Model of the Autophagy-Translation Switch

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***Short Abstract* — We constructed a rule-based model for the regulatory network controlling initiation of autophagy and translation. Autophagy is a process that mediates both recycling of cytoplasmic constituents and cellular survival during starvation. It is induced in response to various stress signals. We investigated responses to stimulation by rapamycin and starvation. Analysis of our model indicates that mTOR-mediated regulation exhibits relaxation oscillations between two distinct states. One is biased toward protein synthesis and the other toward autophagy. Thus, it appears that the circuitry around mTOR may commit a cell to either translation or autophagy, or to alternating periods of translation and autophagy.**

I. Model

EXPERIMENTAL data allowed us for construction of a rule-based model, whose simplified ideogram is presented in Fig.1. The model consists of 173 species and involves 6581 interactions resulting from 29 rules.

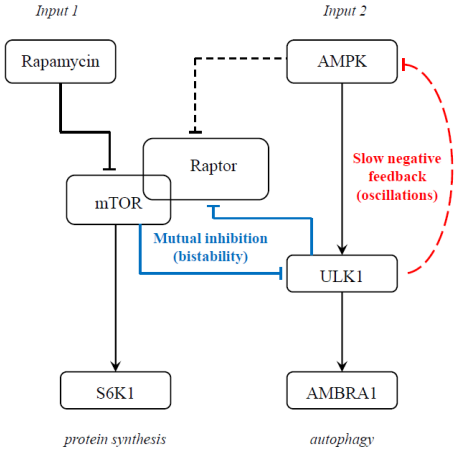

Fig.1. A schematic representation of interactions modeled.

We consider two stimuli: Rapamycin stimulation and AMPK activation resulting from starvation, and two outputs: phosphorylation of S6K1 kinase (marker of translation) and phosphorylation of AMBRA1 (marker of autophagy).

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II. Results

In unstressed cells protein S6K1 is phosphorylated and protein synthesis proceeds. AMBRA1 phosphorylation and autophagy may be induced in response to each of stimuli. The core the system regulation is the mutual inhibition of mTOR-Raptor and kinase ULK1 resulting in system bistability with two distinguished states: autophagy and translation. The strong nonlinearity in regulation assures that either S6K1 or AMBRA1 may be phosphorylated. Inclusion of the slow negative feedback on AMPK leads to relaxation oscillations in which the system sharply transits between phases of autophagy and translation. The length of autophagy phase was found almost independent of the stress level (Rapamycin or phosphorylated AMPK concentration), however the translation phase shortens with the increasing stress until the systems switches to the state of "permanent" autophagy, which inevitably must result in apoptosis or death.

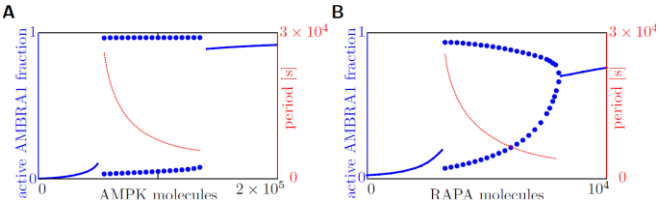

Fig.2. Bifurcation diagrams. Blue lines and points show the fraction of phosphorylated AMBRA1; points indicate the upper and lower limits of a stable limit-cycle oscillation, solid blue lines indicate stable fixed points. Red dotted line is the corresponding period of oscillations with the scale indicated on the right.

III. Conclusions

The theoretical prediction that protein synthesis and autophagy may not occur simultaneously seems biologically plausible. Starvation inevitably leads to stopping protein synthesis until the necessary aminoacids are recycled via autophagy. Autophagic vesicles are formed from rough endoplasmic reticulum, on which rybosomes are located, therefore formation of autophagic vesicles must lead to at least local suppression of translation. Moreover, autophagy is also a way of destroying invading viruses which use rybosomes located on rough reticulum to synthesise their proteins. It seems thus reasonable that infected cell stops protein synthesis and simultaneously destroys virial RNA or DNA via autophagy.