Abstract

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Epidermal growth factor receptor (EGFR) is a known contributor to tumor progression and wound healing. EGFR can retrotranslocate to the nucleus where it acts as a transcription cofactor and activates pro-oncogenic pathways, however the drivers of EGFR retrotranslocation are not well defined. In both a tumor microenvironment and in a wound healing environment, cells are exposed to stressors that increase cellular reactive oxygen species (ROS) levels. ROS can oxidize proteins and impact protein confirmations, protein-protein interactions, and activity levels. *We hypothesize that cellular stressor-induced reactive oxygen species drive nuclear localization of EGFR which activates mesenchymal-like cell migration.* To better understand the drivers of nuclear EGFR (nEGFR) and its role in cell migration, CRISPR/Cas9 was used to insert the mVenus fluorescent protein onto the C-terminus of endogenous EGFR in an immortalized human keratinocyte cell line (HaCaT). Using a live cell imaging platform, it was found that nutrient deprivation and hydrogen peroxide exposure promotes nEGFR expression in HaCaTs. Furthermore, treatment with N-acetyl-L-cysteine (a ROS inhibitor) reduces nEGFR levels. This suggests nutrient deprivation-induced ROS drives nEGFR expression. Scratch assays were conducted in the absence and presence of stressors and a peptide drug that inhibits nuclear localization of EGFR (cSNX1.3) to evaluate the role of nEGFR in cell migration. Inhibition of nEGFR by cSNX1.3 only reduced cell migration in stressed-conditions, suggesting epithelial cells shift to a nEGFR-dependent mechanism of cell migration in stress conditions. Future studies will delve deeper into how ROS drives nEGFR and the specific proteins and gene loci that nEGFR interacts with to affect cell migration. By elucidating the intrinsic role and regulation of nEGFR in epithelial cells, we can better understand the tightly regulated mechanisms of wound healing and how the dysregulation of these molecular pathways can drive tumor progression.