A kinetic model and design principles study of cellular ROS defence and its failure in Parkinson's disease

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Introduction

The pathophysiology of neurodegenerative diseases is attributed to the death of specific neurons, for example the dopaminergic neurons in Parkinson's Disease (PD). Mitochondrial dysfunction and excessive Reactive Oxygen Species (ROS) generation may play an important role in the development of PD. ROS is produced mostly due to the incomplete reduction of oxygen during oxidative phosphorylation. This process takes place in almost all cells as a side effect of respiratory ATP synthesis. In dopaminergic neurons, the problem of excessive ROS generation is aggravated because of the additional generation of ROS during ROS-induced dopamine degradation. The later is a chain reaction: ROS causes the degradation of dopamine, which in turn produces more ROS.

Mechanisms for sensing ROS

In human cells, a complicated regulatory network senses increased ROS concentration and counteracts this process, e.g. by activation of the synthesis of antioxidants or increasing the mitophagy (apoptosis of mitochondria). The precise "tuning" of the latter might be especially crucial: if mitophagy is too active, all mitochondria are lost and the cell dies from the lack of ATP; if mitophagy is not active enough, damaged mitochondria are accumulated, more ROS is produced, the cell is damaged further and finally dies.

Detailed network diagram

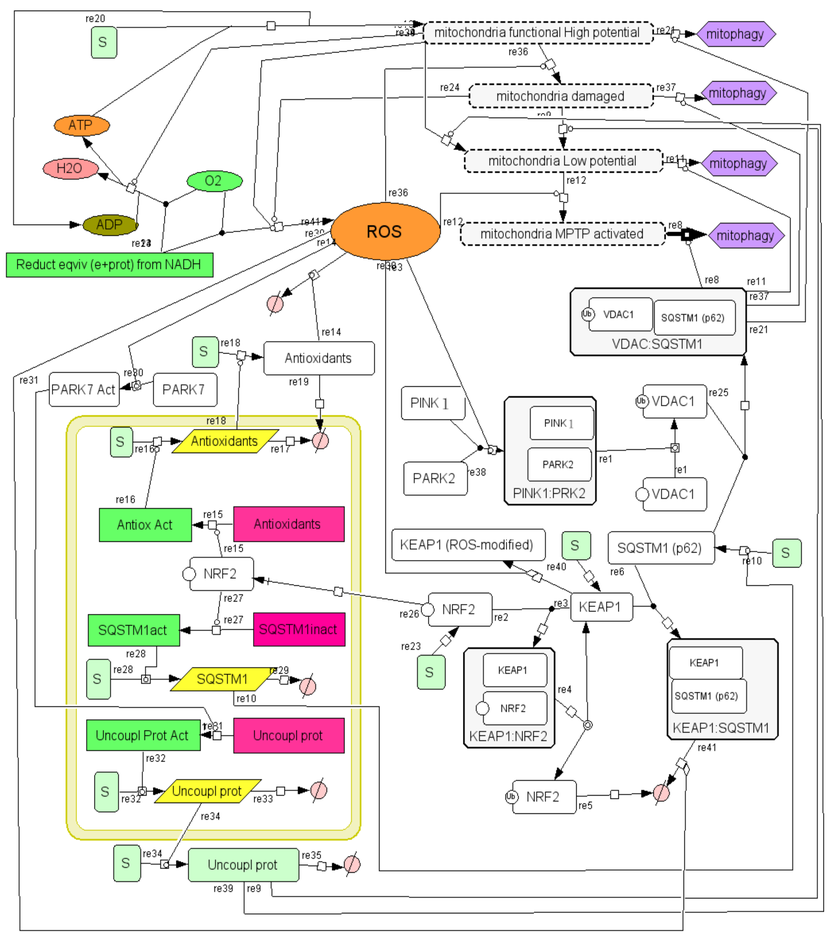


Figure 2. 39 species and 45 reactions. Four different stages of the mitochondrion are considered: (i) functional; synthesising ATP and producing ROS, (ii) damaged; producing more ROS than ATP, (iii) low potential; producing small amounts of ROS and ATP, (iv) activated mitochondrial permeability transition pore (MPTP), producing only ROS and no ATP, and proceeding to high mitophagy.

Simulating the disease

The development of the disease may be connected with the mistuning of the regulatory network. The expression of several components of the regulatory network (Figure 2) is altered in PD. We have collected data (Enrico Glaab, LCSB) on transcription levels of the following genes:

1. KEAP1 (upregulated in PD vs. control)
2. PINK1 (downregulated)
3. PARK7 (downregulated)
4. VDAC1 (downregulated)
5. SQSTM1 (p62) (upregulated)

We have built a kinetic model of the regulatory network based on the diagram of Figure 2. We perturbed the expression of the above genes in the model to simulate PD-related misregulation of the network, which results in increased ROS generation and loss of mitochondria.

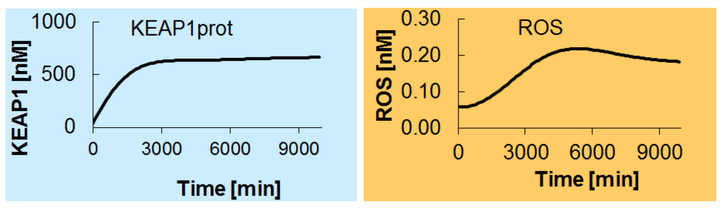
Increasing KEAP1 in the model caused downregulation of p62 (SQSTM1). But our experimental observations have shown upregulation of p62 in PD. We formulate here the hypothesis that the upregulation of p62 is an adaptation to PD.

Preliminary simulations with the kinetic model of cellular ROS defence

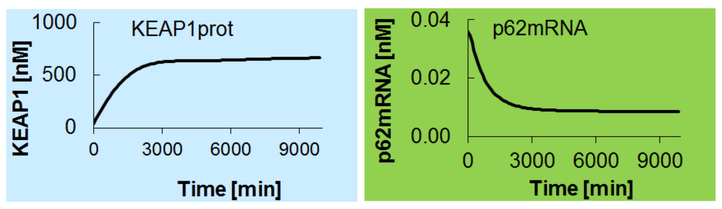
First, all five PD-related perturbations are applied at the same time.

This results in excessive ROS generation and the loss of functional mitochondria:

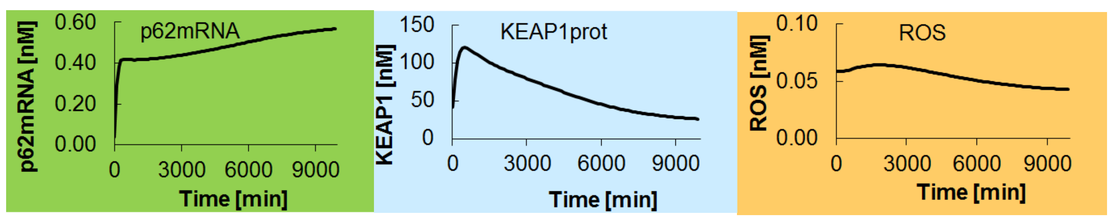
We then applied each perturbation individually. Below, the effect of KEAP1 upregulation on ROS generation is displayed:



But this also caused the decrease of p62. As stated above, experimental observations contradict this; p62 is upregulated in PD:



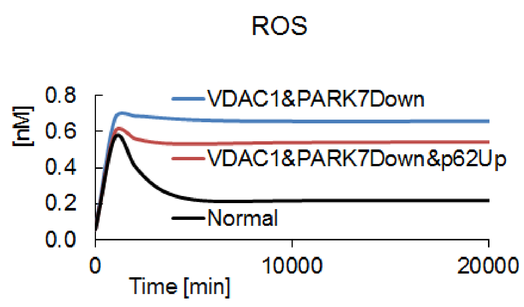
Upregulation of p62 would be advantageous, as it would counteract the increase of KEAP1 and would reduce ROS generation:



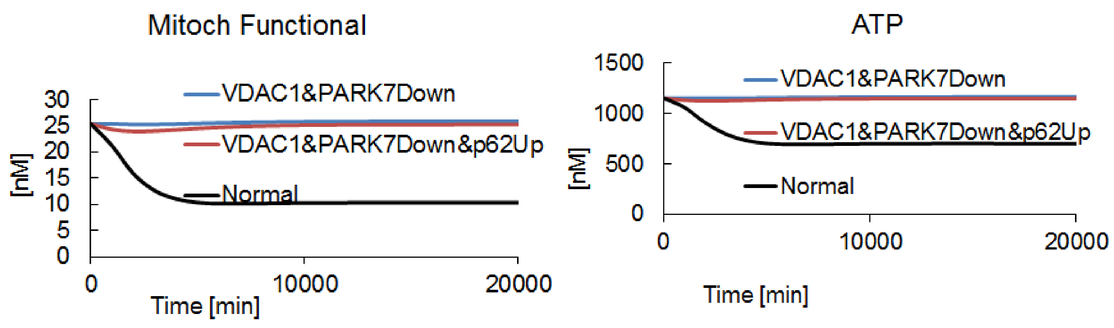
We hypothesize that the upregulation of p62 could be an adaptation to PD.

Next, we introduce a step increase in the rate of ROS production (e.g. from degradation of dopamine)

Under normal conditions (without PD-related perturbations), the system can counteract the excessive ROS generation (black line). But if VDAC1 and PARK7 are down-regulated (as in PD), then ROS reaches a higher steady state concentration (blue line). However, upregulation of p62 may counteract the down-regulation of VDAC1 and PARK7 (red line).



On the other hand, downregulation of VDAC1 and PARK7 helps with the preservation of mitochondria and ATP. Simultaneous upregulation of p62 has almost identical effects on mitochondia and ATP preservation (while ROS concentration is decreased), therefore it is always advantageous!



Conclusions and perspectives

A kinetic model of cellular ROS defence has been built. The model allows the simulation of the dynamic processes of the network related to PD pathologies resulting in the failure of cellular defence against excessive ROS generation.

The model predicts a contradiction related to p62 upregulation, and we hypothesised here a compensatory function of p62 upregulation.

The model will be improved and used for additional design principles studies of this regulatory network in the context of the development of PD.

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