EEF1A2 Drives Dual-Mode Angiogenesis in Breast Cancer in Normoxia and via a HIF1A-Driven Feedback Loop in Hypoxia

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EEF1A2 is an oncogene associated with various solid tumors. In breast cancer, we identified that it promotes epithelial-mesenchymal transition in both ER/PR-positive and triple-negative breast cancers (TNBCs), with a more aggressive effect in TNBCs. Recently, we identified a novel role of EEF1A2 in angiogenesis. We found that elevated EEF1A2 levels in breast cancer cells promoted enhanced cell growth, migration, and tubule formation in HUVECs, confirmed by both ex-vivo and in-vivo assays. This effect could be counteracted by Plitidepsin. EEF1A2 upregulated HIF1A expression under normoxic conditions through ERK-Myc and mTOR signaling in TNBC and ER/PR positive cells, respectively. Hypoxia further induced EEF1A2, establishing a positive feedback loop with HIF1A. Luciferase assays and EMSA revealed HIF1A binding to the EEF1A2 promoter, enhancing its transcription. RT-PCR and polysome profiling validated EEF1A2's positive impact on VEGF transcription and translation, leading to increased VEGF secretion from breast cancer cells, which activated ERK and PI3K-AKT signaling in endothelial cells. Higher EEF1A2 levels in breast cancer tissues corresponded with increased microvessel density. Overall, EEF1A2 demonstrates significant angiogenic potential in both normoxic and hypoxic conditions, indicating its dual role in promoting EMT and angiogenesis, and suggesting its potential as a target for cancer therapy.