Mathematical modeling of the Ras/MAPK and PI3K/AKT signaling networks in the K-Ras-driven mouse Y1 adrenocortical tumor cells

Reis, M.S.[1]; Dias, M.H.S.[1]; Nakano, F.[1,2]; Barrera, J.[1,3]; Armelin, H.A.[1,4]

[1]LETA-CeTICS, Instituto Butantan, SP, Brazil; [2]EACH, USP, SP, Brazil; [3]IME, USP, SP, Brazil; [4]Dep. de Bioquímica, IQ, USP, SP, Brazil

Introduction. The mouse Y1 adrenocortical tumor cell line displays high expression levels of the K-Ras oncoprotein, which have the following implications: a) high constitutive levels of phosphorylated AKT and b) cell cycle arrest induced by Fibroblast Growth Factor 2 (FGF2). However, the underlying mechanisms of these implications are not fully understood. **Objectives.** To model the kinetics of major signaling pathways activated by FGF2, namely Ras/MAPK and PI3K/AKT, in order to: first, to simulate *in silico* the results obtained from experiments *in vitro* on Y1 cells stimulated with serum factors and FGF2; second, to perturbate the defined model, aiming to predict alternative steady states of these pathways. **Materials and methods.** To perform modeling and simulation, we developed a framework that allows: i) network description through a list of reactions, their rate constants and initial concentrations; ii) reaction mapping into system of ordinary differential equations; iii) numerical simulation of the system; iv) results evaluation, which might lead to new simulations with adjusted parameters. **Discussion and results.** Currently, we are simulating the crosstalk between Ras/MAPK and PI3K/AKT signaling pathways under different assumptions and performing curve-fitting analysis. We are also verifying the implications of the addition to the model of RasN17, a dominant negative mutant. Initial results showed that [K-Ras-GTP] relatively high steady basal levels, a condition experimentally observed in Y1 cells, are achieved only with the inclusion in the model of an additional guanine exchange factor (GEF); presently, we are experimentally probing Y1 cells for the expression of such a GEF. **Conclusion.** The results so far suggest that this methodology might provide insights into mechanisms of FGF2-induced cell cycle arrest in Y1 cells. However, our long-term goal is the construction of a multiscale model to simulate cell cycle progression and proliferation of Y1 cells under control of serum factors and FGF2.

Keywords: chemical kinetics, fibroblast growth factor 2, numerical simulation, ordinary differential equations, signaling networks
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