Appendix

Preamble

Neuropathologically, PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNC) and other dopaminergic or noradrenergic nuclei of the brain. Further neuropathological signs are eosinophilic cytoplasmic inclusions (Lewy bodies) composed of extensively ubiquitinated α-synuclein. A major efferent target of the SNC is the striatum (the caudate putamen complex (CPu) in rats). The depletion of dopamine (DA) in the CPu causes, in turn, the typical motor symptoms of the disease.

In mitochondria it is oxidized to build para-quinone[1] and produce reactive oxygen species (ROS) like hydrogen peroxide (H_2O_2), superoxide (O^-_2), and hydroxyl radicals ($OH^\bullet$)[2, 3]. 6-OHDA has also been shown to inhibit mitochondrial complexes I[4, 5] and IV *in vitro*[6] and/or mitochondrial function which may induce axonal damage and cell death[7-9]. Furthermore, it has been shown that 6-OHDA treatment reduces striatal glutathione (GSH) and superoxide dismutase (SOD) enzyme activity[10], and increases levels of malondialdehyde[11]. Finally, 6-OHDA is not only a respiratory toxin, it acts also as clastogen and mutagen[9, 12]. Also, 6-OHDA can be produced endogenously through aminoacid decarboxylase from the amino acid 6-hydroxydopa (6-OHDOPA)[13, 14]. This fact is particularly intriguing as 6-OHDA is found in brain and urine samples of PD patients, suggesting it may be an endogenous component of PD pathogenesis[14-18]. Systemically administered 6-OHDA fails to cross the blood–brain barrier. Thus, 6-OHDA has to be injected stereotactically into the brain.

This contralateral response is attributed to the stimulation of supersensitive D1-receptor and D2-receptor activation, especially in the lesioned hemisphere. Surprisingly, increases of moderate or compensated lesions (less than 80%), no turning or a weak ipsilateral turning has been monitored[19, 20]. The characteristic rotational behavior in this animal model caused by administration of many agents, including clinically used anti-Parkinsonian drugs, make it useful for studies aimed at developing different strategies of therapies and anti-Parkinsonian drugs[21-23].

Oxidative stress in the CNS arises not solely from mitochondrial-generated ROS in neurons but also from activated microglia[24]. Reactive microglia is known to play a role in several neurodegenerative disorders including PD. Indeed, PD patients can have more than six times the number of reactive microglia as compared to controls[25-27]. However, it is unknown whether these microglia initiate or aggravate neurodegeneration[28]. Nevertheless, accumulated evidence has indicated that

neuroinflammation is one of the important etiologic factors of PD where also further factors like the inflammogen lipopolysaccharide (LPS) may induce inflammation of dopaminergic neurons[29]. In addition to microglial reactivity in PD patients this cell population becomes activated after brain damage or exposure to specific immune mediators such as IL-1beta or TNFalpha[30]. Activated microglia in the substantia nigra is found in 6-OHDA models[31] and further models for PD[32-39]. Besides producing cytokines, proteases, and prostanoids, activated microglia also produce superoxide and nitric oxide[40]. The activation of microglia and generation of ROS coincides with neurochemical changes such as the decrease in dopamine synthesis[36, 38]. While some neurochemical changes happen quickly and can be detected before evidence of any lesions, others are delayed and continue to be manifested long after neurotoxin exposure[41]. These results suggest that a brief exposure to an insult can initiate a process of continuous neurodegeneration[42]. Microglia may play a role in initiation and progression of PD and enhance neurotoxicity elicited by neurotoxins[35, 43]. Inhibition of microglial activation by minocycline, an antibiotic, could attenuate the neurotoxicity of 6-OHDA, MPTP, rotenone and other toxins for DA neurons[43, 44].

The extracellular matrix plays a pivotal role in neuronal differentiation especially in the migration and differentiation of neuronal progenitors[45], their axonal growth and synaptic differentiation[46-54]. Therefore, we aimed to find effects of neurotoxic lesions in the neuronal environment. Furthermore, the 6-OHDA model may induce inflammation[55-57] processes that could be detected in pathways of differentially expressed proteins.

Functions, interactions, neurobiological and neuropathological relevance of differential proteins

In the following the differential regulations of the members of 9 protein groups (Fig. 4) and their subgroups (9) as well as their network interactions are interpreted based on Tab. 1. Their functions, appearance in the CNS (summarized in an overview in Fig. 7) and involvement in diseases are put into relation to PD and the 6-OHDA model of PD. In the concluding part of the discussion relations and pathways are interpreted with regard to functional, structural groups and compartments where altered proteins occur. Protein mixes and multiple presentations of proteins in different spots are explicitly presented in Suppl. Tab. 1 and Suppl. Tab. 2 as well as in Suppl. Fig. 3. The number of matches and the extent of up- and down-regulation are documented in Suppl. Tab. 2.

Group 1: Structural proteins

13 structural proteins are elevated (Tab. 1). **Vimentin** (VIME) is up-regulated. It is an intermediate filament in astroglial cells attached to the nucleus, endoplasmic reticulum, and mitochondria, either laterally or terminally. It plays a significant role in supporting and anchoring the position of the

organelles in the cytosol. Aggresomes and aggresome-like inclusions are often surrounded by a vimentin cage-like structure[58]. Also mutations in leucine-rich repeat kinase-2 leads to large perinuclear aggregates with vimentin and γ-tubulin proteins[59].

The cytoplasmic **beta-actin** (ACTB) is down-regulated. It is one of six different actin isoforms. ACTB belongs to the nonmuscle cytoskeletal actins that are involved in cell motility, structure and integrity. ACTB is commonly used to normalize molecular expression studies due to its high conservation as an endogenous housekeeping gene, however, ACTB may significantly change in neurodegenerative diseases[60] and the MPTP model[61]. Furthermore, it may act as a signal through NOS3 affinity[62] and is redox regulated[63] and therefore of interest for the generation of ROS. It was shown that HSP90 has the ability to bind to actin in a Ca^{2+}-calmodulin- dependent manner and interact with many receptors and kinases (for ref. see[64]). An up-regulation of ACTB was documented in a study of a 6-OHDA Hemiparkinsonian model, however, the number of samples and the calculation of differences of spot volumes were not described[65].

Along with the down-regulation of ACTB we found an up-regulation of **actin related protein 3** (ARP3). ARP2/3 complex is a seven-subunit protein that plays a major role in the regulation of the actin cytoskeleton and is therefore ubiquitous in actin cytoskeleton-containing cells, namely in the rat brain[66]. ARP2 and ARP3 closely resemble the structure of monomeric actin and serve as nucleation sites for new actin filaments. The regulation of rearrangements of the actin cytoskeleton is important for processes like cell locomotion, phagocytosis, and intracellular motility of lipid vesicles. In neurons ARP3 has been identified in postsynaptic densities (PSD)[67] and it has been identified in astocytes[68]. ARP2/3 is significantly decreased in fetal DOWN syndrome brains[69] and patients suffering under schizophrenia[70].

Alpha internexin (AINX) is up-regulated and belongs to class IV intermediate filaments. The protein was originally purified from rat optic nerve and spinal cord[71]. Alpha internexin copurifies with other neurofilament subunits, however in some mature neurons only the neurofilament can be expressed. Furthermore, a role in the formation of the mature NFs in the CNS was suggested[72]. The protein is present in developing neuroblasts and in the CNS of adults in post synaptic densities[73]. Moreover, it is a major component of the intermediate filament network in small interneurons and cerebellar granule cells. As development continues into neurons the neurofilament triplet proteins NFL, NFM, NFH are expressed in increasing molecular mass order as AINX expression decreases. Alpha internexin has also been implicated in several neurodegenerative diseases such as PD[74], amyotrophic lateral sclerosis, dementia with Lewy bodies, neuropathies, tropical spastic paraparesis and human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy. Alteration of alpha internexin expression are described in the MPTP model in mice[75]. Of particular interest is its affinity to phosphorylated α-synuclein[76].

Neurofilament light polypeptide (NFL) is down-regulated. Neurofilaments, which are assembled from light, medium, and heavy subunits, are essential for normal nerve function. They form a structural framework that helps to define the shape and size of nerve cells. In particular NFL forms the backbone for other neurofilaments and is essential for the assembly. The phosphorylation of the NFL head domain is believed to regulate the assembly of neurofilaments and acts as a regulator of neurofilament axonal transport[77]. The axonal caliber is highly influenced by NF proteins and cross-linking or bridging between neurofilaments maintains the diameter of the axon. Maintaining the proper axon diameter is essential for the transmission of nerve impulses. Neurofilament proteins are used as highly specific biomarkers for neuronal death and axonal degeneration[78].

Drebrin-like protein (DBNL) is down-regulated. Drebrin has previously been described as an actin binding protein that diminishes in brains during Alzheimer's disease[79] and fetal Down syndrome[69]. Double-labeling studies with anti-SH3P7 antibody and other neuronal marker proteins revealed that DBNL was located primarily in dendrites (postsynaptic densities[67, 73], dendritic spines[80, 81]), and in moderate amounts in cell bodies in the hippocampus and cerebellar cortex[82]. Here, we demonstrate for the first time drebrin-like protein expression and its down-regulation in the 6-OHDA lesioned striatum. Hence, a down-regulation within postsynaptic structures may be a response to a presynaptic 6-OHDA induced degeneration.

Dihydropyrimidinase related protein 2 (DPYL2) is up-regulated and interestingly, absent in control gels. It acts on microtubule reorganization and consequently on axon repulsion. DPYL2 is also a component of the process of axon guidance and necessary at development. **Dihydropyrimidinase related protein 4** (DPYL4) and **Dihydropyrimidinase related protein 5** (DPYL5) have comparable functions as DPYL2 and are also up-regulated supporting the axon repulsion effect induced by 6-OHDA lesions.

The actin bundling protein **fascin fragment** or fascin 1 (FSCN1) is enriched in growth cones and filopodia. FSCN1 is a regulator of actin dynamics[83] and is up-regulated in the striatum of lesioned animals. FSCN1 was found to be synthesized in astrocytes[68]. Alterations of FSCN1 were observed after corticosterone treatment of rats[84]. In patients suffering under schizophrenia alterations of FSCN1 in the prefrontal cortex have been found[70].

Septin 6 (SEPT6) and **septin 8** (SEPT8) are up-regulated. Septins belong to a family of GTP-binding proteins that function as dynamic, regulable scaffolds recruiting other proteins. Septins may polymerize into heteromeric filaments and form microscopic bundles or ring structures *in vitro* and *in vivo*. They have the ability to associate with membranes, F-actin and microtubules. Septins have been generally regarded as cytoskeletal components[85]. Proteins of the septin family required for normal cytokinesis, are proposed to be involved in many processes, including membrane dynamics, vesicle trafficking,

apoptosis, cytoskeletal remodeling, and finally are associated with synaptic vesicle formation[86]. Septin 6 was localized in postsynaptic densities[73]. Septin 8 can be bounded by septin 5 and hence it was suggested that septin 8 plays a role in neuronal signaling[87]. Septin 6 was found to be down-regulated in the hippocampus of morphine exposed rats[88], furthermore, septin 6 is reduced in Down syndrome[86].

Stomatin like protein 2 (STML2) is down-regulated and was found to be involved in $CD4^+$ T cell activation[89]. STML2 is a member of the highly conserved family of stomatin proteins whose homologues span from archae to humans have an N-terminal mitochondrial targeting sequence[90, 91]. It has been suggested that it may be involved in the organization of the peripheral cytoskeleton, and in the assembly of multichain receptors, such as ion channels and mechanosensation receptors.

Most of the α and β **tubulins** are up-regulated. However, tubulin α 1A-chain and tubulin β 5 chain are down-regulated. Microtubules are assembled from dimers of α- and β-tubulin. The up-regulated βIII-tubulin is a microtubule element of the tubulin family found almost exclusively in neurons[92].Tubulin α 1B-chain was found to be up- and down-regulated in several spots.

The ACTB, ARP3, DPYL2, DPYL4, DPYL5, tubulin up-regulations in the perikaryons and axon sites and the drebrin down-regulation at the dendrites indicates a polarized protein differentiation in the axonal direction. Furthermore, cytoskeletal proteins of astroglial origin show common up-regulation that may indicate an activation of the astroglial population (Fig. 7).

Group 2: Regulating protein

In the group of regulating proteins 6 proteins are up- and 3 are down-regulated. **Annexin A3** (ANXA3) and **A7** (ANXA7) are up-regulated and are members of the annexin family. Annexin A3 and A7 of this calcium-dependent phospholipid-binding protein family play a role in the regulation of cellular growth, in signal transduction pathways and through their interaction with phospholipids in the presence of Ca^{2+} they are thought to function in Ca^{2+}-homeostasis. Results from mutant mice showed an altered Ca^{2+}-wave propagation in astrocytes. Annexin A7 is located in the nucleus of adult neurons and in the nucleus and cytoplasm of astroglia[93]. Vemuganti et al.[94] found an up-regulation of annexin A3 gene expression in thiamine deficiency rats in the colliculus and thalamus. Solito[95] described an up-regulation of annexin 1, a further member of the annexin family in microglia in the SNc of idiopathic Parkinson patients.

Calmodulin 1 (CALM) was down-regulated in the lesioned striatum. It belongs to one of two groups of proteins that bind calcium, whereby the other group is the annexin family. CALM mediates processes

such as inflammation, metabolism, apoptosis, smooth muscle contraction, intracellular movement, short-term and long-term memory, nerve growth and immune responses. CALM is expressed in many cell types and can have different subcellular locations. Many of the proteins that CALM binds are unable to bind calcium themselves, and as such use CALM can be considered as a calcium sensor and signal transducer. CALM binds to both wild type and PD-associated mutant α-synucleins in a calcium-dependent manner and accelerates the formation of synuclein fibrils *in vitro*[96].

LIM and SH3 domain protein 1 (LASP1) is up-regulated. LASP1 functions as an actin-binding protein that is concentrated at neuronal synapses where it may be involved in actin cytoskeleton reorganization contributing to synaptic plasticity[97]. LASP1 also binds to dynamin, which is critically required for synaptic vesicle endocytosis[98, 99]. LASP1 has been found in homocysteic acid-induced neuronal stress to be up-regulated. This might induce calcium influx into neurons, with characteristics of an excitotoxic glutamatergic agonist at elevated concentrations[100]. Homocysteine is considered to be neurotoxic and a risk factor for neurodegenerative diseases[101]. A hyperphosphorylation of intermediate filaments can be induced by homocysteine administration at a concentration described to induce neurotoxicity[102]. The protein was also up-regulated in α-synuclein transgenic A30P-mice[103].

Myc box-dependent-interacting protein 1 (BIN1) is down-regulated and may be involved in regulation of synaptic vesicle endocytosis. It was hypothesized by Sakamuro and Prendergast[104] that the endocytosis connection in neurons reflects the link between survival and the achievement of a differentiated and synaptically active state in those cells, which would be associated with neurotransmitter release and hence membrane trafficking. Jin et al.[74] found a down-regulation of BIN1 in a proteome analysis of brain material from Parkinson patients.

Reticulocalbin 1 (RCN1) is down-regulated. RCN1 is a Ca^{2+} binding luminal protein of the endoplasmic reticulum in the secretory pathway[105]. RCN1 is implicated in nerve regeneration[106]. It is located in neurons, astroglia and Schwann cells[107].

The up-regulated **stress-induced-phosphoprotein 1** (STIP1) functions as a co-chaperone which reversibly links together the protein chaperones HSP70 and HSP90. Furthermore, it also modulates the chaperone activities of the linked proteins. Apart from its role in the HSP70/HSP90 "chaperone machine" it seems to participate in other chaperone-protein complexes too. It regulates the activation of the stress response and protects against stress-induced apoptosis in mice[108]. Hence, STIP1 plays an important role in the ability of cells to survive in stressful conditions[109], e.g., the 6-OHDA deafferentiation of the striatum. STIP1 is located in diverse cellular regions and also moves between the cytoplasm and the nucleus. It was located specifically in post synaptic densities[73] and altered in the hippocampus of rats after an exercise paradigm suggesting an involvement in synaptic plasticity[110].

The up-regulated **synapsin II** (SYN2) is the collective name for synapsin IIa and synapsin IIb, two nearly identical phosphoproteins in the synapsin family that in humans are encoded by the SYN2 gene[111]. Synapsins associate as endogenous substrates to the surface of synaptic vesicles and act as key modulators in neurotransmitter release across the pre-synaptic membrane of axonal neurons in the nervous system. Recently, synapsin 2 was found to be dysregulated in PD and controls[112].

WD repeat-containing protein 1 (WDR1) is up-regulated and located in the cytoplasm. WD-repeat protein 1 is a member of the family of WD proteins implicated in a variety of cellular functions including transmembrane signaling, transcription, cell division, cell-fate determination, vesicle fusion, induction of actin filament disassembly and apoptosis[113]. Among other functions, WD family members are related to signaling pathways as e.g. the PKC system[114] that in turn has been shown to be dysregulated by morphine-administration. A translocase of outer mitochondrial membrane 70 homolog A (TOM70) contains the tetratricopeptide (TPR) motif that in turn plays a role in cell-cycle regulation, transcriptional repression, the stress response, protein folding, protein kinase inhibition, neurogenesis, mitochondrial and peroxisomal transport[115]. Aberrant expression of this protein may therefore represent or lead to mitochondrial or peroxisomal damage in morphine-induced brain damage and aberrant levels of TOM70 were shown in brains of a dementing neurodegenerative disease with mitochondrial damage.

Group 3: Transport proteins

The up-regulated **adaptin ear-binding coat-associated protein 1** (NECP1) is partially located to clathrin-coated pits and involved in membrane organization, membrane invagination and vesicle-mediated transport within endocytosis. In the nervous system it acts on endocytosis of synaptic vesicles and receptors[116, 117].

Clathrin light chain A (CLCA) is up-regulated. Clathrin-mediated endocytosis is a major pathway for uptake of lipid and protein cargo at the plasma membrane. A binding partner of CLCA is calyon a neuron-specific vesicular protein located in vesicle and plasma membranes[118, 119]. The regulation of the clathrin assembly is important in neurons that contain large amounts of clathrin needed for the rapid recycling of neurotransmitters[120].

The up-regulated **phosphatidylinositol transfer protein alpha isoform**[121] (PIPNA) is a member of the ubiquitous cytosolic phosphatidylinositol transfer proteins (PITP). PIPNA is involved in the transport of phospholipids from their site of synthesis in the endoplasmic reticulum and Golgi to other cell membranes. PITP has also been shown to be an essential component of the polyphosphoinositide synthesis machinery and is hence required for proper signaling by epidermal growth factor and N-formylmethionyl-leucyl-phenylalanine, as well as for exocytosis. The role of PITP in polyphosphoinositide synthesis may also explain its involvement in intracellular vesicular traffic for

subsequent transport processes which correlates with the observed up-regulation of DCTN2-5 with axon guidance and synaptic formation functions[122].

The **voltage-dependent anion-selective channel protein 1** (VDAC1) is up-regulated. VDAC1 forms a channel through the mitochondrial outer membrane and also the plasma membrane. The channel at the outer mitochondrial membrane allows diffusion of small hydrophilic molecules; in the plasma membrane it is involved in cell volume regulation and apoptosis. VDAC1 may participate in the formation of the permeability transition pore complex responsible for the release of mitochondrial products that trigger apoptosis[123-125]. Iwatzaki et al.[126] reported a VDAC1 change in the striatum of methamphetamine-treated rats. This regulator of mitochondrial stability and degeneration has been found to be down-regulated in the striatum in a Wallerian degeneration mice model (Wld^s mice)[127].

Group 4: Chaperones

The mitochondrial **60 kDa heat shock protein** (CH60) is up-regulated in the lesioned striatum. CH60 is implicated in mitochondrial protein import and macromolecular assembly. It may facilitate the correct folding of imported proteins. Furthermore, it may also prevent misfolding and promote the refolding and proper assembly of unfolded polypeptides generated under stress conditions in the mitochondrial matrix. CH60 interact with β-catenin that is a central effector of Wnt signaling in embryonic and stem cell development as well as in tumorgenesis. HSP60 was found to be differentially phosphorylated in transgenic mice SJLB carrying the human N279K mutant tau, one of the tau mutations causing parkinsonism linked to chromosome 17 (FTDP-17)[128]. Furthermore, HSP60 mRNA up-regulation was found in dopamine-induced apoptosis[129].

Calreticulin (CALR) is down-regulated. It is a multifunctional protein that binds Ca^{2+} ions rendering it inactive. Calreticulin is located in storage compartments associated with the endoplasmic reticulum and binds to misfolded proteins. It prevents them from being exported from the endoplasmic reticulum to the Golgi apparatus. A time dependent up-regulation of CALR was observed in murine dopaminergic neuronal cells *in vitro* after treatment with 6-OHDA within 12 hrs suggesting that regulation of chaperone activity in dopaminergic neurons comprises an additional cellular response to death-inducing stimuli[130]. Because dopaminergic perikarya do not occur in the normal rat striatum CALR down-regulation is located in nondopaminergic cell populations of the striatum.

Chaperonin containing Tcp1, subunit 6A (zeta 1) (CCT6A) is up-regulated. The CCT6A gene encodes a molecular chaperone that is member of the chaperonin containing TCP1 complex. The complex folds various proteins, including actin and tubulin, and interacts transiently with ~10% of newly synthesized proteins. Alternate transcriptional splice variants of this gene, encoding different

isoforms, have been characterized[131]. It is known that PARK2, a component of Lewy bodies, is interacting with CCT6A[132].

T-complex protein 1 subunit beta (TCPB) is up-regulated. CCT2 is a member of the chaperonin containing CCT1 complex, also known as the CCT1 ring complex. The complex folds actin and tubulin among others. An up-regulation of tubulins and actin in the lesioned striatum (see above) correlates with TCPB up-regulation. The human dopaminergic neuroblastoma cell line SH-SY5Y was exposed to oxidative stress induced with 6-OHDA. CCT1 among further proteins were identified by MALDI-TOF MS as stress-responsive[133, 134].

The mitochondrial chaperone **stress 70 protein** (GRP75)[135] is up-regulated and belongs to the heat shock protein 70 family. This protein plays a role in the control of cell proliferation. It may also act as a chaperone. Parkin is an E3-ubiquitin-protein ligase that ubiquitinates itself and specific substrate proteins playing a protective role by sequestering misfolded proteins. Parkin forms a complex with GRP75, STIP1 homologue and U-box containing protein 1, enhancing its E3 enzymatic activity and its ability to inhibit cell death induced by stress of unfolded proteins[136] and an endoplasmatic reticulum stress response[137, 138]. GRP75 decrease was observed following DA oxidation that causes a strong stress response[137]. However, the GRP75 up-regulation in the lesioned 6-OHDA striatum found here in the advanced PD model may be explained by long term effects and reorganization. An elevation of the levels of the endoplasmatic reticulum chaperone GRP58 in 6-OHDA lesioned striata of neonatal rats[138] and 6-OHDA exposure to PC12 cells[139] was described recently.

Heat shock cognate 71kDa protein (HSP7C) localized in the cytoplasm and belonging to the heat shock protein 70 family with chaperone function is down-regulated in the lesioned striatum. In SJLB transgenic mice carrying human N279K mutant tau a decrease of HSP7C was found[128]. An increase has been described in Alzheimer's disease[140] and a decrease *in vitro* of a human dopaminergic mesencephalic cell line followed rotenone exposition[74] as well as a decrease of HSP8 gene (coding HSP70) in a PCR analysis of the substantia nigra of human Parkinson patients[141].

Heat shock protein HSP 90 alpha (HS90A) is up-regulated. HS90 proteins normally associate with other cochaperones and play important roles in morphologic development, signal transduction, folding newly synthesized proteins or stabilizing and refolding denatured proteins after stress. There are 2 major cytosolic HS90 proteins, HS90A, an inducible form, and HS90B, a constitutive form. Other HS90 proteins are found in endoplasmic reticulum and mitochondria[142]. HS90/Cdc37 has been identified as a client kinase for PTEN-induced kinase 1 (Pink1)[143]. The physiological function of Pink1 is unknown, however, Pink1-deficient flies have alterations in mitochondrial morphology[144, 145], and neuronal SH-SY5Y cells and non-neuronal HeLa cells lacking Pink1 are reported to have increased susceptibility to apoptotic cell death[146, 147].

Protein DJ-1 (PARK7) was not differentially regulated. It may also function as a redox-sensitive chaperone, a sensor for oxidative stress, and it apparently protects neurons against oxidative stress and cell death. Defects in this gene are the cause of autosomal recessive early-onset Parkinson disease[148-153]. It was found that DJ-1 and α-synuclein interact with nucleolin which has reduced expression levels in the SNC in human PD[154]. Recently, it was found that PARK7 binds to nuclear and mitochondrial DNA-encoding subunits of mitochondrial complex I, respectively, and is colocalized with complex I and that complex I activity was reduced in DJ-1-knockdown NIH3T3 and HEK293 cells[155].

Group 5: Cell cycle

Glia maturation factor, beta (GMFB) is an up-regulated cell cycle protein[156]. It belongs to the actin-binding proteins ADF family and was localized in neurons and astrocytes[157]. This protein causes differentiation of brain cells, stimulation of neural regeneration, and inhibition of proliferation of tumor cells[158]. The cAMP-dependent protein kinase catalytic subunit alpha phosphorylates GMFB. Then GMFB binds to MAPK1. Moreover, an up-regulation of MAPK1 in the lesioned striatum was observed. MAPK1 phophorylates proto-oncoprotein c-Fos and ETS domain-containing Elk-1 which induces proliferation. This up-regulation of factors converging in a proliferative pathway may suggest mitogenic or differentiative activity of a specific or different cell populations of the lesioned striatum.

Group 6: Energy metabolism

The mitochondrial **ATP synthase subunit alpha** (ATPA) is down-regulated whereas **ATP synthase subunit beta** (ATPB) and **ATP synthase subunit delta** (ATP5H) are up-regulated. The proteomics assessment is based on indirect measurements of respirasome function, since coupled respiration is absent in frozen postmortem mitochondria. If indeed present, dysfunction of the respirasome may lead to inefficient formation of the proton gradient across the inner mitochondrial membrane needed by ATP synthase (complex V) to create ATP, the cell's major metabolic fuel[159]. It was found that ATP synthase is very sensitive to disturbances of the mitochondrial translational system caused by mt-tRNA mutations that could be enhanced by an increase of ROS[160].

NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 10 (NDUAA), **NADH dehydrogenase (ubiquinone) flavoprotein 2**, (NDUF2) and **NADH dehydrogenase (ubiquinone) Fe-S protein 8** (NDUFS8) are up-regulated. NDUF2 is believed to belong to the minimal assembly required for catalysis of complex I functions (Fig. 5). An up-regulation of NDUF2 was found in a cocaine drug abstinence experiment[161]. In a proteome study of antipsychotic drugs applied to Sprague-Dawley rats significant changes in the quantity of proteins of the respiratory transport chain including NDUF2 were found[162]. Interestingly, NDUFS8 is up-regulated in the striatum of Wistar rats that received an i.p.

injection of metamphetamine[163]. So far, no specific alterations of NDUF2 in models of Parkinson disease were published.

Vacuolar ATP synthase catalytic subunit A (VATA) does not significantly change, however, the brain specific **vacuolar ATP synthase subunit B, brain isoform** (VATB2) is up-regulated. VATA and VATB2 are components of vacuolar ATPase (V-ATPase), a multisubunit enzyme that mediates acidification of eukaryotic intracellular organelles. V-ATPase dependent organelle acidification is necessary for protein sorting, zymogen activation, receptor-mediated endocytosis, and synaptic vesicle proton gradient generation[164]. Elevated expressions of heat shock protein 70 cognate 3 and ATP synthase are known to be directly involved in A53T α-synuclein-mediated toxicity and PD. In a drosophila model of PD an up-regulation of ATP synthase have been found[165]. A significant increase of ATP synthase was observed in the frontal cortex of PD patients and a decrease in their SNC[166]. However, a significant increase of ATP synthase in the SNC of PD patients was reported, too[167].

Succinate dehydrogenase flavoproteine subunit (DHSA) is up-regulated in the lesioned striatum. DHSA is a major catalytic subunit of succinate-ubiquinone oxidoreductase, a complex of the mitochondrial respiratory chain localized at the inner mitochondrial membrane. 3-nitropropionic is an irreversible inhibitor of the TCA enzyme DHSA. Animals chronically treated with 3-NPA develop a Huntington disease-like syndrome[168]. Changes of DHSA are correlated with finding in PINK1 mutations of early onset PD[169].

Group 7: Carbohydrate metabolism

The mitochondrial **aconitase 2** (ACO2) is up-regulated. The protein belongs to the aconitase/IPM isomerase family. It was found to be one of the mitochondrial matrix proteins that are preferentially degraded by the serine protease 15, also known as Lon protease, after oxidative modification. Because PD is thought to arise from defects in neuronal iron (free-radical oxidative damage by free cellular iron[170-172]) and energy metabolism, aconitase is of specific interest due to its involvement in the two properties[173].

The mitochondrial **isocitrate dehydrogenase (NAD) subunit beta** (IDH3B) is up-regulated. The up-regulation of IDH3B as well as the up-regulation of aconitase 2 (see above) may be interpreted as a compensation of the impaired energy metabolism induced by the neurotoxic denervation of the striatum. So far, an effect of 6-OHDA or PD to striatal IDH3B has not been reported before.

Fructose-biphosphate aldolase C (ALDOC) is up-regulated in the lesioned striatum. Besides it is know that it is expressed in the hippocampus and in Purkinje cells. The isoenzyme aldolase A was found to be decreased *in vitro* where catecholaminergic PC12 cells were exposed to 150 µM dopamine[139]. An increase of aldolase A oxidation was observed in the frontal cortex after lipoxidative damage[174].

Dopamine (DA) exposure has been shown to cause oxidative damage to this protein through direct modification of cysteinyl residues by DA quinine[175-178].

Gamma enolase (ENOG, NSE) is down-regulated. ENOG is one of the three enolase isoenzymes of mammals. The isoenzyme ENOG, a homodimer, is located in mature neurons and cells of neuronal origin. A switch from alpha enolase to gamma enolase occurs in neural tissue during development in rats and primates. ENOG has neurotrophic and neuroprotective properties on a broad spectrum of central nervous system neurons. It binds, in a calcium-dependent manner, to cultured neocortical neurons and promotes cell survival. An increase of oxidation of the *alpha* enolase was observed in the frontal cortex after lipoxidative damage[174]. An up-regulation of ENOG was found after L-Dopa induced dyskinesia in the rat striatum[179]. α-type subunits of enolase occur in glial cells[180] and were found to be up-regulated in another proteome study of the 6-OHDA lesioned striatum[65]. In agreement with the results observed here ENOG have be found to be down-regulated of an axonal injury model in rat and primates[181].

L-lactate dehydrogenase B (LDHB) is up-regulated. LDHB can be used as a marker for cytotoxicity and was measured *in vitro* (mesencephalic cells from embryonic brains of female Wistar rats)[182]. LDHB was elevated after 6-OHDA[183] or rotenone application[184] to organotypic striatal slice cultures. It was also up-regulated following NMDA administration to striatal cell cultures[185].

Mitochondrial malate dehydrogenase (MDHM) is down-regulated whereas the cytosolic malate dehydrogenase do not show changes. The protein may play pivotal roles in the malate-aspartate shuttle that operates in the metabolic coordination between cytosol and mitochondria. MDHM enzyme activity in the cerebellar cortex of *Cynomolgus* monkeys (*Macaca fascicularis*) followed after MPTP application have been found to be changed[186]. A down-regulation of MDHM in the rat CPu after 6-OHDA application was not described before.

The mitochondrial **pyruvate dehydrogenase E1 component subunit alpha, somatic form** (ODPA) is down-regulated. The pyruvate dehydrogenase complex provides the primary link between glycolysis and the TCA cycle by catalyzing the irreversible conversion of pyruvate into acetyl-CoA. Pyruvate dehydrogenase deficiency in humans causes primary lactic acidosis and neurological dysfunctions in infancy and early childhood. The episodic dystonia, hypotonia and ataxia are motoric symptoms comparable with those of PD patients[187, 188]. Tricarboxylic acid intermediates as pyruvate, oxaloacetate, a-ketoglutarate, reduced glutathione (GSH) and N-acetyl-L-cysteine act as antioxidants and protect against 6-OHDA induced H_2O_2 production[189].

Pyruvate kinase isoenzyme M1/M2 (KPYM) is up-regulated and involved in glycolysis. A decrease of the specific carbonyl level of KPYM was found in the striatum in a caloric restriction model[190]. However, no reports exist on KPYM dysregulation in PD or the 6-OHDA model of PD in rats.

Group 8: Amino acid metabolism

The cytoplasmic **aspartate aminotransferase 1** (AATC) is up-regulated. AATC is a pyridoxal phosphate-dependent enzyme, which plays a role in amino acid metabolism as well as the urea and TCA cycle. It is generally believed that one of the most important functions of AATC is to transport reducing equivalents from cytosolically reduced NAD into mitochondria by the "malate-aspartate shuttle" for production of energy. In fronto-parietal decortication[191] and corticostriatal lesion[192] experiments no changes of AATC were found. However, AACT was found to be decreased after stereotactic injection of glutamate into the striatum of rats[193, 194].

Aspartoacylase 2 (ACY2) is up-regulated. ACY2 catalyzes the conversion of N-acetyl-L-aspartic acid (NAA) to aspartate and acetate. NAA is abundant in the brain where hydrolysis by aspartoacylase is thought to help maintain white matter. No investigations have been performed reporting changes of ACY2 in PD or 6-OHDA models of PD, however, it is well known that a defect in ACY2 causes the autosomal recessive leukodystrophy (Canavan disease)[195].

Creatine kinase (KCRB) is up-regulated. KCRB is a cytoplasmic enzyme involved in energy homeostasis. It acts as a homodimer in the brain as well as in other tissues. KCRB can be covalently modified by dopamine ^{14}C as shown in a proteome study using radiolabeled dopamine quinone[196]. It may be concluded that a 6-OHDA induced decrease of dopamine may trigger the up-regulation of KCRB. With regard to 6-OHDA lesions this is the first observation of striatal KCRB up-regulation.

The mitochondrial matrix **Delta-1-pyrroline-5-carboxylate dehydrogenase** (AL4A1) is down-regulated. AL4A1 is a NAD-dependent dehydrogenase which catalyzes the irreversible step of the proline degradation pathway, converting pyrroline-5-carboxylate to the excitatory neurotransmitter glutamate. There have not been any reports on AL4A1 activity in 6-OHDA lesioned rat striatum before.

The mitochondrial **succinate-semialdehyde dehydrogenase** (SSDH) is up-regulated. A deficiency of SSDH known as 4-hydroxybutyricaciduria, is a rare inborn error in the metabolism of the neurotransmitter 4-aminobutyric acid (GABA)[197, 198]. In response to the defect, physiologic fluids from patients accumulate γ-hydroxybutyric acid (GHB), a compound with numerous neuromodulatory properties. A selective involvement of GHB within the globus pallidus as part of the basal ganglia and the dentate nucleus has been found[199]. An inhibition of SSDH results in a loss of striatal dopamine as shown by a striatal infusion of the SSDH-inhibitor malonate[200]. An up-regulation of SSDH may have the converse effect to support an increase of dopamine that is missing after the 6-OHDA lesion. Furthermore, the up-regulation of SSDH was found after 6-OHDA lesioning of the SNC by histochemical quantification[201].

Dihydrolipoyl dehydrogenase (DLDH) is up-regulated. DLDH is part of the mitochondrial glycine cleavage system and a component of various enzyme complexes. DLDH deficient mice showed reduced expression of doublecortin (DCX), proliferating cell nuclear antigen (PCNA) and polysialic acid-neural adhesion molecule. The reduction of DCX-positive neuroblasts was found in the subgranular zone (SGZ) of the hippocampal dentate gyrus. DLDH deficiency did not alter the lesion-induced increase and migration of DCX-positive cells from the SVZ into the ipsilateral striatum.[202]. Furthermore, it was reported that DLD-deficient mice have significantly increased levels of the lipid peroxidation marker malondialdehyde in the striatum[203].

L-glutamate dehydrogenase (DHE3) is up-regulated. DHE3 is a mitochondrial enzyme that has a central role in nitrogen metabolism, and catalyzes the oxidative deamination of 1-glutamate to 2-oxoglutarate[204]. Glutamate is a major excitatory neurotransmitter in mammalian brains and the main substrate of DHE3. It is present in brains in concentrations higher than in other organs. In nervous tissue, DHE3 appears to function in both the synthesis and the catabolism of glutamate and perhaps detoxification functions. A transgenic (Tg) mouse model of lifelong excess synaptic glutamate release in the CNS by introducing the gene for glutamate dehydrogenase 1 under the control of the neuron-specific enolase promoter has been established[205]. In the Tg-model an increase in the *in vivo* release of glutamate after neuronal depolarization in striatum and miniature EPSPs in regions of the hippocampus was observed. Glutamate was stereotactically injected into the striatum where it induces alterations in *in vivo* glutamate and energy metabolism[193]. In a proteome analysis of complete spinal cord transection DHE3 was up-regulated[206]. In a corticostriatal deafferentiation study a decrease of enzymes involved in glutamate/aspartate transmitter metabolism up to 7 days after destruction was measured. After seven weeks, an increase for glutamate dehydrogenase activity[192] was observed. A significant diminution of DHE3 was found in autopsies from the putamen of PD patients[207]. These data suggest a secondary up-regulation after neurotoxic or mechanical damage of nervous tissue with DHE3 activity. The excitatory effects of glutamate may lead to an increase of energy consumption with up-regulation of those enzymes (see above) involved in energy metabolism.

Glutamine synthetase (GLNA) is down-regulated. Glutamine is a main source of energy and is involved in cell proliferation, inhibition of apoptosis, and cell signaling[208]. Glutamine synthetase is expressed throughout the body and plays an important role in controlling body pH and in removing ammonia from the circulation. The enzyme clears L-glutamate, the major excitatory neurotransmitter in the central nervous system, from neuronal synapses (see references in Clancy et al.[209]). The enzyme catalyzes the synthesis of glutamine from glutamate and ammonia in astrocytes. It is known that metamphetamine has long-lasting neurotoxic effects on dopamine, forebrain serotonin systems and induction of glutamate within the striatum[210]. In a 3-nitropropionic acid-induced oxidative stress

experiment in rats and in spheroid neuron cultures a decrease of GLNA was observed. This goes in line with our findings were oxidative stress was induced in the SNC and indirectly propagated by dopaminergic deafferentiation of CPu[211].

NAD dependent deacetylase sirtuin 2 (SIRT2, sirt: (silent mating type information regulation 2, S. cerevisiae, homolog)) is down-regulated. The sirtuins are members of the histone deacetylase family of proteins that participate in a variety of cellular functions and play a role in aging. NAD-dependent deacetylase deacetylates the 'Lys-40' of alpha-tubulin that was found to be up-regulated (Tab. 1) in the 6-OHDA lesioned striatum. SIRT2 is involved in the control of mitotic exit in the cell cycle, probably via its role in the regulation of cytoskeleton. Selective inhibitors of SIRT2 protect against alpha-synuclein-mediated toxicity in cellular models of PD and ameliorate dopaminergic cell death *in vitro* and in a Drosophila model of Parkinson's disease[212, 213]. Caloric restriction and oxidative stress generally up-regulates SIRT2 expression. The down-regulation of SIRT2 may be considered like a "SIRT inhibition" giving rise to a recovering of striatal cell populations after 6-OHDA damage of the dopaminergic SN efferents.

Group 9: Cofactors and vitamin metabolism

Flavin reductase or biliverdin reductase B (BLVRB) is up-regulated. It plays a possible role in protecting cells from oxidative damage or in regulating iron metabolism. Recently it was shown that an increased α-synuclein gene dosage, associated with autosomal dominant PD form, a block of tightly correlated heme metabolism genes (BLVRB, ALAS2, FECH) and that these genes are co-induced by the transcription factor GATA-1 which is able to induce a 6.9-fold increase in α-synuclein[214].

The cytoplasmic **pyridoxal kinase** (PDXK) is down-regulated. PDXK phosphorylates vitamin B6, a step required for the conversion of vitamin B6 to pyridoxal-5-phosphate. Recently PDXK was identified among 4 differentially expressed genes in the SNC of PD patients supporting the idea of the impact of vitamin B6 status and metabolism on disease risk and therapy in PD[215].

Pyridoxine-5'-phosphate oxidase (PNPO) is down-regulated. PNPO catalyzes the terminal, rate-limiting step in the synthesis of the biologically active form pyridoxal 5'-phosphate (P5P). Vitamin B6 is a required co-factor for enzymes involved in both homocysteine metabolism and synthesis of neurotransmitters such as catecholamine. Mutations in this gene result in PNPO deficiency, a form of neonatal epileptic encephalopathy. P5P is a cofactor for glutamic acid decarboxylase (GAD) that decarboxylize glutamate to GABA. GABA-transaminase produces succinic semialdehyde from GABA which can be converted from SSDH (SSDH is up-regulated in the 6-OHDA lesioned striatum) to succinic acid for the TCA cycle. So far, there is not much known about PNPO deficits[216] and the

involvement of PNPO in absorption of L-DOPA in the intestine, however, no data exists about the role of PNPO at the neuronal level in PD.

Group 10: Lipid metabolism

The mitochondrial **aldehyde dehydrogenase 2** (ALDH2) is up-regulated. In addition to removing acetaldehyde produced during the metabolism of ethanol, ALDH2 functions in the pathway by which aldehyde metabolites of the monoamines dopamine (DA) and serotonin (5-HT) are converted to their acidic metabolites (3,4-dihydroxphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindolacetic acid (5-HIAA))[217]. ALDH2 was down-regulated in the olfactory epithelium of old mice[218]. This enzyme is a known target for oxidation under conditions of oxidative stress[219] and is thought to be protective against oxidative stress[220]. Hence, an up-regulation of ALDH2 in the striatum may be a reaction due to the oxidative stress induced by 6-OHDA.

Cytosolic acyl coenzyme A thioester hydrolase or brain acyl-CoA hydrolase (BACH) is up-regulated. Acyl-CoA thioesterases are a group of enzymes that regulate intracellular levels of acyl-CoAs, free fatty acids and CoASH. BACH modulates the cellular levels of fatty acyl-CoA ligands for certain transcription factors as well as the substrates for fatty acid metabolizing enzymes, contributing to lipid homeostasis. There are only few informations available regarding BACH in the CNS, e.g., decreased expression of the BACH gene may be associated with mesial temporal lobe epilepsy[221], however, BACH protein is up-regulated here and has not been described to be dysregulated within PD or animal models of PD before.

The cytoplasmic **glycerol-3-phosphate dehydrogenase 1 like protein** (GPD1L) is up-regulated. It is involved in glycerophospholipid metabolism. The cytosolic together with the mitochondrial glycerol-3-phosphate dehydrogenase work in concert whereby glycerol-3-phosphate formation reaction is cytosolic in astrocytes, and mitochondrial in neurons[222]. The malate–aspartate shuttle and the glycerol phosphate shuttle act to transfer reducing equivalents from NADH in the cytosol to the mitochondria since the inner mitochondrial membrane is impermeable to NADH and NAD^+. This transfer of reducing equivalents is essential for maintaining a favourable NAD^+/NADH ratio required for the oxidative metabolism of glucose and synthesis of neurotransmitters in the brain. There is evidence that both the malate–aspartate shuttle and glycerol phosphate shuttle function in brain, however, there is controversy about the relative importance and cellular localization of these shuttles[223]. Oxidation of cytoplasmic NADH by the cytosolic form of the enzyme creates glycerol-3-phosphate from dihydroxyacetone phosphate. Once the glycerol-3-phosphate has moved through the inner mitochondrial membrane it can then be oxidised by a separate isoform of glycerol-3-phosphate dehydrogenase. Glycerol may have two roles in energy production in the brain[224]. First, it may fuel ATP formation by entering glycolysis and

oxidative metabolism. Second, glycerol-3-phosphate may serve in the glycerol-3-phosphate shuttle, which translocates reducing equivalents into mitochondria. In this shuttle cytosolic glycerol-3-phosphate dehydrogenase reduces dihydroxyacetone phosphate at the expense of NADH and H^+ to glycerol-3-phosphate which, as a substrate for mitochondrial glycerol-3-phosphate dehydrogenase, leads to intramitochondrial formation of $FADH_2$. GPD1L dysregulation have not been described so far in PD or neurotoxic animal models of PD.

Palmitoyl-protein thioesterase 1 (PPT1) is down-regulated. PPT1 is a small glycoprotein involved in the catabolism of lipid-modified proteins during lysosomal degradation. Defects in this gene are a cause of infantile neuronal ceroid lipofuscinosis 1 (CLN1, or INCL) and neuronal ceroid lipofuscinosis 4 (CLN4)[225]. A mutation of PPT1 leads to an increase of sphingolipid activator proteins[226]. PPT1 has not been found to be changed in PD or animal models of PD.

Group 11: Nucleic acid metabolism

The cytosolic **adenylate kinase 1** (KAD1) is up-regulated. KAD1 is involved in regulating the adenine nucleotide composition[227]. So, it plays an important role in cellular energy homeostasis and nucleotide synthesis that is essential for maintenance and cell growth. KAD1 was found to be age-related in the striatum of mice[228]. An increase of KAD1 with age was measured in the temporal cortex of rats[229]. In PD and animal models of PD no changes of KAD1 were described so far.

The cytoplasmic **biofunctional purine biosynthesis protein PURH** (PUR9) is up-regulated. It is involved in energy metabolism (conversion of ATIC to AMP through IMP) and nucleotide synthesis. An up-regulation of PUR9 was found in the hypothalamus of energy restricted cows[230], however, no measurements of PUR9 with regard to PD or PD animal models have been reported so far.

Guanine deaminase (GUAD) is up-regulated. It is also known as a cytosolic regulator of PSD-95 postsynaptic targeting[231, 232]. An increase of GUAD in the nucleus accumbens was observed in a cocaine self-administration experiment with rhesus monkeys[233]. Guanine nucleotides in the form of cyclic GMP, GDP, and GTP have significant roles in neuronal signaling pathways, so that the regulation of these nucleotides could alter cellular signaling[234]. Furthermore, it is involved in dendritic pattern formation via cypin, a protein that has GUAD enzyme activity[235]. The up-regulation of GUAD may support postsynaptic differentiation and reorganization that may be necessary to enhance the very few surviving synaptic contacts following 6-OHDA deafferentiation. However, the observed down-regulation of the dendritic protein drebrin (see above) may be the effect of a decrease of dendritic sprouting due to absent presynaptic dopaminergic targets.

The up-regulated **inosine triphosphatase** (ITPA) is located in the nuclei of neurons in the brain[236] and hydrolyzes inosine triphosphate and deoxyinosine triphosphate to the monophosphate nucleotide

and diphosphate. ITPA is a ubiquitous key regulator of cellular non-canonical nucleotide levels. It breaks down inosine and xanthine nucleotides generated by deamination of purine bases. The enzymatic action of ITPA prevents accumulation of ITP and reduces the risk of incorporation of potentially mutagenic inosine nucleotides into nucleic acids[237].

Group 12: Antioxidants

N(G),N(G)-dimethylarginin, dimethylaminotransferase 2 (DDAH2) is up-regulated. DDAH2 is involved in nitric oxide generation by regulating cellular concentrations of methylarginines, which in turn inhibit nitric oxide synthase activity. DDAH2 is known to be expressed during foetal development as well as neurogenesis[238]. DDAH2 enzyme has not, to the best of our knowledge, earlier been implicated in PD models, however, it is well known that nitric oxide is possible source of oxidative stress. NO is produced by NOS by converting of L-agrinine to L-citrulline utilizing NADPH and O_2 as cofactors. The constitutive NOS isoforms, to which brain NOS belongs, require calcium and calmodulin (down-regulated here, see above) for activity and the inducible NOS requires de novo synthesis of the enzyme upon activation of transcriptional pathway by cytokines or LPS[55].

Protein disulfide isomerase (PDIA1) and **protein disulfide isomerase 3** (PDIA3) are up-regulated. PDIA1 is an enzyme in the endoplasmic reticulum that catalyzes the formation and breakage of disulfide bonds between cysteine residues during protein folding. This allows proteins to quickly find the correct arrangement of disulfide bonds in their fully-folded state. Furthermore, the enzyme is responsible for degradation of hypoxia inducible factor-1α, a primary constituent associated with hypoxic angiogenesis and a regulator of neuroprotective responses. PDIA1 can be inhibited by intracellular succinate. Since succinate dehydrogenase flavoproteine subunit (DHSA) is up-regulated (see above) and irreversibly inhibits the TCA enzyme succinate dehydrogenase succinate levels may counteract PDIA1. Also PDIA1 gene product has not been described before to be altered in PD or PD models.

The mitochondrial **superoxide dismutase 2** (SODM) is up-regulated. SODM protein binds to the superoxide by-products of oxidative phosphorylation and converts them to hydrogen peroxide and diatomic oxygen. Though an effective SODM scavenger system is present within normal mitochondria, damaged mitochondria may be less effective in combating free radical production, contributing to an increase in oxidative stress. In an *in vitro* study dopamine quinine was applied to PC12 cells and SODM was found to be decreased[196]. Our contrasting results must be considered by the aspects of timing and location: the proteome of the lesioned striatum was processed 134 days after lesioning and striatal proteome is affected indirect whereas the SNC is affected directly as those PC12 cells in the study of van Laar et al.[196].

The mitochondrial **thioredoxin-dependent peroxide reductase** (PRDX3) is up-regulated, whereas peroxiredoxin 5 and 6 do not show any alteration. PRDX3 is involved in redox regulation of the cell. Hence, it protects radical-sensitive enzymes from oxidative damage. Furthermore, it acts synergistically with MAP3K13 to regulate the activation of NF-kappa-B in the cytosol. In an *in vitro* mRNA silencing study it was shown that PRDX-depleted SH-SY5Y cells are more prone to oxidative stress and apoptosis induced by the complex I inhibitor MPP^+ [239]. These findings are correlated with an *in vivo* ibotenic acid inhibition of the PRDX3 enzyme in rat hippocampal neurons[240].

Group 13: Dopamine biosynthesis

The cytosolic oxygenase **tyrosine hydroxylase** (TH) is extremely down-regulated. TH catalyzes the conversion of the amino acid L-tyrosine to dihydroxyphenylalanine (DOPA)[241, 242]. It is the rate limiting enzyme in the production of catecholamines[243]. TH is synthesized in several nuclei of the rat CNS. The TH synthesizing neurons of the SNC have been destroyed by stereotactic 6-OHDA injection into the MFB. Hence, a down-regulation of TH in the striatal proteome was found and validated by immunohistochemistry (Figs. 2, 5).

Group 14: Proteasomal protein

Ubiquitin carboxyl terminal hydrolase L1 (UCHL1, PARK5) also known as neuron cytoplasmic protein 9.5 or PGP 9.5 is up-regulated. UCHL1 is a deubiqutinating enzyme and member of a gene family whose products hydrolyze small C-terminal adducts of ubiquitin to generate the ubiquitin monomer. Expression of UCHL1 is highly specific to neurons and to cells of the diffuse neuroendocrine system and their tumors. It is present in all neurons[244]. UCHL1 has previously been found to co-localize with Parkin and α-synuclein in Lewy bodies[58, 245]. Mutations give rise to PD[246]. A point mutation (I93M) in the gene encoding this protein is implicated as the cause of PD[247]. Furthermore, a polymorphism (S18Y) in this gene has been found to be associated with a reduced risk for Parkinson's disease[248 249]. The up-regulation of UCHL1 in the striatum 134 days after lesioning may be a reaction to an increase of misfolded proteins under oxidative stress.

Neural F box protein 42-kDa protein (NFB42) is up-regulated and a component of the SCF^{NFB42} E3 ubiquitin ligase that is only expressed in the cytoplasm of neurons in all major areas of the brain[250]. NFB 42 contains a F box motif that couples cell cycle regulation to the proteasome pathway[251]. The occurrence of F box in NFB42 indicates cell cycle regulation and seems to act in postmitotic neurons as a regulator for keeping them in a postmitotic state[252].

Group 15: Signal transduction

The cytopolasmic **14-3-3 protein epsilon** (1433E) and **14-3-3 protein gamma** (1433G) are both down-regulated whereby **14-3-3 protein zeta** (1433Z) is up-regulated. The 14-3-3 proteins are involved in intracellular signaling, cell division, cell differentiation, apoptosis, ion channel functioning, and neurotransmission[253]. TH may be activated through 14-3-3 proteins. 14-3-3 proteins are also attributed to cytoplasmic chaperones[254], some of which have been reported to bind to α-synuclein[255] and be a component of Lewy bodies[256]. 1433E is known to interact with Parkin and negatively regulates its activity[257]. It is possible that it may have the same effect on the two forms of 14-3-3 proteins (Z and E) found to associate with Parkin[258]. Of particular interest is the finding that 1433Z is decreased in Parkin knockout mice[259], however, we found an up-regulation in the 6-OHDA lesioned striatum. Furthermore, 1433Z interacts specifically with CH60 in the mitochondria[260] which is up-regulated in the lesioned striatum as well.

Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta 1 (GBB1) and **guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta 5** (GBB5) are down-regulated, however, **guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta 2** (GBB2) is up-regulated. Guanine nucleotide-binding proteins (G proteins) are a family of proteins involved as a modulator or transducer in various transmembrane signaling systems. The beta and gamma chains are required for the GTPase activity. The normal role of the beta-gamma complex is inhibition of the G_{α} subunit. However, the free $G_{\beta\gamma}$ complex can act as a signaling molecule itself, by activating other second messengers or by gating ion channels directly. Some functions include activation of phospholipase A2 when bound to histamine receptors, direct opening of G-protein coupled inward rectifying potassium channels (GIRKs) when bound to muscarinic acetylcholine receptors this is of particular relevance for the cholinergic interneurons of the striatum, activation L-type calcium channels, as in H_3 receptor pharmacology.

The inhibitory D2-like dopamine receptors (D2, D3, and D4) are coupled to the $G_{i/o}$ family of G proteins[261, 262], however, these G proteins are less relevant because in the striatum D1 and D2 receptors are expressed in the direct and in indirect pathways. Dopamine may act by different signaling pathways: phosphokinase C, inositol phosphate and Ca^{2+} production through the G_i (adenylate cyclase) and G_s ($PIP_2 \rightarrow PKC \rightarrow IP3$) family on D1 and D2 receptors[263]. Furthermore, cytokines that could be released by activated microglia may bind to G-protein coupled receptors (GPCRs). The down-regulation of GBB1 and GBB5 can be explained by a postsynaptic response on the reduced or missing dopamine signal due to 6-OHDA lesioning.

Mitogen activated protein kinase 1 (MK01) is up-regulated and occurs in the cytoplasm and in the nucleus. MAP kinases, also known as extracellular signal-regulated kinases (ERKs) are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. Degenerating neurons of PD patient brains exhibit granules of phosphorylated

extracellular signal-regulated protein kinase 1/2 (ERK1/2) that localize to autophagocytosed mitochondria[264].

Our results coincide with findings *in vitro* where 6-OHDA elicits activity-related localization of ERK1/2 in mitochondria of SH-SY5Y cells, and these events coincide with induction of autophagy and precede mitochondrial degradation[264]. Furthermore it is known that neurotoxins such as 6-OHDA promote large increases in cytosolic and mitochondrial ROS, activation/translocation of ERK and JNK to mitochondria and induction of beclin 1-independent autophagy, accompanied by decreased nuclear trafficking and neuroprotective transcription. Both JNK and ERK have been shown to contribute directly to mitochondrial dysfunction by suppressing oxidative respiration[148]. Glial cell line-derived neurotrophic factor (GDNF) has been shown to be neuroprotective in animal models of the dopamine deficiency in PD. It was demonstrated that GDNF infusion into mice striata increase phosphorylated ERK1/2 and protect striatal neurons after intrastriatal administration of 6-OHDA[265]. A further protective effect through ERK1/2 phophorylation was demonstrated in a 6-OHDA in vitro study with MN9D cells[266].

The activation of Ca^{2+}-permeable N-methyl-D-aspartate (NMDA) receptors up-regulates the phosphorylation of MAPKs, respectively, ERK1/2 and it was shown that ERK1/2 kinases are differentially involved in linking NMDA receptors to ERK1/2 in striatal neurons[267]. Striatal enriched protein tyrosine phosphatase (STEP) is involved in regulating synaptic plasticity and seems to regulate ERK1/2[268]. An increase of phosphorylation of ERK1/2 was also demonstrated in 6-OHDA lesioned striata that were treated with L-DOPA[269, 270] and 8-(3-chlorostyryl) caffeine (CSC), a selective adenosine A2A receptor antagonist[271].

The up-regulation of MK01 in the 6-OHDA lesioned striatum can be an induction of a neuroprotective mechanism. However, the phosphorylation state of MK01 has to be clarified.

Dual specifity mitogen activated protein kinase kinase 1 (MP2K1) is up-regulated. This protein kinase stimulates the enzymatic activity of MAP kinases (ERK1/2) upon wide variety of extra- and intracellular signals. A down-regulation of the MP2K1 gene was measured in the dopaminergic mesencephalon-derived N27 cell line under oxidative stress[272]. Furthermore, it was found that glutamate neurotoxicity involves different MAPK pathways in dopaminergic and nondopaminergic neurons[273]. Recently, it was found that microtubule-depolymerizing agents such as colchicine or nocodazole induce strong activation of MAP kinases including JNK, ERK, and p38 suggesting that parkin protects midbrain dopaminergic neurons against microtubule-depolymerizing PD toxins such as rotenone by stabilizing microtubules to attenuate MAP kinase activation[274]. In primary mesencephalic neuron-glia co-cultures it was shown that dopaminergic neurons from MP2K1-deficient mice were significantly more resistant to lipopolysaccharide-induced neurotoxicity compared with cells from wild-type mice

associated with a reduced inflammatory response[275]. The basic effect of MP2K1 with regard to in vitro and *in vivo* studies of SNC dopaminergic neurons seems to be the initialization of a degrading process. Hence, the measured up-regulation of MP2K1 in the 6-OHDA lesioned striatum may provide hints of neurotoxin induced degenerative processes in the striatum.

Group 16: Proteins involved in transcription

Heterogeneous nuclear ribonucleoprotein A3 (ROA) and the **isoform A2/B1** (ROA2) is down-regulated. HNRPs play a role in cytoplasmic trafficking of RNA and they are formed when nascent pre-mRNA transcripts are bound by a number of nuclear proteins forming a large multiprotein-RNA complex. Moreover, HNRP's play important roles in the splicing and transport of mRNAs and participate in early heat shock-induced splicing arrest. The ROA2 of HNRNPs was observed in the striatum and further brain regions[276]. A rapid phosphorylation of HNRP-C1/C2 in response to low concentrations of H_2O_2 in human endothelial cells was described[277]. Similarly, H_2O_2-stimulated phosphorylation of HNRP-C by protein kinase CK1α modulates their RNA binding activity[278]. In 6-OHDA exposed SH-SY5Y cells an increase in the phosphorylated form of HNRP H3 was reported and interpreted as a protective cellular response[133]. Furthermore, HNRP-L is up-regulated in the rat striatum after administration of the endogenous tripeptide Pro-Leu-Gly-NH2[279]. A down-regulation of ROA2 was found in ageing mice and interpreted as a consequence of the increase of DNA damage and transcription detuning[280]. The pattern of expression of HNRPs in the 6-OHDA lesioned striatum coincides with these findings, however, it has not been described before in this specific neurotoxic model. Down-regulation of ROA2 and ROA3 fits to the increase of DNA damage and transcription detuning due to lesioned 6-OHDA neurons and up-regulation of HNRPK indicates the involvement of strial astroglia through neuron-astrocyte synaptic complexes.

Nucleosome assembly protein 1-like 4 (NP1L4) is up-regulated. It can shuttle between the cytoplasm and nucleus, suggesting a role as a histone chaperone. The NP1L2 controls the neurulation in a mutant mouse model[281]. Defects were correlated with an overproduction of neuronal precursor cells. In a proteome mapping study of the rat forebrain NP1L4 was also found[66]. A down-regulation of NP1L1 in the differentiating human fetal midbrain stem cell line (ReNcell VM) was measured[282]. A down-regulation of NLP1L1 was also found in the hippocampus of old rats in comparison to young rats[283]. An alteration of the specific subtype NP1L4 in PD or animal models of PD have not been described before. An up-regulation of NP1L4 may result from an inflammatory response of microglia cells that were shown to be increased[284, 285]. The up-regulated NP1L4 may be a response to an increase of repair mechanisms due to an increase of transcription for the altered protein turnover following 6-OHDA deafferentiation of the striatum.

RuvB-like 1 (RUVB1)[286] is up-regulated. It is mainly localized in the nucleus. It is a component of the NuA4 histone acetyltransferase complex which is involved in transcriptional activation of select genes principally by acetylation of nucleosomal histones H4 and H2A. This modification may both alter nucleosome - DNA interactions and promote interaction of the modified histones with other proteins which positively regulate transcription. This complex may be required for the activation of transcriptional programs associated with oncogene and proto-oncogene mediated growth induction, tumor suppressor mediated growth arrest and replicative senescence, apoptosis, and DNA repair. The appearance of RuvB-like 1 in the CNS has been described here for the first time. However, it is known that RUVB1 is involved in the WNT signaling pathway[287]. The up-regulation may indicate an increase of transcriptional activity of cell populations under oxidative stress due to 6-OHDA.

Transcriptional activator protein Pur-alpha (PURA) is absent in the control striatum, however, expressed in the 6-OHDA deafferentiated striatum. PURA binds preferentially to the single strand of the purine-rich element termed PUR, which may act as a transcription activator and hence may play a role in the initiation of DNA replication and in recombination. The amino acid composition and partial amino acid sequence were determined to be identical to those of CALM, which enhanced the binding of glutathione *S*-transferase-PURA to various PUR elements in the 5' noncoding regions of the neuropeptide Y, myelin basic protein and nicotinic Ach receptor β 4 subunit genes. This gene expression pathway is mediated by Ca/CALM-PURA which may regulate a variety of genes in addition to those regulated through the CREB pathway[288]. Transgenic mice with inactivation of the PURA gene that encodes PURA has revealed that PURA is critical for postnatal brain development and has unraveled an essential role of PURA in the transport of specific mRNAs to the dendrites and the establishment of the postsynaptic compartment in the developing neurons[289, 290]. An epression of PURA in the 6-OHDA lesioned striatum could indicate an increase of transcriptional activity of a certain cell population, e.g., to boost mitogen activity of astrocytes for astrogliosis. It remains to be open if this could be a temporary or long term effect following 6-OHDA lesions. Cell types that are concerned by this massive up-regulation need to be identified.

Group 17: Unknown function

The mitochondrial precursor **ES1 protein homolog** (ES1) is up-regulated and contains a potential targeting sequence to mitochondria in its N-terminal region[291]. It was reported by Shin et al. [291] that ES1 elevation was found in Down syndrome (overexpression of genes of chromosome 21) where mitochondrial deficits were also reported[292]. Neurons in Down syndrome patients have a three- to four-fold increased level of intracellular ROS with elevated levels of lipid peroxidation preceding neuronal death[293]. In alignment analysis it was shown that ES1 is a DJ-1/PfpI (pryococcus furiosus protease I)

family member. Mutations of the DJ-1 or PARK7 gene results in a genetic form of Parkinson disease[294]. In conjunction with mitochondrial deficits in Down syndrome recent findings of DJ-1 binding to the mitochondrial complex 1 are interesting[155].

Suppl. Tab. 1: Striatal proteins identified by peptide mass fingerprinting in spots from Coomassie-stained gels (see Supplementary Fig. 3). Acc. #: Accession number from Swiss Prot, Entry name: from Swiss Prot. Score: Mascot MOWSE-score. Cov: Coverage of the entire protein sequence by the detected tryptic peptides in %.Q/Qm: Number of mass values searched / Number of mass values (tryptic peptides) assigned to the identified protein. RMS: Root mean square (RMS) error of the set of matched mass values in ppm. Mw, pI: Theoretical molecular mass (Da) and theoretical pI value taken from the Mascot report.

Acc. #	Spot #	Entry name	Protein name	Score	Cov	Q/Qm	RMS	Mw	pI
P47942	1911	DPYL2_RAT	Dihydropyrimidinase-related protein 2	247	55	31/21	28	62638	5.95
P11980	2054	KPYM_RAT	Pyruvate kinase isozymes M1/M2	173	32	25/16	27	58294	6.63
P69897	2631	TBB5_RAT	Tubulin beta-5 chain	82	27	40/13	33	50095	4.78
P13233	2631	CN37_RAT	2',3'-cyclic-nucleotide 3'-phosphodiesterase	61	22	40/8	32	47638	9.03
Q68FX0	2730	IDH3B_RAT	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial	98	31	42/14	41	42612	8.89
P13221	2730	AATC_RAT	Aspartate aminotransferase, cytoplasmic	74	27	42/9	37	46628	6.73
Q9Z1X8	2830	Q9Z1X8_RAT	Neural F box protein NFB42	163	49	36/12	25	34021	4.3
P81155	3059	VDAC2_RAT	Voltage-dependent anion-selective channel protein 2	162	59	36/13	21	32353	7.44
P08081	3179	CLCA_RAT	Clathrin light chain A	84	19	30/8	37	27078	4.41
B5DF65	3805	B5DF65_RAT	Biliverdin reductase B (Flavin reductase (NADPH)) (Biliverdin reductase B (Flavin reductase (NADPH)) (Predicted), isoform CRA_b)	212	87	30/14	17	22194	6.29
D3ZW55	3844	D3ZW55_RAT	Inosine triphosphatase (Nucleoside triphosphate pyrophosphatase) (Mapped), isoform CRA_a	139	66	38/11	27	22255	5.48
O35244	3877	PRDX6_RAT	Peroxiredoxin-6	208	77	38/16	28	24860	5.64
B0BNE6	3946	B0BNE6_RAT	NADH dehydrogenase (Ubiquinone) Fe-S protein 8 (Predicted), isoform CRA_a	131	41	35/11	20	24411	5.87
P62161	4567	CALM_RAT	Calmodulin	102	41	18/8	27	16827	4.09
P62161	4569	CALM_RAT	Calmodulin	121	42	18/10	18	16827	4.09
Q6AYZ1	4581	TBA1C_RAT	Tubulin alpha-1C chain	65	23	39/8	20	50590	4.96
Q63228	4613	GMFB_RAT	Glia maturation factor beta	78	42	31/7	24	16897	5.32
Q00981	4738	UCHL1_RAT	Ubiquitin carboxyl-terminal hydrolase isozyme L1	120	54	31/9	13	25165	5.14
Q00981	4740	UCHL1_RAT	Ubiquitin carboxyl-terminal hydrolase isozyme L1	121	50	27/9	26	25165	5.14
P19234	4767	NDUV2_RAT	NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial	140	55	34/14	20	27703	6.23
P63102	4821	1433Z_RAT	14-3-3 protein zeta/delta	148	62	104/24	13	27925	4.73
P63102	4858	1433Z_RAT	14-3-3 protein zeta/delta	108	53	85/18	22	27925	4.73
P69897	4858	TBB5_RAT	Tubulin beta-5 chain	99	29	85/20	25	50095	4.78
P10719	4858	ATPB_RAT	ATP synthase subunit beta, mitochondrial	71	28	85/15	31	56318	5.19
P62260	4871	1433E_RAT	14-3-3 protein epsilon	111	49	63/17	19	29326	4.63
P54311	4871	GBB1_RAT	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1	104	47	63/13	22	38151	5.6

P60711	4908	ACTB_RAT	Actin, cytoplasmic 1	178	45	40/18	25	42052	5.29
P69897	4918	TBB5_RAT	Tubulin beta-5 chain	75	18	36/12	20	50095	4.78
P69897	4931	TBB5_RAT	Tubulin beta-5 chain	69	25	29/8	39	50095	4.78
P07171	4931	CALB1_RAT	Calbindin	58	33	29/6	37	30203	4.71
O88767	5137	PARK7_RAT	Protein DJ-1	264	91	41/22	12	20190	6.32
Q9Z0V6	5140	PRDX3_RAT	Thioredoxin-dependent peroxide reductase, mitochondrial	111	52	39/10	9	28563	7.14
P31399	5170	ATP5H_RAT	ATP synthase subunit d, mitochondrial	133	67	36/11	28	18809	6.17
P61983	5180	1433G_RAT	14-3-3 protein gamma	147	50	67/22	31	28456	4.8
P63102	5180	1433Z_RAT	14-3-3 protein zeta/delta	124	56	67/18	32	27925	4.73
Q63610	5193	TPM3_RAT	Tropomyosin alpha-3 chain	253	69	74/27	27	29217	4.75
P62260	5193	1433E_RAT	14-3-3 protein epsilon	77	54	74/13	31	29326	4.63
Q64119	5223	MYL6_RAT	Myosin light polypeptide 6	100	52	30/9	26	17135	4.46
P62161	5224	CALM_RAT	Calmodulin	133	57	25/12	17	16827	4.09
O88794	5256	PNPO_RAT	Pyridoxine-5'-phosphate oxidase	95	27	18/8	25	30507	8.66
P48500	5267	TPIS_RAT	Triosephosphate isomerase	198	67	19/12	28	27345	6.89
P07895	5312	SODM_RAT	Superoxide dismutase [Mn], mitochondrial	101	42	37/9	29	24887	8.96
P39069	5312	KAD1_RAT	Adenylate kinase isoenzyme 1	94	59	37/10	21	21684	7.66
P56571	5356	ES1_RAT	ES1 protein homolog, mitochondrial	120	51	19/9	22	28497	9.11
P20788	5356	UCRI_RAT	Cytochrome b-c1 complex subunit Rieske, mitochondrial	57	11	19/5	20	29712	9.04
Q9R063	5423	PRDX5_RAT	Peroxiredoxin-5, mitochondrial	137	47	32/10	22	22507	8.94
P19804	5436	NDKB_RAT	Nucleoside diphosphate kinase B	225	89	26/17	23	17386	6.92
P04905	5624	GSTM1_RAT	Glutathione S-transferase Mu 1	299	79	44/28	22	26068	8.27
P15999	5679	ATPA_RAT	ATP synthase subunit alpha, mitochondrial	205	30	19/16	20	59831	9.22
P15999	5681	ATPA_RAT	ATP synthase subunit alpha, mitochondrial	183	28	21/16	24	59831	9.22
Q9Z2L0	5694	VDAC1_RAT	Voltage-dependent anion-selective channel protein 1	128	59	38/11	13	30851	8.62
P81155	5694	VDAC2_RAT	Voltage-dependent anion-selective channel protein 1	55	33	38/6	10	32353	7.44
Q9Z2L0	5715	VDAC1_RAT	Voltage-dependent anion-selective channel protein 1	103	48	42/9	40	30851	8.62
P13803	5722	ETFA_RAT	Electron transfer flavoprotein subunit alpha, mitochondrial	145	44	22/11	30	35272	8.62
P45479	5759	PPT1_RAT	Palmitoyl-protein thioesterase 1	86	29	10/6	8	34946	7.1
Q9Z2L0	5774	VDAC1_RAT	Voltage-dependent anion-selective channel protein 1	164	62	29/12	21	30851	8.62
Q99MZ8	5834	LASP1_RAT	LIM and SH3 domain protein 1	166	43	28/16	13	30351	6.61
P63086	5857	MK01_RAT	Mitogen-activated protein kinase 1	180	41	51/15	26	41648	6.5
Q5RJQ4	5869	SIRT2_RAT	NAD-dependent deacetylase sirtuin-2	286	63	32/21	25	39921	6.67
Q5RJQ4	5872	SIRT2_RAT	NAD-dependent deacetylase sirtuin-2	185	47	22/13	24	39921	6.67
P09117	5886	ALDOC_RAT	Fructose-bisphosphate aldolase C	219	59	19/14	22	39658	6.67
P63018	5933	HSP7C_RAT	Heat shock cognate 71 kDa protein	84	19	41/12	24	71055	5.37
Q3ULJ0	5933	GPD1L_MOUSE	Glycerol-3-phosphate dehydrogenase 1-like protein (Mus musculus)	78	29	41/9	28	38828	6.34

Q64559	5956	BACH_RAT	Cytosolic acyl coenzyme A thioester hydrolase	115	39	34/14	34	43164	8.8
Q64559	5960	BACH_RAT	Cytosolic acyl coenzyme A thioester hydrolase	114	40	36/14	20	43164	8.8
B1WC26	5960	B1WC26_RAT	N-acetylneuraminic acid synthase	62	29	36/8	20	40482	6.39
P09606	6004	GLNA_RAT	Glutamine synthetase	178	35	42/18	28	42982	6.64
P26284	6043	ODPA_RAT	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mitochondrial	142	30	24/14	17	43883	8.49
P63018	6250	HSP7C_RAT	Heat shock cognate 71 kDa protein	253	36	43/24	15	71055	5.37
P04636	6319	MDHM_RAT	Malate dehydrogenase, mitochondrial	181	59	53/19	25	36117	8.93
A7VJC2	6319	ROA2_RAT	Heterogeneous nuclear ribonucleoproteins A2/B1	144	40	53/16	17	37512	8.97
Q6URK4	6351	ROA3_RAT	Heterogeneous nuclear ribonucleoprotein A3	78	20	24/8	19	39856	9.1
P13221	6435	AATC_RAT	Aspartate aminotransferase, cytoplasmic	142	46	45/17	32	46628	6.73
P10860	6494	DHE3_RAT	Glutamate dehydrogenase 1, mitochondrial	116	37	85/23	32	61719	8.05
Q08163	6494	CAP1_RAT	Adenylyl cyclase-associated protein 1	60	29	85/14	29	51899	7.16
B2GV06	6494	SCOT1_RAT	Succinyl-CoA:3-ketoacid-coenzyme A transferase 1, mitochondrial	52	27	85/13	31	56624	8.7
P10860	6496	DHE3_RAT	Glutamate dehydrogenase 1, mitochondrial	100	30	64/15	22	61719	8.05
Q08163	6496	CAP1_RAT	Adenylyl cyclase-associated protein 1	54	24	64/10	23	51899	7.16
P11980	6547	KPYM_RAT	Pyruvate kinase isozymes M1/M2	186	40	40/20	32	58294	6.63
Q63537	6563	SYN2_RAT	Synapsin-2	139	31	31/16	30	63702	8.73
	6607		no hit						
Q6P6R2	6688	DLDH_RAT	Dihydrolipoyl dehydrogenase, mitochondrial	143	38	35/14	18	54574	7.96
P10860	6688	DHE3_RAT	Glutamate dehydrogenase 1, mitochondrial	62	19	35/9	20	61719	8.05
Q63537	6701	SYN2_RAT	Synapsin-2	144	28	31/18	28	63702	8.73
P0C2X9	6711	AL4A1_RAT	Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	125	23	20/11	31	62286	7.14
P62815	6755	VATB2_RAT	V-type proton ATPase subunit B, brain isoform	129	29	28/13	33	56857	5.57
P68370	6755	TBA1A_RAT	Tubulin alpha-1A chain	90	29	28/9	31	50788	4.94
P47942	6765	DPYL2_RAT	Dihydropyrimidinase-related protein 2	208	47	33/19	41	62638	5.95
Q4V7C7	6784	ARP3_RAT	Actin-related protein 3	212	52	35/19	35	47783	5.61
P11598	6822	PDIA3_RAT	Protein disulfide-isomerase A3	222	35	28/19	19	57044	5.88
B0BNF1	6825	SEPT8_RAT	Septin-8	159	30	30/13	24	51562	5.74
Q5XIM9	6879	TCPB_RAT	T-complex protein 1 subunit beta	328	61	45/31	29	57764	6.01
B0BNF1	6934	SEPT8_RAT	Septin-8	265	56	45/24	21	51562	5.74
Q5XIF6	6962	TBA4A_RAT	Tubulin alpha-4A chain	219	49	43/18	24	50634	4.95
P42123	7066	LDHB_RAT	L-lactate dehydrogenase B chain	215	55	58/26	26	36874	5.7
Q5XIF6	7079	TBA4A_RAT	Tubulin alpha-4A chain	143	45	44/14	25	50634	4.95
P42123	7087	LDHB_RAT	L-lactate dehydrogenase B chain	273	61	40/26	28	36874	5.7
P62882	7213	GBB5_RAT	Guanine nucleotide-binding protein subunit beta-5	73	26	19/6	16	39505	5.67
O35331	7232	PDXK_RAT	Pyridoxal kinase	191	48	29/18	15	35114	6.32
Q561S0	7258	NDUAA_RAT	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mitochondrial	226	63	33/18	25	40753	7.64

P85108	7297	TBB2A_RAT	Tubulin beta-2A chain	246	54	44/24	15	50274	4.78
Q01986	7304	MP2K1_RAT	Dual specificity mitogen-activated protein kinase kinase 1	196	44	40/20	23	43779	6.18
P16446	7332	PIPNA_RAT	Phosphatidylinositol transfer protein alpha isoform	207	70	57/22	24	32115	5.97
	7348		no hit						
P85845	7391	FSCN1_RAT	Fascin	179	35	25/15	26	55198	6.29
P85845	7450	FSCN1_RAT	Fascin	181	44	36/16	27	55198	6.29
P85834	7493	EFTU_RAT	Elongation factor Tu, mitochondrial	233	60	50/24	42	49890	7.23
B5DFG5	7495	B5DFG5_RAT	RCG53214, isoform CRA_d	176	44	30/17	28	49147	6.23
P60123	7500	RUVB1_RAT	RuvB-like 1	87	28	43/12	27	50524	6.02
P51650	7500	SSDH_RAT	Succinate-semialdehyde dehydrogenase, mitochondrial	67	21	43/9	29	56723	8.35
P11884	7501	ALDH2_RAT	Aldehyde dehydrogenase, mitochondrial	71	20	45/10	39	56966	6.63
P85845	7505	FSCN1_RAT	Fascin	92	21	29/10	28	55198	6.29
P09117	7546	ALDOC_RAT	Fructose-bisphosphate aldolase C	138	49	34/13	23	39658	6.67
P14669	7593	ANXA3_RAT	Annexin A3	293	68	37/22	30	36569	5.96
Q6MG60	7603	DDAH2_RAT	N(G),N(G)-dimethylarginine dimethylaminohydrolase 2	195	53	23/15	29	30011	5.66
P69897	7618	TBB5_RAT	Tubulin beta-5 chain	110	30	37/13	14	50095	4.78
P69682	7618	NECP1_RAT	Adaptin ear-binding coat-associated protein 1	76	36	37/7	18	29831	5.97
Q4FZT0	7620	STML2_RAT	Stomatin-like protein 2	138	34	11/9	10	38504	8.74
Q9R1T5	7689	ACY2_RAT	Aspartoacylase	172	51	36/17	11	35747	5.95
P11980	7690	KPYM_RAT	Pyruvate kinase isozymes M1/M2	134	23	14/10	23	58294	6.63
P85845	7701	FSCN1_RAT	Fascin	106	29	32/11	23	55198	6.29
Q5XIM9	7701	TCPB_RAT	T-complex protein 1 subunit beta	79	27	32/11	23	57764	6.01
P63018	7856	HSP7C_RAT	Heat shock cognate 71 kDa protein	99	21	36/13	21	71055	5.37
	7946		no hit						
Q6P9V9	7977	TBA1B_RAT	Tubulin alpha-1B chain	124	31	35/11	32	50804	4.94
Q4QRB4	7991	TBB3_RAT	Tubulin beta-3 chain	172	49	70/25	21	50842	4.82
Q6P9T8	7999	TBB2C_RAT	Tubulin beta-2C chain	156	40	39/17	26	50225	4.79
P85108	8005	TBB2A_RAT	Tubulin beta-2A chain	162	44	52/19	33	50274	4.78
P07323	8006	ENOG_RAT	Gamma-enolase	138	61	82/20	17	47510	5.03
P85108	8006	TBB2A_RAT	Tubulin beta-2A chain	77	30	82/17	16	50274	4.78
P07335	8036	KCRB_RAT	Creatine kinase B-type	156	40	56/15	32	42983	5.39
Q9WTT6	8086	GUAD_RAT	Guanine deaminase	309	53	33/25	17	51554	5.56
Q9WTT6	8089	GUAD_RAT	Guanine deaminase	293	71	58/31	26	51554	5.56
P07335	8146	KCRB_RAT	Creatine kinase B-type	136	50	53/15	40	42983	5.39
P60711	8203	ACTB_RAT	Actin, cytoplasmic 1	140	45	42/15	27	42052	5.29
P82995	8280	HS90A_RAT	Heat shock protein HSP 90-alpha	120	23	44/18	18	85161	4.93
D3ZPE4	8280	D3ZPE4_RAT	Putative uncharacterized protein Anxa7	95	30	44/17	21	52667	5.27

P10719	8315	ATPB_RAT	ATP synthase subunit beta, mitochondrial	263	59	65/32	17	56318	5.19
P31000	8356	VIME_RAT	Vimentin	241	56	51/27	30	53757	5.06
P23565	8356	AINX_RAT	Alpha-internexin	118	31	51/17	37	56253	5.2
P18418	8412	CALR_RAT	Calreticulin	98	19	16/8	30	48137	4.33
O08839	8418	BIN1_RAT	Myc box-dependent-interacting protein 1	108	29	35/11	30	64721	4.95
	8445		no hit						
P07323	8504	ENOG_RAT	Gamma-enolase	191	67	57/22	34	47510	5.03
P07323	8530	ENOG_RAT	Gamma-enolase	220	64	50/22	36	47510	5.03
P60711	8581	ACTB_RAT	Actin, cytoplasmic 1	164	56	63/20	27	42052	5.29
Q68FY0	8581	QCR1_RAT	Cytochrome b-c1 complex subunit 1, mitochondrial	86	32	63/14	18	53500	5.57
P62815	8590	VATB2_RAT	V-type proton ATPase subunit B, brain isoform	316	69	70/36	28	56857	5.57
P07335	8609	KCRB_RAT	Creatine kinase B-type	223	51	38/19	17	42983	5.39
Q9JHL4	8671	DBNL_RAT	Drebrin-like protein	60	24	42/8	39	48925	4.89
Q5U2Z3	8679	NP1L4_RAT	Nucleosome assembly protein 1-like 4	95	30	54/12	20	44118	4.58
P69897	8679	TBB5_RAT	Tubulin beta-5 chain	76	25	54/13	31	50095	4.78
P19527	8683	NFL_RAT	Neurofilament light polypeptide	138	34	48/18	30	61355	4.63
P69897	8683	TBB5_RAT	Tubulin beta-5 chain	53	20	48/10	32	50095	4.78
P63039	8714	CH60_RAT	60 kDa heat shock protein, mitochondrial	75	26	30/9	45	61088	5.91
P23565	8714	AINX_RAT	Alpha-internexin	54	18	30/7	34	56253	5.2
P23565	8717	AINX_RAT	Alpha-internexin	153	35	37/16	22	56253	5.2
P63039	8719	CH60_RAT	60 kDa heat shock protein, mitochondrial	202	50	69/24	23	61088	5.91
P61980	8719	HNRPK_RAT	Heterogeneous nuclear ribonucleoprotein K	65	27	69/13	28	51230	5.39
P54313	8742	GBB2_RAT	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	171	39	32/14	28	38048	5.6
P69897	8786	TBB5_RAT	Tubulin beta-5 chain	172	42	50/21	42	50095	4.78
P07323	8805	ENOG_RAT	Gamma-enolase	194	61	43/20	41	47510	5.03
Q5XIF6	8813	TBA4A_RAT	Tubulin alpha-4A chain	154	44	39/14	33	50634	4.95
P69897	8817	TBB5_RAT	Tubulin beta-5 chain	130	41	77/22	39	50095	4.78
P85108	8822	TBB2A_RAT	Tubulin beta-2A chain	117	35	67/20	44	50274	4.78
D3ZUB0	8830	D3ZUB0_RAT	Putative uncharacterized protein Rcn1	121	40	21/11	26	38067	4.67
	8889		no hit						
	8894		no hit						
P18418	8939	CALR_RAT	Calreticulin	257	53	38/21	31	48137	4.33
D4A133	9131	D4A133_RAT	Putative uncharacterized protein Atp6v1a	201	40	57/27	21	68564	5.42
P47942	9131	DPYL2_RAT	Dihydropyrimidinase-related protein 2	110	35	57/15	24	62638	5.95
P47942	9139	DPYL2_RAT	Dihydropyrimidinase-related protein 2	186	41	40/18	24	62638	5.95
P23565	9167	AINX_RAT	Alpha-internexin	325	56	63/33	30	56253	5.2
P23565	9169	AINX_RAT	Alpha-internexin	341	56	56/33	17	56253	5.2

P23565	9186	AINX_RAT	Alpha-internexin	311	55	62/32	30	56253	5.2
P23565	9189	AINX_RAT	Alpha-internexin	295	49	47/28	31	56253	5.2
P19527	9283	NFL_RAT	Neurofilament light polypeptide	242	54	76/32	27	61355	4.63
P19527	9288	NFL_RAT	Neurofilament light polypeptide	109	23	22/11	36	61355	4.63
P47942	9314	DPYL2_RAT	Dihydropyrimidinase-related protein 2	184	50	51/21	22	62638	5.95
P48721	9328	GRP75_RAT	Stress-70 protein, mitochondrial	195	29	21/17	21	74097	5.97
P48721	9354	GRP75_RAT	Stress-70 protein, mitochondrial	158	22	18/14	20	74097	5.97
P47942	9561	DPYL2_RAT	Dihydropyrimidinase-related protein 2	225	41	28/18	35	62638	5.95
P47942	9562	DPYL2_RAT	Dihydropyrimidinase-related protein 2	206	42	26/18	37	62638	5.95
P02770	9572	ALBU_RAT	Serum albumin	132	24	26/13	21	70682	6.09
P47942	9572	DPYL2_RAT	Dihydropyrimidinase-related protein 2	85	25	26/9	22	62638	5.95
P02770	9573	ALBU_RAT	Serum albumin	272	40	31/22	18	70682	6.09
P47942	9593	DPYL2_RAT	Dihydropyrimidinase-related protein 2	297	69	53/29	28	62638	5.95
Q920L2	9603	DHSA_RAT	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	342	52	42/28	22	72596	6.75
P47942	9617	DPYL2_RAT	Dihydropyrimidinase-related protein 2	205	38	22/17	21	62638	5.95
P04177	9639	TY3H_RAT	Tyrosine 3-monooxygenase	92	30	34/10	28	56330	5.74
P47942	9652	DPYL2_RAT	Dihydropyrimidinase-related protein 2	281	58	38/26	17	62638	5.95
P47942	9653	DPYL2_RAT	Dihydropyrimidinase-related protein 2	341	59	27/25	28	62638	5.95
P47942	9665	DPYL2_RAT	Dihydropyrimidinase-related protein 2	175	52	52/21	36	62638	5.95
Q5RKI0	9691	WDR1_RAT	WD repeat-containing protein 1	232	50	41/21	29	66824	6.15
P47942	9691	DPYL2_RAT	Dihydropyrimidinase-related protein 2	96	31	41/11	29	62638	5.95
	9741		no hit						
Q63537	9758	SYN2_RAT	Synapsin-2	118	29	29/14	21	63702	8.73
Q62951	9761	DPYL4_RAT	Dihydropyrimidinase-related protein 4 (Fragment)	136	33	30/13	32	61617	6.3
P47942	9766	DPYL2_RAT	Dihydropyrimidinase-related protein 2	177	50	42/18	28	62638	5.95
P47942	9768	DPYL2_RAT	Dihydropyrimidinase-related protein 2	173	47	48/19	27	62638	5.95
O35814	9768	STIP1_RAT	Stress-induced-phosphoprotein 1	114	29	48/18	34	63158	6.4
Q9ER34	9973	ACON_RAT	Aconitate hydratase, mitochondrial	297	42	33/26	38	86121	7.87
Q9ER34	10061	ACON_RAT	Aconitate hydratase, mitochondrial	237	35	33/22	20	86121	7.87
Q9JHU0	10085	DPYL5_RAT	Dihydropyrimidinase-related protein 5	118	29	41/13	22	62071	6.6
O35567	10085	PUR9_RAT	Bifunctional purine biosynthesis protein PURH	92	27	41/13	22	64681	6.69
Q3MHS9	10090	Q3MHS9_RAT	Chaperonin containing Tcp1, subunit 6A (Zeta 1)	154	34	33/18	26	58437	6.63
Q9JHU0	10092	DPYL5_RAT	Dihydropyrimidinase-related protein 5	233	41	19/16	23	62071	6.6
Q6P9V9	10102	TBA1B_RAT	Tubulin alpha-1B chain	141	49	59/15	26	50804	4.94
P13221	10107	AATC_RAT	Aspartate aminotransferase, cytoplasmic	262	69	70/26	22	46628	6.73
	10116		no hit						
P04785	10119	PDIA1_RAT	Protein disulfide-isomerase	238	54	53/24	30	57315	4.82

P86252	16237	PURA_RAT	Transcriptional activator protein Pur-alpha (Fragments)	115	72	29/9	21	15370	4.69
P47942	16723	DPYL2_RAT	Dihydropyrimidinase-related protein 2	294	65	55/30	20	62638	5.95

Suppl. Tab. 2: Differentially expressed striatal proteins identified by peptide mass fingerprinting in spots from Coomassie-stained gels (see Supplementary Fig. 3). Matched hits: the number of matches of a specific spot from the 6 gels (each derived from an individual rat) in the reference gel. Lesions / control: < 0.5: down-regulated, > 2: up-regulated. Acc. #: Accession number from Swiss Prot, Entry name: from Swiss Prot. Score: Mascot MOWSE-score. Sq.: Sequence coverage of the entire protein sequence by the detected tryptic peptides in %. Q/Qm: Number of mass values searched / number of mass values (tryptic peptides) assigned to the identified protein. RMS: Root mean square (RMS) error of the set of matched mass values in ppm. Mw, pI: Theoretical molecular mass (Da) and theoretical pI value taken from the Mascot report.

Acc. #	Spot #	Entry name	Protein name	Matched Hits	Lesion / control	Score	Sq.	Q/Qm	RMS	MW	pI
P62260	4871	1433E_RAT	14-3-3 protein epsilon	6	0.45	111	49	63/17	19	29326	4.63
P61983	5180	1433G_RAT	14-3-3 protein gamma	6	0.35	147	50	67/22	31	28456	4.8
P63102	4821	1433Z_RAT	14-3-3 protein zeta/delta	6	2.51	148	62	104/24	13	27925	4.73
P63039	8714	CH60_RAT	60 kDa heat shock protein, mitochondrial	6	2.99	75	26	30/9	45	61088	5.91
P63039	8719	CH60_RAT	60 kDa heat shock protein, mitochondrial	5	3.04	202	50	69/24	23	61088	5.91
Q9ER34	9973	ACON_RAT	Aconitate hydratase, mitochondrial	6	2.04	297	42	33/26	38	86121	7.87
P60711	4908	ACTB_RAT	Actin, cytoplasmic 1	6	0.28	178	45	40/18	25	42052	5.29
P60711	8203	ACTB_RAT	Actin, cytoplasmic 1	5	0.42	140	45	42/15	27	42052	5.29
Q4V7C7	6784	ARP3_RAT	Actin-related protein 3	6	2.66	212	52	35/19	35	47783	5.61
P69682	7618	NECP1_RAT	Adaptin ear-binding coat-associated protein 1	5	2.63	76	36	37/7	18	29831	5.97
P39069	5312	KAD1_RAT	Adenylate kinase isoenzyme 1	4	2.25	94	59	37/10	21	21684	7.66
P11884	7501	ALDH2_RAT	Aldehyde dehydrogenase, mitochondrial	3	2.74	71	20	45/10	39	56966	6.63
P23565	8714	AINX_RAT	Alpha-internexin	6	2.99	54	18	30/7	34	56253	5.2
P23565	9167	AINX_RAT	Alpha-internexin	6	3.79	325	56	63/33	30	56253	5.2
P23565	9186	AINX_RAT	Alpha-internexin	6	5.21	311	55	62/32	30	56253	5.2
P23565	9189	AINX_RAT	Alpha-internexin	4	3.18	295	49	47/28	31	56253	5.2
P14669	7593	ANXA3_RAT	Annexin A3	3	2.49	293	68	37/22	30	36569	5.96
P13221	6435	AATC_RAT	Aspartate aminotransferase, cytoplasmic	6	2.04	142	46	45/17	32	46628	6.73
Q9R1T5	7689	ACY2_RAT	Aspartoacylase	3	3.18	172	51	36/17	11	35747	5.95
P15999	5679	ATPA_RAT	ATP synthase subunit alpha, mitochondrial	4	0.43	205	30	19/16	20	59831	9.22
P10719	8315	ATPB_RAT	ATP synthase subunit beta, mitochondrial	6	3.02	263	59	65/32	17	56318	5.19
P31399	5170	ATP5H_RAT	ATP synthase subunit delta, mitochondrial	4	2.95	133	67	36/11	28	18809	6.17
O35567	10085	PUR9_RAT	Bifunctional purine biosynthesis protein PURH	5	2.55	92	27	41/13	22	64681	6.69
B5DF65	3805	B5DF65_RAT	Biliverdin reductase B (Flavin reductase (NADPH))	3	2.38	212	87	30/14	17	22194	6.29
P62161	4567	CALM_RAT	Calmodulin	4	0.48	102	41	18/8	27	16827	4.09

P18418	8412	CALR_RAT	Calreticulin	3	0.40	98	19	16/8	30	48137	4.33
Q3MHS9	10090	Q3MHS9_RAT	Chaperonin containing Tcp1, subunit 6A (Zeta 1)	6	2.02	154	34	33/18	26	58437	6.63
P08081	3179	CLCA_RAT	Clathrin light chain A	3	2.26	84	19	30/8	37	27078	4.41
P07335	8036	KCRB_RAT	Creatine kinase B-type	6	2.22	156	40	56/15	32	42983	5.39
P07335	8146	KCRB_RAT	Creatine kinase B-type	6	2.09	136	50	53/15	40	42983	5.39
P07335	8609	KCRB_RAT	Creatine kinase B-type	6	2.54	223	51	38/19	17	42983	5.39
Q68FY0	8581	QCR1_RAT	Cytochrome b-c1 complex subunit 1, mitochondrial	4	4.78	86	32	63/14	18	53500	5.57
Q64559	5956	BACH_RAT	Cytosolic acyl coenzyme A thioester hydrolase	4	4.75	115	39	34/14	34	43164	8.8
P0C2X9	6711	AL4A1_RAT	Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	5	0.40	125	23	20/11	31	62286	7.14
Q6P6R2	6688	DLDH_RAT	Dihydrolipoyl dehydrogenase, mitochondrial	5	2.44	143	38	35/14	18	54574	7.96
P47942	1911	DPYL2_RAT	Dihydropyrimidinase-related protein 2	6	2.15	247	55	31/21	28	62638	5.95
P47942	6765	DPYL2_RAT	Dihydropyrimidinase-related protein 2	4	2.13	208	47	33/19	41	62638	5.95
P47942	9139	DPYL2_RAT	Dihydropyrimidinase-related protein 2	5	2.25	186	41	40/18	24	62638	5.95
P47942	9314	DPYL2_RAT	Dihydropyrimidinase-related protein 2	6	2.11	184	50	51/21	22	62638	5.95
P47942	9561	DPYL2_RAT	Dihydropyrimidinase-related protein 2	5	2.04	225	41	28/18	35	62638	5.95
P47942	9562	DPYL2_RAT	Dihydropyrimidinase-related protein 2	5	2.33	206	42	26/18	37	62638	5.95
P47942	9593	DPYL2_RAT	Dihydropyrimidinase-related protein 2	6	2.27	297	69	53/29	28	62638	5.95
P47942	9653	DPYL2_RAT	Dihydropyrimidinase-related protein 2	5	2.10	341	59	27/25	28	62638	5.95
P47942	9766	DPYL2_RAT	Dihydropyrimidinase-related protein 2	3	2.26	177	50	42/18	28	62638	5.95
P47942	9652	DPYL2_RAT	Dihydropyrimidinase-related protein 2	6	2.30	281	58	38/26	17	62638	5.95
Q62951	9761	DPYL4_RAT	Dihydropyrimidinase-related protein 4	3	5.29	136	33	30/13	32	61617	6.3
Q9JHU0	10092	DPYL5_RAT	Dihydropyrimidinase-related protein 5	6	2.07	233	41	19/16	23	62071	6.6
Q9JHL4	8671	DBNL_RAT	Drebrin-like protein	4	0.40	60	24	42/8	39	48925	4.89
Q01986	7304	MP2K1_RAT	Dual specificity mitogen-activated protein kinase kinase 1	6	2.29	196	44	40/20	23	43779	6.18
P56571	5356	ES1_RAT	ES1 protein homolog, mitochondrial	5	2.01	120	51	19/9	22	28497	9.11
P85845	7450	FSCN1_RAT	Fascin	5	2.08	181	44	36/16	27	55198	6.29
P85845	7505	FSCN1_RAT	Fascin	4	2.53	92	21	29/10	28	55198	6.29
P09117	5886	ALDOC_RAT	Fructose-bisphosphate aldolase C	5	2.19	219	59	19/14	22	39658	6.67
P09117	7546	ALDOC_RAT	Fructose-bisphosphate aldolase C	5	2.08	138	49	34/13	23	39658	6.67
P07323	8504	ENOG_RAT	Gamma-enolase	6	0.31	191	67	57/22	34	47510	5.03
P07323	8805	ENOG_RAT	Gamma-enolase	6	0.45	194	61	43/20	41	47510	5.03
Q63228	4613	GMFB_RAT	Glia maturation factor beta	6	2.13	78	42	31/7	24	16897	5.32
P10860	6494	DHE3_RAT	Glutamate dehydrogenase 1, mitochondrial	5	2.48	116	37	85/23	32	61719	8.05
P10860	6496	DHE3_RAT	Glutamate dehydrogenase 1, mitochondrial	5	2.38	100	30	64/15	22	61719	8.05
P09606	6004	GLNA_RAT	Glutamine synthetase	6	0.40	178	35	42/18	28	42982	6.64
P04905	5624	GSTM1_RAT	Glutathione S-transferase Mu 1	4	0.42	299	79	44/28	22	26068	8.27
Q3ULJ0	5933	GPD1L_MOUSE	Glycerol-3-phosphate dehydrogenase 1-like protein	4	2.07	78	29	41/9	28	38828	6.34
Q9WTT6	8086	GUAD_RAT	Guanine deaminase	6	2.99	309	53	33/25	17	51554	5.56
Q9WTT6	8089	GUAD_RAT	Guanine deaminase	6	2.71	293	71	58/31	26	51554	5.56

P54311	4871	GBB1_RAT	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1	6	0.45	104	47	63/13	22	38151	5.6
P54313	8742	GBB2_RAT	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	5	2.43	171	39	32/14	28	38048	5.6
P62882	7213	GBB5_RAT	Guanine nucleotide-binding protein subunit beta-5	5	0.49	73	26	19/6	16	39505	5.67
P63018	6250	HSP7C_RAT	Heat shock cognate 71 kDa protein	3	0.47	253	36	43/24	15	71055	5.37
P63018	7856	HSP7C_RAT	Heat shock cognate 71 kDa protein	5	0.44	99	21	36/13	21	71055	5.37
P82995	8280	HS90A_RAT	Heat shock protein HSP 90-alpha	5	2.14	120	23	44/18	18	85161	4.93
Q6URK4	6351	ROA3_RAT	Heterogeneous nuclear ribonucleoprotein A3	3	0.17	78	20	24/8	19	39856	9.1
A7VJC2	6319	ROA2_RAT	Heterogeneous nuclear ribonucleoproteins A2/B1	5	0.44	144	40	53/16	17	37512	8.97
D3ZW55	3844	D3ZW55_RAT	Inosine triphosphatase, isoform CRA_a	6	2.29	139	66	38/11	27	22255	5.48
Q68FX0	2730	IDH3B_RAT	Isocitrate dehydrogenase [NAD] subunit beta, mitochondrial	4	3.57	98	31	42/14	41	42612	8.89
Q99MZ8	5834	LASP1_RAT	LIM and SH3 domain protein 1	6	2.85	166	43	28/16	13	30351	6.61
P42123	7066	LDHB_RAT	L-lactate dehydrogenase B chain	3	2.96	215	55	58/26	26	36874	5.7
P42123	7087	LDHB_RAT	L-lactate dehydrogenase B chain	3	2.29	273	61	40/26	28	36874	5.7
P04636	6319	MDHM_RAT	Malate dehydrogenase, mitochondrial	5	0.44	181	59	53/19	25	36117	8.93
P63086	5857	MK01_RAT	Mitogen-activated protein kinase 1	4	2.91	180	41	51/15	26	41648	6.5
O08839	8418	BIN1_RAT	Myc box-dependent-interacting protein 1	5	0.37	108	29	35/11	30	64721	4.95
Q6MG60	7603	DDAH2_RAT	N(G),N(G)-dimethylarginine dimethylaminohydrolase 2	3	2.11	195	53	23/15	29	30011	5.66
Q5RJQ4	5872	SIRT2_RAT	NAD-dependent deacetylase sirtuin-2	4	0.42	185	47	22/13	24	39921	6.67
B0BNE6	3946	B0BNE6_RAT	NADH dehydrogenase (Ubiquinone) Fe-S protein 8 (Predicted), isoform CRA_a	6	2.87	131	41	35/11	20	24411	5.87
Q561S0	7258	NDUAA_RAT	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 10, mt	6	2.55	226	63	33/18	25	40753	7.64
P19234	4767	NDUV2_RAT	NADH dehydrogenase [ubiquinone] flavoprotein 2, mt	6	2.10	140	55	34/14	20	27703	6.23
Q9Z1X8	2830	Q9Z1X8_RAT	Neural F box protein NFB42	5	2.33	163	49	36/12	25	34021	4.3
P19527	9288	NFL_RAT	Neurofilament light polypeptide	6	0.46	109	23	22/11	36	61355	4.63
Q5U2Z3	8679	NP1L4_RAT	Nucleosome assembly protein 1-like 4	6	2.79	95	30	54/12	20	44118	4.58
P45479	5759	PPT1_RAT	Palmitoyl-protein thioesterase 1	3	0.41	86	29	10/6	8	34946	7.1
P16446	7332	PIPNA_RAT	Phosphatidylinositol transfer protein alpha isoform	6	2.11	207	70	57/22	24	32115	5.97
P04785	10119	PDIA1_RAT	Protein disulfide-isomerase	5	5.04	238	54	53/24	30	57315	4.82
P11598	6822	PDIA3_RAT	Protein disulfide-isomerase A3	5	2.01	222	35	28/19	19	57044	5.88
D3ZPE4	8280	D3ZPE4_RAT	Putative uncharacterized protein Anxa7	5	2.14	95	30	44/17	21	52667	5.27
O35331	7232	PDXK_RAT	Pyridoxal kinase	5	0.46	191	48	29/18	15	35114	6.32
O88794	5256	PNPO_RAT	Pyridoxine-5'-phosphate oxidase	6	0.50	95	27	18/8	25	30507	8.66
P26284	6043	ODPA_RAT	Pyruvate dehydrogenase E1 component subunit alpha, somatic form, mt	3	0.33	142	30	24/14	17	43883	8.49
P11980	2054	KPYM_RAT	Pyruvate kinase isozymes M1/M2	5	2.81	173	32	25/16	27	58294	6.63
P11980	6547	KPYM_RAT	Pyruvate kinase isozymes M1/M2	6	2.37	186	40	40/20	32	58294	6.63
D3ZUB0	8830	D3ZUB0_RAT	Reticulocalbin 1	6	0.49	121	40	21/11	26	38067	4.67
P60123	7500	RUVB1_RAT	RuvB-like 1	5	3.14	87	28	43/12	27	50524	6.02
B5DFG5	7495	B5DFG5_RAT	Sept6 protein	6	2.64	176	44	30/17	28	49147	6.23

B0BNF1	6825	SEPT8_RAT	Septin-8	6	2.16	159	30	30/13	24	51562	5.74
B0BNF1	6934	SEPT8_RAT	Septin-8	6	2.35	265	56	45/24	21	51562	5.74
Q4FZT0	7620	STML2_RAT	Stomatin-like protein 2	4	0.49	138	34	11/9	10	38504	8.74
P48721	9328	GRP75_RAT	Stress-70 protein, mitochondrial	6	2.68	195	29	21/17	21	74097	5.97
P48721	9354	GRP75_RAT	Stress-70 protein, mitochondrial	4	2.43	158	22	18/14	20	74097	5.97
O35814	9768	STIP1_RAT	Stress-induced-phosphoprotein 1	5	2.38	114	29	48/18	34	63158	6.4
Q920L2	9603	DHSA_RAT	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mt	6	2.04	342	52	42/28	22	72596	6.75
P51650	7500	SSDH_RAT	Succinate-semialdehyde dehydrogenase, mitochondrial	5	3.14	67	21	43/9	29	56723	8.35
P07895	5312	SODM_RAT	Superoxide dismutase [Mn], mitochondrial	4	2.25	101	42	37/9	29	24887	8.96
Q63537	6563	SYN2_RAT	Synapsin-2	6	2.58	139	31	31/16	30	63702	8.73
Q63537	6701	SYN2_RAT	Synapsin-2	6	2.18	144	28	31/18	28	63702	8.73
Q63537	9758	SYN2_RAT	Synapsin-2	5	2.61	118	29	29/14	21	63702	8.73
Q5XIM9	6879	TCPB_RAT	T-complex protein 1 subunit beta	6	2.09	328	61	45/31	29	57764	6.01
Q9Z0V6	5140	PRDX3_RAT	Thioredoxin-dependent peroxide reductase, mitochondrial	6	2.42	111	52	39/10	9	28563	7.14
P86252	16237	PURA_RAT	Transcriptional activator protein Pur-alpha (Fragments)	6	absent in controls	115	72	29/9	21	15370	4.69
P68370	6755	TBA1A_RAT	Tubulin alpha-1A chain	4	0.28	90	29	28/9	31	50788	4.94
Q5XIF6	6962	TBA4A_RAT	Tubulin alpha-4A chain	5	2.77	219	49	43/18	24	50634	4.95
Q5XIF6	7079	TBA4A_RAT	Tubulin alpha-4A chain	4	3.45	143	45	44/14	25	50634	4.95
Q5XIF6	8813	TBA4A_RAT	Tubulin alpha-4A chain	6	2.01	186	43	34/12	21	50634	4.95
P85108	7297	TBB2A_RAT	Tubulin beta-2A chain	5	2.04	246	54	44/24	15	50274	4.78
P85108	8005	TBB2A_RAT	Tubulin beta-2A chain	6	2.04	162	44	52/19	33	50274	4.78
Q6P9T8	7999	TBB2C_RAT	Tubulin beta-2C chain	6	2.08	156	40	39/17	26	50225	4.79
Q4QRB4	7991	TBB3_RAT	Tubulin beta-3 chain	4	3.28	172	49	70/25	21	50842	4.82
P69897	4918	TBB5_RAT	Tubulin beta-5 chain	3	0.29	75	18	36/12	20	50095	4.78
P69897	8786	TBB5_RAT	Tubulin beta-5 chain	3	0.29	172	42	50/21	42	50095	4.78
P04177	9639	TY3H_RAT	Tyrosine 3-monooxygenase	3	0.49	92	30	34/10	28	56330	5.74
Q00981	4738	UCHL1_RAT	Ubiquitin carboxyl-terminal hydrolase isozyme L1	4	2.18	120	54	31/9	13	25165	5.14
Q00981	4740	UCHL1_RAT	Ubiquitin carboxyl-terminal hydrolase isozyme L1	4	3.47	121	50	27/9	26	25165	5.14
P31000	8356	VIME_RAT	Vimentin	5	3.16	241	56	51/27	30	53757	5.06
Q9Z2L0	5694	VDAC1_RAT	Voltage-dependent anion-selective channel protein 1	5	2.46	128	59	38/11	13	30851	8.62
P62815	8590	VATB2_RAT	V-type proton ATPase subunit B, brain isoform	6	2.17	316	69	70/36	28	56857	5.57
Q5RKI0	9691	WDR1_RAT	WD repeat-containing protein 1	5	2.12	232	50	41/21	29	66824	6.15

Legends

Suppl. Fig. 1: Overview of differentially epressed proteins and the functional compartments. a) 45% of the differentially expressed proteins belong the class of enzymes. b) The differentiation of enzymes. Most enzymes belong to the group of energy metabolism (10%) and amino acid metabolism (10%).

Suppl. Fig. 2: Summary and classification of differentially expressed proteins to functional groups, metabolic functions and compartments. Red: up-regulated, blue: down-regulate, green: absent in the control striatum, brown: absent in the deafferentiated striatum.

Suppl. Fig. 3: Annotation of accession numbers from Swiss Prot in the striatal reference gel (gel identifier: 16-2-2). Protein mixes and multiple protein presentations in different spots can be derived from branching lines.

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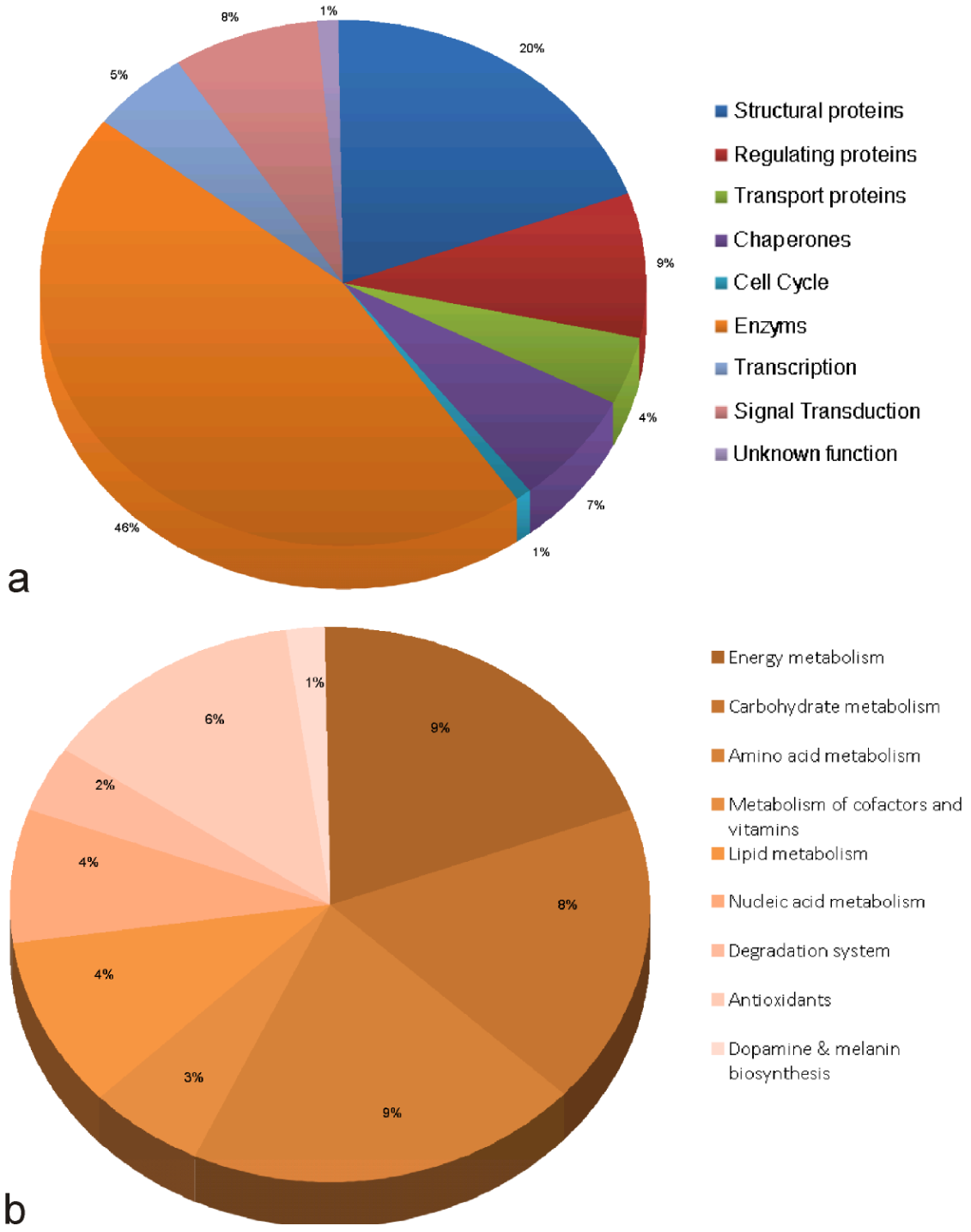
Suppl. Fig. 1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Chaperones
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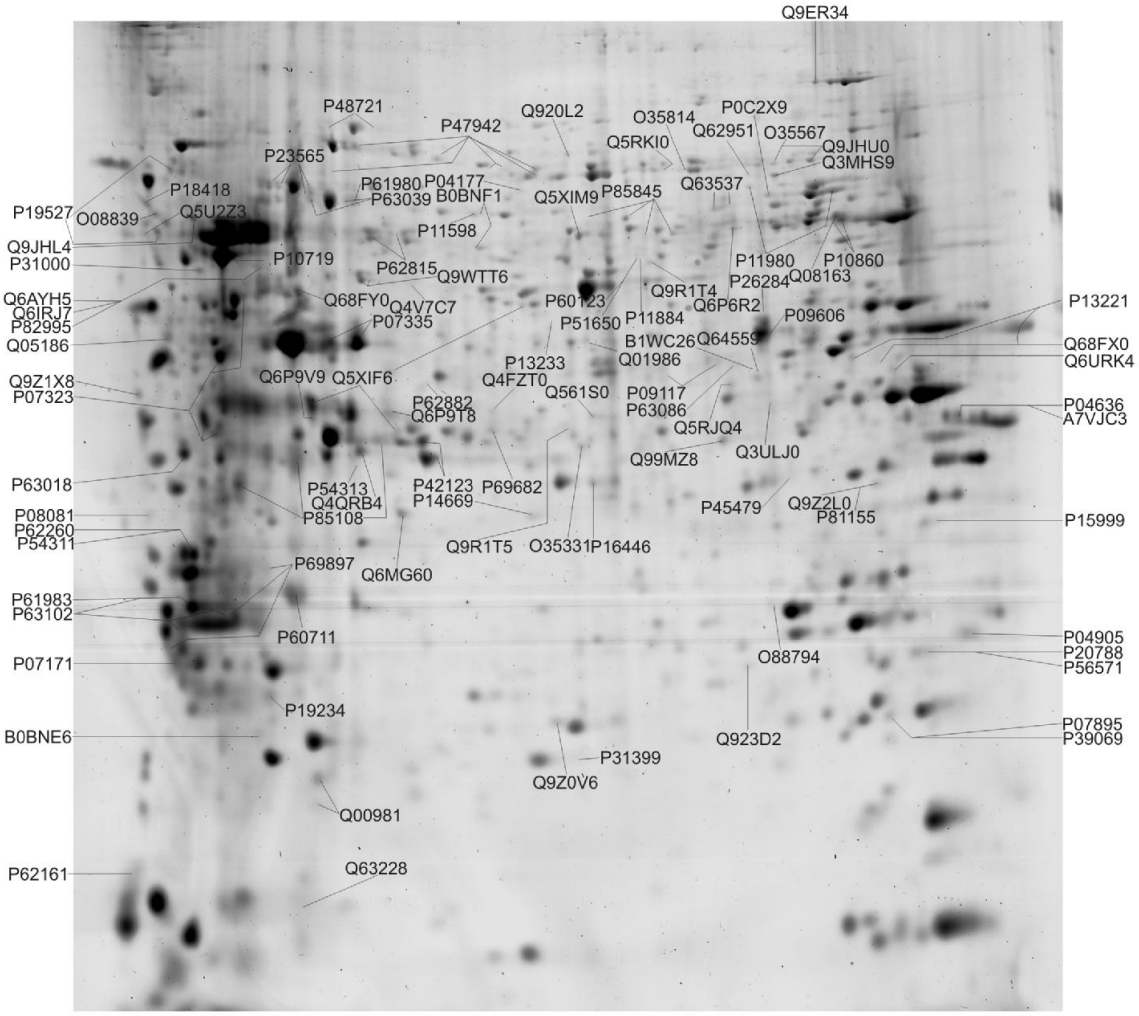
Energy metabolism
Carbohydrate metabolism
Amino acid metabolism
Metabolism of cofactors and vitamins
Lipid metabolism
Nucleic acid metabolism
Degradation system
Antioxidants
Dopamine & melanin biosynthesis
b

Suppl. Fig. 2


Transcription
Nucleosome assembly protein 1-like 4,
RuvB like 1,
Heterogeneous nuclear ribonucleoprotein A3,
Transcriptional activator protein Pur-alpha
Astrocytes
Vimentin
Signal transduction
Guanine nucleotide-binding protein subunit beta-2 (GTPase activity),
Mitogen activated protein kinase 1,
Mitogen activated protein kinase 2,
14-3-3 protein zeta/delta,
14-3-3 protein epsilon,
14-3-3 protein gamma,
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1 (GTPase activity),
Guanine nucleotide-binding protein subunit beta-5 (GTPase activity)
Cell differentiation & proliferation
Glial maturation factor beta,
Gamma enolase
Nucleid acid metabolism
Adenylate kinase isoenzyme 1,
Biofunctional purine biosynthesis protein PURH,
Guanine deaminase,
Inosine triphospatase
Axonal cytoskeleton
ß III tubulin,
a internexin,
Dihydropyrimidinase related protein 4,
Dihydropyrimidinase related protein 5,
Neurofilament light polypeptide,
Stomatin like protein 2,
Dihydropyrimidinase related protein 2
Synapses
Septin 6, Septin 8,
Myc box dep.-interacting protein 1,
Synapsin II
Adaptin ear-binding coat-associated protein 1,
Clathrin light chain A,
Phosphatidylinositol transfer protein a-isoform,
WD repeat containing protein 1
Lipid metabolism
Aldehyde dehydrogenase 2,
Glycerol-3-phosphate dehydrogenase 1 like protein
Chaperons
Stress induced phosphoprotein 1,
Heat Shock protein HSP 90 alpha,
Chaperonin containing Tcp1, subunit 6A (Zeta 1),
T-complex protein 1 subunit beta ,
Heat shock cognate 71kDa protein
Actin
Actin related protein 3,
Lim & SH3 domain protein 1,
WD repeat containing protein 1,
Fascin fragment,
beta Actin
Dendrites
Drebrin
Cofactors and vitamins
Flavin reductase,
Pyridoxal kinase,
Pyridoxine-5'-phosphate oxidase
Proteasome
Stress protein 70
Ubiquitine carboxyl terminal hydrolase L1,
Neural F box protein NFB42
Mitochondrium & energy metabolism
Voltage dep. anion selective channel proteins 1,
60kDa heat shock protein,
Protein DJ1
ATP synthase subunit beta,
ATP synthase subunit delta,
NADH dehydrogenase 1 alpha subcomplex subunit 10, NDUFV2,
Ndufs8 protein (NADH dehydrogenase (ubiquinone) Fe-S protein 8 predicted),
Succinate dehydrogenase [ubiquinone] flavoprotein subunit,
Aconitase,
Aspartate aminotransferase 1,
Fructose-bisphosphate aldolase C,
Aspartoacylase-2,
Pyruvat kinase isoenzyme M1/M2,
Succinate-semialdehyde dehydrogenase,
Isocitrat dehydrogenase subunit beta,
Glutamate dehydrogenase 1,
Dihydrolipoyl dehydrogenase,
Apartate aminotransferase
Dihydrolipoyl dehydrogenase
NAD-dep. deacetylase sirtuin-2,
ATP synthase subunit alpha,
Pyruvat dehydrogenase E1component subunit alpha, somatic form,
Delta-1-pyrroline-5-carboxylate dehydrogenase,
Malat dehydrogenase
Calcium homeostasis
Annexin A3,
Annexin A7,
Calmodulin,
Calreticulin
Reticulocalbin 1
Antioxidants
N(G),N(G)-Dimethylarginin, dimethylaminotransferase 2,
Protein disulfid isomerase,
Superoxide dismutase,
Thioredoxin-dep. peroxide reductase,

Suppl. Fig. 3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