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TFEB TRANSLOCATION DYNAMICS: QUANTITATIVE MODELLING AND EXPERIMENTAL ANALYSIS

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Mammalian cells can be described as dynamical systems. They detect, adapt and respond to time-varying inputs, such as environmental cues, secreted molecules and mechanical stimuli. In particular, we focused on their response upon starvation stimulus. Under nutrient stress, cell metabolism adapts to sustain cell survival by initiating autophagy. During autophagy, cytoplasmic components, damaged proteins and entire organelles are degraded and recycled to generate building blocks for the synthesis of proteins that are essential for survival.

The Transcription Factor EB (TFEB) plays a pivotal role in organelle biogenesis and cell metabolism. TFEB acts as a global controller of autophagy (as well as of lysosomal biogenesis, lysosomal exocytosis, lipid catabolism, energy metabolism, and in the modulation of the immune response). TFEB is often deregulated in different types of cancer, suggesting that the pharmacological modulation of TFEB activity may represent a relevant therapeutic approach for a wide number of diseases [1].

As shown in Figure 1 (a), under nutrient-rich conditions, TFEB is phosphorylated and sequestered in the cytoplasm. Upon amino-acid starvation, TFEB is dephosphorylated and can freely translocate to the nucleus where it transcriptionally activates lysosomal and autophagic pathways [2, 3]. Phosphorylation of TFEB in the nucleus has been reported as responsible for its nuclear export [1].

Here, we investigated the dynamics of TFEB shuttling between the cytoplasm and the nucleus upon starvation and feeding stimuli.

We derived a nonlinear dynamical model to describe TFEB translocation. The model consists of two compartments (nucleus and cytoplasm), where two species (de/phosphorylated TFEB) were considered for each. Both de/phosphorylation and transport were modeled as first order kinetics whereas the input (the nutrients concentration) acts by changing the de/phosphorylation rates. The model parameters were inferred from the available experimental data of [1].

We experimentally measured the response of TFEB upon starvation by means of a microfluidics plat-

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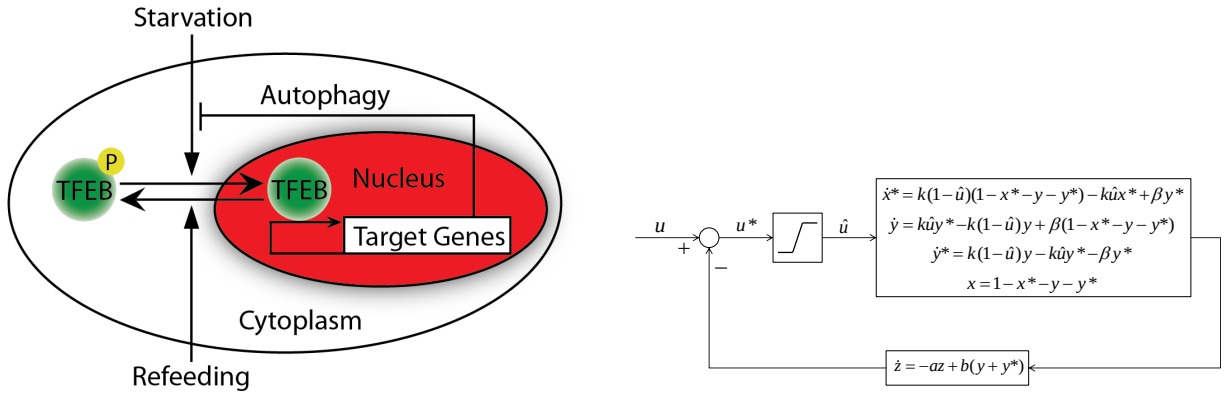

(a) *TFEB nuclear-cytoplasmic shuttling.* (b) *Closed-loop model of TFEB translocation.*

Figure 1: (*a*) TFEB is phosphorylated and sequestered in the cytoplasm under normal feed condition. In the absence of amino-acids, TFEB is dephosphorylated and translocates into the nucleus, where it activates the transcription of its target genes. In turn, these genes activate autophagy to modulate the starvation response. (*b*) The translocation model is represented by a system of nonlinear differential equations of the third order. A feedback action has been hypothesized to explain the overshoot experimentally observed.

form, observing two characteristic dynamics. The first is the rapid translocation of TFEB from the cytoplasm to the nucleus (of the order of minutes) upon switching from feeding to starvation, and can be explained by the open-loop model proposed above. The second is an overshoot dynamics (of the order of hours), and can be explained by hypothesizing the presence of a negative feedback action closing the loop (Figure 1 (b)).

The closed-loop model was based on biological reasonable hypotheses and recapitulated the whole dynamics behaviour observed experimentally. We investigated the TFEB response to starvation in deep by using different drugs (Torin 1, Bafilomycin A1, Cycloheximide) to prove this hypothesis. At present, further analysis is required in order to confirm our thesis.

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