4cm Epidermal Growth Factor-Mediated Proliferation Requires Tcf/Lef Signaling

Nicholas A. Graham and Anand R. Asthagiri

Quantitative engineering analysis is required to understand how intricate networks of intracellular signaling pathways regulate cell proliferation, both in tumorigenic and normal cell systems. One particular challenge is to decipher how signaling pathways that drive hyperproliferation in cancerous cells function in non-cancerous cells. For example, constitutive transcription of target genes by T-Cell Factor/Lymphoid Enhancer Factor (Tcf/Lef) proteins is known to drive aberrant proliferation in many cancerous cell systems. Since Tcf/Lef target genes regulate passage through the cell cycle, the untested hypothesis remains that Tcf/Lef transcription has a more pervasive role in proliferation of non-tumorigenic cells. Here, we demonstrate that Epidermal Growth Factor (EGF) stimulates Tcf/Lef transcriptional activity in non-cancerous epithelial cells, and that its transcriptional activity is essential for EGF-mediated proliferation. Thus, re-wiring the intracellular signaling network to block Tcf/Lef transcriptional activity blocks EGF-mediated proliferation; however, this suppression of cell cycle activity is not related to attenuation of parallel signaling pathways such as MAPK, since blocking Tcf/Lef transcriptional activity did not affect EGF-induced MAPK signaling. Importantly, while Tcf/Lef transcription is essential for EGF-mediated cell cycle progression, it is not sufficient for proliferation, as stimuli like serum induce Tcf/Lef transcriptional activity but not DNA synthesis. Taken together, these findings suggest that Tcf/Lef-mediated transcription may be globally required, but not sufficient, for cell cycle activity. Ultimately, elucidating both the molecular mechanisms and the quantitative, dynamical aspects of Tcf/Lef transcriptional activity will lead to a better understanding of this signaling network that appears to have broad relevance for both normal and cancer cell behavior.