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Novel Functions for BNIP3L/NIX in Promoting Breast Cancer Growth and Metastasis

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Mitophagy is a cellular process that involves the selective degradation of dysfunctional mitochondria at the autolysosome. BNIP3L/NIX is a hypoxia-inducible mitochondrial cargo receptor, that localizes to the outer mitochondrial membrane where it interacts with processed LC3 to promote mitophagy in response to physiological stresses including hypoxia, DNA damage, and nutrient deprivation. Mitophagy is a critical homeostatic mechanism limiting mitochondrial ROS production, maintaining cellular energy balance, and reducing inflammatory responses. Defective mitophagy has been implicated in deregulated tumor cell growth and cancer. However, the specific mechanisms by which BNIP3L/NIX or other mitophagy receptors regulate tumor growth and progression are not fully understood. Our preliminary data shows that elevated BNIP3L/NIX expression in basal-like breast cancers correlates with worse overall patient survival. To understand the role of BNIP3L/NIX in regulating the growth and progression of breast cancer, we used CRISPR/Cas9 gene editing to delete Bnip3l/Nix in the mouse 4T1 mammary tumor model system to determine how the loss of BNIP3L/NIX affected tumor progression and metastasis. Using this *in vivo* model, we showed that *Bnip3l/Nix* deletion attenuates 4T1 primary tumor growth and suppresses spontaneous metastasis to the lungs. Additionally, loss of Bnip3l/Nix prevented the recruitment of GM-CSF-dependent Ly6G-positive granulocytes to the primary tumor and secondary sites. These results showed that Bnip3l/Nix plays an important role in breast cancer tumor growth and metastasis. RNA-seq analysis demonstrated that these striking findings were associated with a decrease in molecular expression signatures of epithelial-mesenchymal transition (EMT) genes, including *Twist* and *Vimentin*. In addition, the expression of Vimentin was reduced in 4T1 *Bnip3l/Nix* deficient tumors *in vivo*. Reduction of Vimentin gene expression correlated with significantly reduced ability of 4T1 *Bnip3l/Nix* deficient tumor cells to migrate and invade *in vitro*. Taken together these results demonstrate that Bnip3l/Nix acts as a growth promoter in breast cancer by upregulating expression of EMT genes and stimulating tumor cell growth and migration. Future work will investigate the specific mechanism by which Bnip3l/Nix regulates EMT in breast cancer. Understanding these Bnip3l/Nix-dependent mechanisms may lead to novel therapeutic strategies to prevent breast cancer metastasis.