

**Table S1.** Pathways and the pathological processes involved in insulin resistance and Parkinson`s disease.

Pathological process	Dysregulated Pathway	IR effects in PD
$\alpha$ -synuclein aggregates	PI3K/Akt	Insulin signaling disrupted $\alpha$ -synuclein overproduction Abnormal $\alpha$ -synuclein folding Lewy Bodies formation Neurotoxicity
Dopaminergic Neuronal Death	PI3K/Akt/GSK-3  Ubiquitin Proteasome System	Ir and IGF-1r Under-phosphorylation IRS-1 and IRS-2 hyperphosphorylation Akt inhibition GSK3 $\beta$ activation  Insulin receptor and insulin signaling molecules degradation Ubiquitin ligase enzymes (E3) dysfunction <ul style="list-style-type: none"> <li>- Neuronal pro-survival protein proteolysis</li> <li>- Neuronal pro-apoptotic caspase proteolysis inhibition</li> </ul>
Neuroinflammation	NF- $\kappa$ B	PI3K/Akt/GSK3 $\beta$ pathway disruption Overactivated GSK3 $\beta$ <ul style="list-style-type: none"> <li>- High <math>\alpha</math>-synuclein levels</li> <li>- NF-<math>\kappa</math>B pathway upregulation</li> <li>- Proinflammatory cytokines release</li> </ul>
Mitochondrial dysfunction	Parkin/PINK1/PGC-1 $\alpha$	High $\alpha$ -synuclein levels <ul style="list-style-type: none"> <li>- Mitochondrial membrane depolarization</li> <li>- Mitochondrial fragmentation</li> <li>- Oxidative stress</li> </ul>
Neuronal autophagy	PI3K/AKT/mTOR  AMPK/mTOR	Decreased IGF-2 mTOR inhibition Misfolded proteins accumulation  Autophagy development Energetic metabolism alteration Synaptic and cognitive impairment