q-bio analysis of the Akt/mTOR pathway

Anisur Rahman[1] and Jason Haugh[2]

Mamalian Target of Rapamycin (mTOR) is a serine-threonine protein kinase that plays a vital role in cell growth, proliferation, and protein synthesis. It has also received much attention for its role in cancer progression, yet no significant work has been done to characterize this important pathway in a quantitative manner. mTOR activation has been linked to two major regulatory pathways: MEK/ERK and PI3K/Akt pathways. We show that, in the signaling network mediated by platelet-derived growth factor (PDGF) receptors, PI3K/Akt signaling is the dominant mode of mTOR Complex 1 (mTORC1) activation. Through quantitative measurements and modeling, we have explored the consistency of a conceptual model linking Akt to inhibition of TSC2, a negative regulator of mTOR.

***Keywords* — signal transduction, mTOR pathway, kinetic modeling, receptor tyrosine kinase.**

I. Introduction

The mTORC1 multi-protein complex is a master regulator of cell growth and protein synthesis. Both MEK/ERK and PI3K/Akt pathways have been implicated in the activation of mTORC1 [1], linking this important signaling hub to the action of receptor tyrosine kinases and other signal transducers. Rapamycin, a drug used to suppress immune function during organ transplantation, specifically blocks mTORC1 as its mechanism of action [2]. Activated ERK and Akt mobilize mTORC1 activation by phosphorylating different sites on TSC2, resulting in inhibition of the TSC1/2 complex, a GTPase-activating protein for the small GTPase, Rheb [3]. Rheb, in its active, GTP-bound form, is thus permitted to activate mTORC1, in a manner that is disrupted in the presence of rapamycin [4]. Upon activation, mTORC1 phosphorylates a host of substrates, leading to cell growth, protein synthesis, and other important functions. Despite its central role in normal and aberrant signaling networks, the mTOR pathway has yet to be studied using a quantitative approach.

II. Results

We first set out to acquire a suitable data set. Mouse fibroblasts were stimulated with platelet-derived growth factor (PDGF), and detergent lysates were prepared for quantitative immunoblotting. The dose and time of stimulation were varied, and pharmacological inhibitors were used to dissect the pathway. In these experiments, we established that signaling through PI3K/Akt, and not through MEK/ERK, is the major route of mTORC1 activation. Inhibition of Akt blocked phosphorylation of S6K1, a canonical mTORC1 substrate, as did rapamycin, confirming the specificity of the readout. Hence, the quantitative data were used to fit the kinetic model illustrated in Fig. 1 below. The fit to the data (phosphorylation time courses of Akt, TSC2, and S6K1 for 4 PDGF doses) is considered reasonable given the coarse granularity of this initial model.

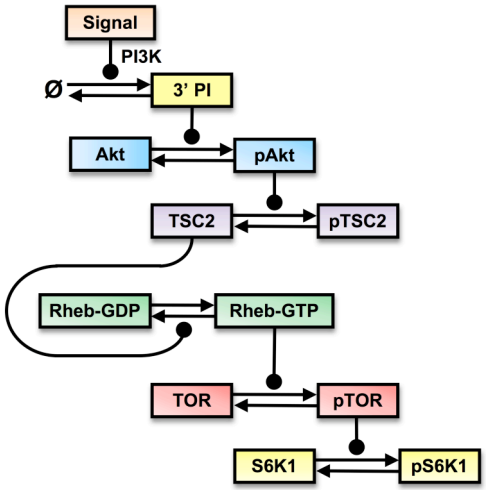

Figure 1: Simple kinetic model of the Akt/mTOR pathway

III. Conclusion

We have successfully initiated a quantitative and integrative study of the Akt/mTOR pathway. Future work will be focused on the analysis of the current model structure, its refinement (in conjunction with deeper experimentation), and its applicability in other cellular contexts.

References

[1] Jeremiah NW, Leonard SJ, Scot RK (2011) ERK and Akt signaling pathways function through parallel mechanisms to promote mTORC1 signaling. *AJP-Cell Physiol* **300**, C1172-C1180.

[2] Mathieu L, David MS (2009) mTOR signaling at a glance. *Journal of Cell Science* **122**, 3589-3594.

[3] Jingxiang H, Brendan DM (2008) The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. *Biochem. J.* **412**, 179-190.

[4] Albanell J, Dalmases A, Roivra A, Rojo F (2007) mTOR signaling in human cancer. *Clin Transl Oncol* **9**, 484-493.

Acknowledgment: This work was funded by NIH grant R01-GM088987.

[1]Department of Chemical and Biomolecular Engineering, North Carolina State University. E-mail: arahman3@ncsu.edu

[2]Department of Chemical and Biomolecular Engineering, North Carolina State University. E-mail: jason_haugh@ncsu.edu