Hierarchical Model of the Ras-MAPK signalling pathway in mouse Y1 adrenocortical tumor cells

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The K-Ras-driven mouse adrenocortical tumor cell line Y1 displays a surprising association of phenotypic traits, i.e., high basal levels of activated K-Ras in starved cells and induction of cell cycle arrest upon stimulation by FGF2. In addition, ectopic expression of the dominant negative mutant Ras-N17 reduced activated K-Ras basal levels and eliminated cell cycle arrest by FGF2. We are working to uncover the molecular basis of this unexpected phenomenon by modeling the kinetics of the Ras-MAPK signalling pathway in Y1. We started by modelling the K-Ras molecular switch through a list of reactions, rate constants and initial concentrations, using the standard SBML format. With this simple model, containing only SOS to activate K-Ras, we were not able to reproduce the high basal level of activated K-Ras. This led us to add another GEF to our model, responsible for basal K-Ras activation. With this modification, our model was able to reproduce experimental data. We are currently planning to validate experimentally this hypothesis by knocking out GRP4, a GEF which has been shown to be very strongly expressed in Y1. We then moved to a Hierarchical Model representation using the SBML package comp, which enables us to represent models as a set of modules. We first included a simple module to describe the SOS activation by FGF2, which enabled us to represent the FGF treatment on our system. We then included another module representing how activated K-Ras induces the activation of the MAPK pathway. We finally added a module for describing Ras-N17 action, which reproduces observed behavior of Ras-N17 expression for both starved and FGF2-stimulated cells. We were able to start building a model to describe the unusual behavior of Y1 cells. Our model reproduces the behavior of K-Ras and MAPK activation in starved cells and FGF2-stimulated cells. We now need to improve it to include more treatments activating the pathway, and the consequences of these activations on the cell cycle control mechanism, to be able to describe and investigate the cell cycle blockage upon FGF2 stimulation. Our model is developed using standard representation, enabling collaborators to quickly start testing or improving our model. More precisely, the use of the SBML comp package enables us to build more modular models, which makes it easier when working with larger and larger models.

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