A Mathematical Model of Homeostatic Regulation of JNK by NF-kB in Response to TNF Stimulation

Paul Loriaux[1], Rebecca Delker[2], Shannon L. Werner[2] and Alexander Hoffmann[2]

Short Abstract — **We present a mathematical model of JNK kinase regulation by nuclear factor kappa B (NF-kB) and the importance of this crosstalk mechanism in the decision to undergo cell death in response to stimulation by tumor necrosis factor alpha (TNF). In addition to induced NF-kB regulation of JNK, our model examines homeostatic regulation and suggests, in agreement with experimental data, that homeostatic regulation of JNK and the JNK degradation target cFLIP predisposes the cell towards life or death in response to TNF.**

Keywords — **NF-kB, JNK, TNF, cFLIP, apoptosis, crosstalk, model.**

I. INTRODUCTION

TUMOR necrosis factor alpha (TNF) is a pro-inflammatory cytokine that is released in response to trauma or infection. Binding of TNF to its receptor (TNFR) results in direct activation of caspase-8 and the apoptotic machinery via the intracellular death domain of TNFR. Healthy cells, however, are highly resistant to TNF-induced apoptosis owing to concurrent activation of nuclear factor kappa B (NF-kB), a pro-inflammatory, anti-apoptotic transcription factor. Recent studies suggest that the anti-apoptotic function of NF-kB may be mediated through cFLIP, whose pseudo-caspase domain prevents activation of caspase-8 by ligand-bound TNFR [1].

Several mechanisms by which NF-kB regulates cFLIP have been proposed. Expression of cFLIP is known to be induced by active NF-kB. Additional regulation of cFLIP levels may be achieved by controlling the activity of JNK kinase [2]. JNK has recently been shown to induce the degradation of cFLIP by activating the E3 ubiquitin ligase, Itch [3]. The anti-apoptotic protein A20, also induced by NF-kB, functions upstream of JNK by inhibiting activation of the MAP3K responsible for activating JNK [4]. Similarly, accumulation of oxygen radicals (ROS) promote JNK activity by inhibiting the inactivating MAPK phosphatase [5]. Anti-ROS molecules FHC and Mn-SOD are induced by active NF-kB and have also been implicated in the regulation of JNK.

II. RESULTS

To investigate the relative importance of these mechanisms under different physiological conditions, we have constructed a mathematical model of TNF-induced NF-kB activation and regulation of the JNK pro-apoptotic pathway. To investigate explicit homeostatic states and their effect on the induced response to TNF stimulation, we systematically apply steady-state and kinetic constraints that allow us to back calculate model parameters from the model structure. Extensive model simulation over a range of physiological steady states in conjunction with experimental data from our lab suggests an intriguing hypothesis: that homeostatic versus induced regulation of the pro-apoptotic JNK signal by NF-kB predetermines the cellular response to TNF stimulation.

REFERENCES

[1] Irmler, M., et al., *Inhibition of death receptor signals by cellular FLIP.* Nature, 1997. **388**(6638): p. 123-125.

[2] Nakano, H., *Signaling crosstalk between NF-kappaB and JNK.* Trends Immunol, 2004. **25**(8): p. 402-5.

[3] Chang, L., et al., *The E3 ubiquitin ligase itch couples JNK activation to TNFalpha-induced cell death by inducing c-FLIP (L) turnover.* Cell, 2006. **124**(3): p. 601-13.

[4] Lee, E.G., et al., *Failure to Regulate TNF-Induced NF-?B and Cell Death Responses in A20-Deficient Mice.* 2000.

[5] Kamata, H., et al., *Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases.*

[1]Graduate Program in Bioinformatics, University of California San Diego. E-mail: ploriaux@ucsd.edu

[2]Department of Chemistry and Bioechmistry, University of California San Diego