOLA**[90] and **DDX1**[90]. HDAC1 deacetylates the NFKB subunit RELA and in this way inhibits the transcriptional activity of NFKB[11].

In addition to binding to **NFKBIA** and NFKB (see above), **ACTG1** also binds to LRRK2[173], PARK2[177], SNCA[159] and **YWHAZ**[182]. The adaptor protein **YWHAZ** binds (in addition to the proteins mentioned above) to the 60S ribosomal protein **RPL10A**[12], the ATP-dependent RNA helicases **DDX1**[12] and **DDX5**[182], GIGYF2[12], AKT1[80] and FOXO1[226]. GIGYF2, AKT1 and FOXO1 are all associated with PD[227,228,208] and dysreglation of **YWHAZ** may interfere with their function. On its turn, **DDX1** binds to **NDRG1**[91] and SNCA[229] and acts as a coactivator to enhance NFKB-mediated transcriptional activation[11].

DA neuron signature.**NR4A2** and **SOX2** are important transcription factors for establishing and maintaining a DA-neuron-like expression pattern,[230] as is also apparent from their requirement for reprogramming fibroblasts towards a dopaminergic phenotype[231].
NR4A2 increases the expression of **TH**[232], **SLC6A3**[232], PITX3[232], **RET**[233] and SLC18A2[232], and decreases the expression of SNCA[234]. In addition to binding to HDAC1, **NR4A2** binds to **GTF2I**[235] and NFKB[236]. **SATB1** decreases expression of **NR4A2**[237] and increases the expression of **ACTG1**[237]. The HDAC1-binding **SOX2** (see above)[195] also binds to **YWHAZ**[238], **RANBP9**[238], **CTBP2**[195] and **NFIB**[195], and its expression is increased by AKT1[239] and FOXO1[240].

Other transcriptional regulators. PTEN is a phosphatase that dephosphorylates PIP3 to PIP2 and hence inhibits AKT1 signaling[241,11]. **RET** activates AKT1[242] that subsequently translocates to the nucleus[11] and increases the expression of **NDRG1**[243] and **SOX2** (see above)[239]. Furthermore, PTEN binds to and activates the familial PD protein PINK1[244] and affects the expression of multiple proteins in the landscape by increasing the expression of **PAPOLA**[245], **GTF2I**[245], **MXD4**[245] and **NDRG1**[246], and decreasing the expression of **NR4A2**[247], **MAPK8**[248] and **TH**[247]. The expression of PTEN itself is decreased by the 60S ribosomal protein **RPL5**[249] and the transcriptional repressor **CTBP2**[250].

Alternative pre-mRNA splicing. The polymerase **PAPOLA** creates the 3'-poly(A) tail of mRNAs[11], is required for endoribonucleolytic cleavage at poly(A) sites[11] and binds to HDAC1 (see above). **YTHDF2** has also a role in mRNA stability and splicing, by binding to N6-methyladenosine[11]. Of note, multiple other proteins involved in mRNA splicing are dysregulated in both human PD and the MPTP mouse model. MAGOH1 and **CASC3** are core components of the exon junction complex that is deposited at splice junctions on mRNAs, regulating mRNA splicing, nuclear export, cellular localization and translation efficiency[11]. MAGOH1 binds to **CASC3**[251], **ZC3H11A**[251], **SRSF7**[251], **RBM39**[251], and **SRPK2** (not shown)[252]. **RBM39** also binds to **SRSF7**[253] as well as **YWHAZ**[182] and **SRPK2**[254]. **SRPK2** is required for spliceosome complex formation[255] and, together with MAGOH1 and **RBM39**, binds to **SRSF7**[252] and MAPT[256], and increases the phosphorylation of **RBM39** (not shown)[252], **SRSF7** (not shown)[252] and MAPT (not shown)[256]. Phosphorylation of **SRPK2** at Thr-492 by AKT1 promotes its nuclear translocation and enhances its activity[11]. Like **CASC3**, MAGOH1 and **SRPK2, RBM39** and **SRSF7** are involved in pre-mRNA splicing[257,258]. For instance, **SRSF7** is involved in mRNA export out of the nucleus[259] and is known to prevent splicing of exon 10 of MAPT (not shown)[260]. **CLK4** phosphorylates proteins of the spliceosome complex[11] and regulates the alternative splicing of MAPT[261]. MAPT itself increases the expression of **MAPK8**[262].
Other proteins that also affect alternative splicing and are involved in nucleosome/ histone regulation are **HNRNPH3**, **CRMP1**, **H2AFJ** and **ANP32B**. **HNRNPH3** associates with pre-mRNA in the nucleus[11], and binds to PARK2[263] and **CRMP1**[264]. **H2AFJ** is a H2A histone variant and core component of the nucleosome[11] and **ANP32B** stimulates core histones to assemble into a nucleosome[11]. Nucleosomes define the exon-intron border and since pre-mRNA splicing occurs co-transcriptionally, nucleosome organization, transcription elongation rate or epigenetic marks can affect pre-mRNA splicing[265,266]. Moreover, histone deacetylation by HDAC1 affects pre-mRNA splicing, resulting in local repression of transcription[267,268,265]. HDAC1 is up-regulated in the SN of human PD patients and interacts with multiple proteins in the landscape (see also above).
Taken together, the central position of HDAC1 and the occurrence of multiple proteins involved in

histone regulation and pre-mRNA splicing in the SN landscape suggest that dysregulation of nucleosome organization and the splicing machinery are important factors in the biological processes that overlap between PD and the MPTP mouse model.

(Vesicle) trafficking and exocytosis

In Figure 1a, the involvement of the SNARE complex in (DA) exocytosis is shown, however, the SNARE complex also regulates intracellular transport, as is apparent from the binding of **SNAP25** to both **NAPB**[269] and **KLC1**[270]. **NAPB** is required for vesicular transport between the ER and the Golgi apparatus[11], and **KLC1** is a microtubule-associated protein that regulates the transport of organelles such as mitochondria. Like the SNARE complex, the familial PD protein SNCA may be involved in DA release and transport[11], but also in ER-to-Golgi vesicle trafficking[271,272]. SNCA modulates vesicle trafficking by binding to RABAC1 (not shown)[273], a protein that regulates the interaction between Rab GTPases and the SNARE complex[274]. Overexpression of SNCA disrupts vesicle trafficking and increases accumulation of vesicles in the cytoplasm[273]. Four Rab GTPases (**RAB4A**, **RAB6A**, **RAB11A** and **RAB14**) are overlapping between PD and the MPTP mouse. These proteins are involved in vesicular trafficking between compartments of the cell. **RAB4A** regulates localization of **VAMP2** to early endosomes and vesicles[275] and the membrane-bound form of **RAB4A** binds to **NDRG1**[276], a protein that is required for vesicular recycling[11]. **NDRG1** binds to actin filaments by binding to **ACTG1**[91] as well as to **ACOT7**[277] and **PPP2R2A**[91], and activates CASP3[278]. The RAB proteins **RAB6A**, **RAB11A** and **RAB14** are located in the Golgi complex and regulate protein trafficking to other organelles and the plasma membrane of the cell. Dysfunctioning of these proteins results in defective protein trafficking and membrane fusion, which can result in protein aggregation. **RAB6A** is located at the Golgi[279] and regulates vesicular transport from early and recycling endosomes to the Golgi (not shown)[280] but also transport from the Golgi to the ER[281]. Furthermore, **RAB6A** affects release of the SNARE (**SNAP25** and **VAMP2**) complex, which itself is involved in membrane fusion (see also Figure 1a) by binding and activating **NSF**[282]. **RAB11A** is located in recycling endosomes, the Golgi complex and on the cytoplasmic side of cytoplasmic vesicles, and regulates transport from the Golgi to the endosome[283] and from the Golgi to the plasma membrane[283]. **RAB11A** binds to the neuronal cell adhesion protein **L1CAM**[284] and therefore is probably involved in its trafficking. The RAB protein **RAB14** regulates vesicular transport between the Golgi and early endosomes, and is involved in **CDH2** shedding (not shown)[285] and as such affects cell-cell adhesion (not shown)[285]. Lastly, also the ER-shaping protein **RTN2**[286] is involved in vesicular ER to Golgi transport[287].
Dysregulated (vesicle) trafficking affects exocytosis, receptor trafficking, (membrane) recycling and ultimately decreases the viability of the neuron.

Proteasomal degradation

The proteasome is involved in removal of unwanted, damaged or aggregated proteins[288,289]. **PSMA1** and **PSMB5** are both part of the 26S proteosomal complex[290], bind to each other[291] and both bind to PARK2[292,293]. Moreover, **PSMA1** binds to PTEN[294] and **NFKBIA**[221], whereas **PSMB5** binds to the NFKB complex[291]. Dysregulation of the 26S proteasome can heavily affect the PD protein landscape, for it degrades **RGS7**[295], **NR4A2**[296], **GRIN1** (NMDAR)[297], **NFKBIA**[298], SNCA[299], NFKB[300,301], SIRT1[302], HDAC1[303], MAPT[304], MAP3K7[305], PTEN[306,307] and **SOX2**[308]. Reduced activation of the proteosomal complex could therefore increase protein (e.g., SNCA) aggregation, which would affect neuronal functioning.

Mitochondrial function and apoptosis

Mitochondrial dysfunction is associated with both familial and sporadic PD[309]. **BCL2,** located in the nuclear membrane and in the mitochondrial outer membrane**,** is an important anti-apoptotic factor that binds to, inhibits and decreases the expression of the proapoptotic protein BAX[310-313]. BAX inhibition is mediated via the inhibition of **MAPK8** that inhibits the binding of **YWHAZ** and BAX, and in this way increases the translocation of BAX to the mitochondrial membrane[314]. **BCL2** is bound and regulated by multiple proteins in the landscape, i.e., **SATB1** decreases and **NFKBIA** increases **BCL2** expression[315,316]. **MAPK8** also increases **BCL2** expression[317], but inhibits **BCL2** function[318,319]. **BCL2** in turn inhibits **MAPK8**[319], decreases expression of **NFKBIA**[320], **NDRG1**[321] and PTEN[322], increases expression of **SNAP25**[321], and decreases cleavage of **SRPK2**[323]. **BCL2** binds **MAPK8**[324], **CASP3**[325]and PARK2[326], and inhibits apoptotic pathways in that it, in addition to inhibiting BAX, also inhibits **CASP3**[327] and HTRA2[328] and HTRA2 translocation out of mitochondria[329]. In the cytoplasm, HTRA2 binds EIF4G1[330], PARK2 (not shown)[331], PINK1 (not shown)[332] and **CDK5**[332]. **CDK5** in turn inhibits PARK2[176] and increases **TH** expression[7]. SNCA binds to PARK2[333] and, in contrast to **CDK5,** decreases **TH** expression[334,166].

Other proteins in the landscape that affect mitochondrial function are **MRPL15**, **ATP5C1** and **RET**. The 39S ribosomal protein **MRPL15** is located in mitochondria and involved in mitochondrial-specific protein expression. Moreover, **MRPL15** binds to the transcription factor **SOX2** (not shown)[238] and as such may affect DA-neuron-specific expression (see paragraph 'DA neuron signature' in the section 'Transcriptional and translational regulation'). The ATPase **ATP5C1** is part of complex V of the respiratory chain that uses the proton gradient across the mitochondrial membrane to produce ATP from ADP[11]. SNCA may also affect the respiratory chain directly by binding to **ATP5C1**[159]. Lastly, the tyrosine kinase **RET** increases the expression of **TH** and **SLC6A3** (Figure 1a), and ameliorates complex I dysfunction in a PD model[335].

Detailed description of the biological processes depicted in Figure 2. Molecular landscape of interacting proteins, encoded by the mRNAs that are differentially expressed in the striatum of *both* human PD patients and MPTP-treated mice located in the post-synapse of a striatal neuron.

As a result of the dysregulation of the biological processes constituting the molecular landscape of the processes shared in the SN (summarized in figure 1), the release of DA to the striatum is decreased. Due to the lower DA release into the synaptic cleft, affecting protein expression in the striatal post-synapse, the activation of the DA receptors DRD2 and DRD3 is diminished; these receptors are associated with PD[336,337]. When activated, DRD2 (long variant) and DRD3 increase intracellular calcium[338], but they also inhibit the function of the NMDA receptor(NMDAR)[339] and the VDCC[340,341]. The VDCC binds to **ITSN1**[39], a protein involved in actin reorganization and assembly[342,343]. **DCLK1** and **ENC1** are also involved in actin regulation, i.e. **DCLK1** regulates the distribution of actin[344] and **ENC1** is an actin-binding protein[345] that also binds to SNCA[161]. DRD2 also binds to calmodulin (CaM)[346,347] and thereby exerts influence on calcium signaling in the striatal neuron. Namely, CaM binds to the VDCC[142], the NMDAR (not shown)[348], SNCA[349], LRRK2[173], **TGM2**[350], **KCNQ5**[351], **DIRAS2**[352] and **DCLK1**[352], and can thereby affect multiple proteins in the landscape. Furthermore, CaM regulates **KCNQ5**[353] and inhibits calcium flux through the NMDAR into the cell[354,355]. In addition, calcium-bound CaM activates CREB1[356,357] and **CAMK1G**[358], and regulates **TGM2** function (not shown)[350]. **CAMK1G** also activates CREB1[358], and **TGM2** activates ERK1/2[359] and CREB1[360], but also binds to CASP3[361], decreases the expression of **KCNQ5**[362] and increases the expression of LRRK2[362]. **TGM2** is also activated by calcium[363], increases the efflux of calcium out of the cell[364], binds to SNCA[365] and increases its aggregation (not shown)[365,366]. Calcium and CaM therefore affect the activity of ERK1/2 and CREB1 either directly or via the activation of **TGM2** or **CAMK1G**.
Activation of DRD2 by DA also results in the activation of ERK1/2[367] and CREB1[368]. ERK1/2 binds to **CHGB**[369] and the familial proteins SNCA[370] and PARK7[371]. Furthermore, in addition to DRD2 and **TGM2** (see above), **S100A10**[372] and **ITSN1**[373] activate ERK1/2, whereas the nuclear membrane protein **TMEM176B** inhibits ERK1/2 activation[374]. Of note, all these processes converge on CREB1. ERK1/2 activates CREB1[375,376], and CREB1 is activated by CaM, **CAMK1G**, **TGM2** and DRD2 (see above), but also by the NMDAR[356,377] and the (L-type) VDCC (not shown)[356] due to their ability to increase calcium influx, which is necessary for CREB1 activation[378,379]. Thus, CREB1 is regulated by the majority of the proteins in the striatal landscape, either directly or via ERK1/2 activation. Moreover, DA activates both ERK1/2[367] and CREB1 (via the DA receptors)[380,368], suggesting that ERK1/2 and CREB1 activation (via phosphorylation) is reduced in PD or after MPTP treatment due to the absence of DA.

These pathways also play a role in the effect of L-DOPA, the mainstay of treatment in PD. L-DOPA administration activates ERK1/2 in the striatum[381]. DA-induced, CREB1-dependent transcription in the intact striatum in a PD model[382] is further potentiated by NMDAR activation[377]. The secretory granule protein **CHGB** is one of the proteins of which the expression is regulated by CREB1, i.e. CREB1 binds to the CRE element of the **CHGB** gene promoter[383]. Furthermore, calcium decreases the expression of **CHGB**[384] and **CHGB** binds to PARK2[263]. In addition to ERK1/2 and CREB1, L-DOPA also activates DRD2[385 (DB01235#target-831)], DRD3[385 (DB01235#target-683)]

and NMDAR[385 (DB01235#target-683),386], and increases the expression of DRD3[386], CASP3[387] and **S100A10**[388]. In a PD rat model, **S100A10** is involved in L-DOPA-induced abnormal involuntary movements[389]. The activation of striatal ERK1/2 by L-DOPA also appears involved in L-DOPA-induced dyskinesias[389], but not the L-DOPA induced CREB1 activation[390,391,381]. These processes could therefore not only give insights into the PD-related disease mechanisms in the striatum, but also in the beneficial, and adverse, effects of pharmacological treatment.
CREB1 and ERK1/2 are also known for their role in epilepsy. Brain areas prone to epileptic seizures show an increased activation of CREB1 and ERK1/2[382], and an up regulation of **CHGB**[392], CREB1[392], **ENC1**[356] and **NPTX2**[392]. **NPTX2** is thought to play a role in long-term plasticity [392] and increases apoptosis[11]. Further, **KCNQ5**[393], the NMDAR[394] and the VDCC[395] are associated with epileptic seizures. Therefore, the landscape cannot only give insight in treatment outcome, but can also explain the associations seen in functional studies with PD, in this respect with epilepsy[396].

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LIST OF ABBREVIATIONS

Abbreviation	Protein name
ACHE	acetylcholinesterase (Yt blood group)
ACOT7	acyl-CoA thioesterase 7
ACTG1	actin, gamma 1
AKT1	v-akt murine thymoma viral oncogene homolog 1
AKT1S1	AKT1 substrate 1 (proline-rich)
ANP32B	acidic (leucine-rich) nuclear phosphoprotein 32 family, member B
ATP5C1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1
ATP6V0D1	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d1
ATXN10	ataxin 10
BAX	BCL2-associated X protein
BCL2	B-cell CLL/lymphoma 2
CaM	calmodulin
CAMK1G	calcium/calmodulin-dependent protein kinase IG
CASC3	cancer susceptibility candidate 3
CASP3	caspase 3, apoptosis-related cysteine peptidase
CCDC6	coiled-coil domain containing 6
CDH2	cadherin 2, type 1, N-cadherin (neuronal)
CDH8	cadherin 8, type 2
CDK5	cyclin-dependent kinase 5
CHGB	chromogranin B (secretogranin 1)
CHP1	calcineurin-like EF-hand protein 1
CLK4	CDC-like kinase 4
CREB1	cAMP responsive element binding protein 1
CRMP1	collapsin response mediator protein 1
CTBP2	C-terminal binding protein 2
DCLK1	doublecortin-like kinase 1
DDX1	DEAD (Asp-Glu-Ala-Asp) box helicase 1
DDX5	DEAD (Asp-Glu-Ala-Asp) box helicase 5
DHX36	DEAH (Asp-Glu-Ala-His) box polypeptide 36
DIRAS2	DIRAS family, GTP-binding RAS-like 2
DLK1	delta-like 1 homolog (Drosophila)
DRD2	dopamine receptor D2
DRD3	dopamine receptor D3
DUSP19	dual specificity phosphatase 19
EIF1B	eukaryotic translation initiation factor 1B
EIF4G1	eukaryotic translation initiation factor 4 gamma, 1
ENC1	ectodermal-neural cortex 1 (with BTB domain)
ERK1/2	extracellular-signal-regulated kinase 1/2
FOXO1	forkhead box O1
FRAT2	frequently rearranged in advanced T-cell lymphomas 2
FYN	FYN proto-oncogene, Src family tyrosine kinase
GABRG2	gamma-aminobutyric acid (GABA) A receptor, gamma 2
GIGYF2	GRB10 interacting GYF protein 2
GNAI2	guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2

GRIN1	glutamate receptor, ionotropic, N-methyl D-aspartate 1
GTF2I	general transcription factor IIi
H2AFJ	H2A histone family, member J
HDAC1	histone deacetylase 1
HNRNPH3	heterogeneous nuclear ribonucleoprotein H3 (2H9)
HTRA2	HtrA serine peptidase 2
ITSN1	intersectin 1 (SH3 domain protein)
KCNQ5	potassium voltage-gated channel, KQT-like subfamily, member 5
KIFAP3	kinesin-associated protein 3
KLC1	kinesin light chain 1
L1CAM	L1 cell adhesion molecule
LPAR1	lysophosphatidic acid receptor 1
LRRK2	leucine-rich repeat kinase 2
MAGED1	melanoma antigen family D, 1
MAGOH1	Protein mago nashi homolog 1
MAP2K4	mitogen-activated protein kinase kinase 4
MAP3K7	mitogen-activated protein kinase kinase kinase 7
MAP4	microtubule-associated protein 4
MAPK8	mitogen-activated protein kinase 8
MAPRE2	microtubule-associated protein, RP/EB family, member 2
MAPT	microtubule-associated protein tau
MARK2	MAP/microtubule affinity-regulating kinase 2
MRPL15	mitochondrial ribosomal protein L15
mTORC1	mammalian target of rapamycin complex 1
MXD4	MAX dimerization protein 4
NAPB	N-ethylmaleimide-sensitive factor attachment protein, beta
NDRG1	N-myc downstream regulated 1
NFIB	nuclear factor I/B
NFKB	nuclear factor kappa-light-chain-enhancer of activated B cells
NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
NMDAR	N-methyl-D-aspartate receptor
NPTX2	neuronal pentraxin II
NR4A2	nuclear receptor subfamily 4, group A, member 2
NSF	N-ethylmaleimide-sensitive factor
PAPOLA	poly(A) polymerase alpha
PARK2	parkin RBR E3 ubiquitin protein ligase
PARK7	parkinson protein 7
PDXK	pyridoxal (pyridoxine, vitamin B6) kinase
PFKM	phosphofructokinase, muscle
PINK1	PTEN induced putative kinase 1
PITX3	paired-like homeodomain 3
PPP2R2A	protein phosphatase 2, regulatory subunit B, alpha
PSMA1	proteasome (prosome, macropain) subunit, alpha type, 1
PSMB5	proteasome (prosome, macropain) subunit, beta type, 5
PTEN	phosphatase and tensin homolog
RAB11A	RAB11A, member RAS oncogene family
RAB14	RAB14, member RAS oncogene family
RAB4A	RAB4A, member RAS oncogene family
RAB6A	RAB6A, member RAS oncogene family
RABAC1	Rab acceptor 1 (prenylated)

RAC1	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1)
RANBP9	RAN binding protein 9
RAP1GDS1	RAP1, GTP-GDP dissociation stimulator 1
RBM39	RNA binding motif protein 39
RELA	v-rel avian reticuloendotheliosis viral oncogene homolog A
RET	ret proto-oncogene
RGS4	regulator of G-protein signaling 4
RGS7	regulator of G-protein signaling 7
RPL10A	ribosomal protein L10a
RPL5	ribosomal protein L5
RTN2	reticulon 2
S100A10	S100 calcium binding protein A10
SASH1	SAM and SH3 domain containing 1
SATB1	SATB homeobox 1
SIRT1	sirtuin 1
SLC18A2	solute carrier family 18 (vesicular monoamine transporter), member 2
SLC4A3	solute carrier family 4 (anion exchanger), member 3
SLC4A8	solute carrier family 4, sodium bicarbonate cotransporter, member 8
SLC6A3	solute carrier family 6 (neurotransmitter transporter), member 3
SLC8A1	solute carrier family 8 (sodium/calcium exchanger), member 1
SNAP25	synaptosomal-associated protein, 25kDa
SNCA	synuclein, alpha (non A4 component of amyloid precursor)
SOX2	SRY (sex determining region Y)-box 2
SRPK2	SRSF protein kinase 2
SRSF7	serine/arginine-rich splicing factor 7
STXBP1	syntaxin binding protein 1
TGM2	transglutaminase 2
TH	tyrosine hydroxylase
TMEM176B	transmembrane protein 176B
TNK2	tyrosine kinase, non-receptor, 2
TSPAN7	tetraspanin 7
UCHL1	ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)
USP22	ubiquitin specific peptidase 22
VAMP2	vesicle-associated membrane protein 2 (synaptobrevin 2)
VDCC	voltage-dependent calcium channel
VSNL1	visinin-like 1
YTHDF2	YTH domain family, member 2
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta
ZC3H11A	zinc finger CCCH-type containing 11A