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Anticipatory Activation of the Unfolded Protein Response by Epidermal Growth Factor is Required for Immediate Early Gene Expression and Cell Proliferation

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Abstract

The onco-protein epidermal growth factor (EGF) initiates a cascade that includes activation of the ERK and AKT signaling pathways and alters gene expression. We describe a new action of EGF-EGF receptor (EGFR), rapid anticipatory activation of the endoplasmic reticulum stress sensor, the unfolded protein response (UPR). Within 2 min., EGF elicits EGFR dependent activation of phospholipase C γ (PLCγ), producing inositol triphosphate (IP_3), which binds to IP_3 receptor (IP_3R), opening the endoplasmic reticulum IP_3R Ca^{2+} channels, resulting in increased intracellular Ca^{2+}. This calcium release leads to transient and moderate activation of the IRE1α and ATF6α arms of the UPR, resulting in induction of BiP chaperone. Knockdown or inhibition of EGFR, PLCγ or IP_3R blocks the increase in intracellular Ca^{2+}. While blocking the increase in intracellular Ca^{2+} by locking the IP_3R calcium channel with 2-APB had no effect on EGF activation of the ERK or AKT signaling pathways, it abolished the rapid EGF-mediated induction and repression of gene expression. Knockdown of ATF6α or XBP1, which regulate UPR-induced chaperone production, inhibited EGF stimulated cell proliferation. Supporting biological relevance, increased levels of EGF receptor during tumor progression were correlated with increased expression of the UPR gene signature. Anticipatory activation of the UPR is a new role for EGF. Since UPR activation occurs in <2 minutes, it is an initial cell response when EGF binds EGFR.

1. Introduction

Epidermal growth factor (EGF) stimulates cell proliferation and tumor growth by binding to a family of epidermal growth-factor receptors (EGFRs). The EGFR family consists of four members: ErbB1 (EGFR), ErbB2 (HER2/neu), ErbB3, and ErbB4 (1). Binding of EGF to EGFR leads to formation of activated EGFR dimer, which exhibits increased autophosphorylation. Phosphorylated EGFR activates several cell signaling pathways, including the ERK and AKT