ROS systems biology: In silico reconstruction of the emergence of cellular ROS-managing system

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One of the aims of Systems Biology is to understand how biological function that is absent from macromolecules in isolation emerges when they are components of a system. The systems biology approach is reductionist, because we deduce the properties of the whole from studying the systems' parts in interaction, but it is also holistic, because knowledge of the relationship among system parts (e.g. knowledge of component properties which depend on the state of the system) is required but considered not enough: what emerges in their interactions is considered essential. For example, to understand cell function it is not enough to know the properties of each biomolecule in isolation, but we need to take into account how an enzyme interacts with other components, e.g. its activators and inhibitors, and how the concentration of all these interacting components are set in the cell by the collective behavior of all enzymes, mRNAs and genes. There are millions of interactions in the living cell, making the system too complex to be handled intuitively in a human brain or on the back of an envelope and requiring a computer replica of reality. Using the ROS management system as an example we here demonstrate how an emergent behavior of the cell may be reconstructed in a computer model.

Reactive Oxygen Species (ROS) generation is an unavoidable background process in the normal functioning of the cell. The greatest contributor to ROS production is the electron transport chain (ETC) where O_2 is reduced to $2H_2O$. In this process, some incompletely-reduced oxygen species escape and oxidize a variety of organic molecules (e.g.

proteins and lipids in the mitochondrial membrane), leading to molecular dysfunction and initiating a positive feedback loop leading to the generation of even more active ROS. Healthy cells manage ROS enzymatically with superoxide dismutase and other enzymes, various antioxidants, and if all this fails through increased mitophagy of damaged mitochondria, which be called mitoptosis as it averts cell death. The precise tuning of the latter mechanism is crucial for cell survival and is controlled in the cell by a ROS-induced regulatory network, which consists of many components such as Nrf2, Keap1, Parkin and p62 with a rather complicated cross-talk. In other words, ROS management emerges from the interactions among components with highly state-dependent component properties. In many diseases (cancer, Parkinson's disease (PD), Huntington's disease (HD), etc.), various components of the ROS management network are altered. Deconstructing the molecular mechanisms underlying or resulting from these alterations might contribute to better understanding of the dynamics of these and other pathophysiological processes.

We have built a kinetics-based model of ROS management with the aim of reconstructing also the emergent behaviour of cellular defence against ROS. If not reproducing all details, this model may still offer insight into the design underlying the functionality of the system. Our model enables simulation of various pathological scenarios related to mitochondrial dysfunctions and/or the failure of the ROS management system in human cells, e.g. PD -related mis-regulation of mitophagy occurring when p62 is sequestered by ROS-induced polymerization of alfa-synuclein. We discuss the prospect of model extension (incorporating the Parkin-dependent activation of NF-kB signalling, a detailed model of ETC, the cross-links with the TCA cycle, and iron metabolism) and anticipate the use of the model for the study of ROS related pathologies.