OXIDATIVE STRESS IS A LIMITING FACTOR FOR METASTASIS

Reactive oxygen species (ROS) have been suggested to promote tumor initiation and progression by increasing mutation rates and activating oncogenic pathways, raising the possibility that antioxidants may reduce tumorigenesis. However, dietary antioxidant supplementation has been shown to increase the incidence and progression of some cancers in clinical trials and to have detrimental effects in mice. To evaluate the role of oxidative stress in distant metastasis, Piskounova and colleagues analyzed the metastatic potential of patient-derived human melanoma samples in immunodeficient mice. In contrast to the high rate of subcutaneous tumor formation by melanoma cells, intravenous or intrasplenic injection of melanoma cells resulted in significantly decreased formation of distant metastases. Metabolomic profiling revealed the presence of increased oxidative stress in circulating melanoma cells in the blood and metastatic nodules compared with subcutaneous tumors, as measured by elevated ROS levels and a decreased ratio of glutathione (GSH) to oxidized glutathione (GSSG) in metastasizing cells. Treatment with the antioxidant N-acetylcysteine (NAC) enhanced metastatic disease burden, but not subcutaneous tumor growth. The ability of melanoma cells to successfully metastasize was mediated by reversible adaptive metabolic changes that enabled cells to withstand oxidative stress, including increased expression of NADPH-regenerating enzymes and elevated flux through the folate pathway. Inhibition of the folate pathway using methotrexate or knockout of folate pathway enzymes decreased the frequency of circulating melanoma cells and reduced metastatic burden. Consistent with these findings, Le Gal and colleagues found that NAC treatment augmented lymph node and lung metastasis in a genetically engineered mouse model of malignant melanoma, which was accompanied by a higher GSH/GSSG ratio in metastases. In addition, antioxidants enhanced the migration and invasion of malignant melanoma cells and resulted in increased RHOA activation. Together, these findings demonstrate that oxidative stress limits distant melanoma metastasis in vivo and suggest that antioxidants may enhance tumor progression.

Major finding: Increased oxidative stress in metastasizing human melanoma cells suppresses distant metastasis.

Mechanism: Reversible metabolic adaptations that promote NADPH regeneration facilitate successful metastasis.

Impact: Dietary supplementation with antioxidants or folate may promote tumor metastasis and progression.

ERYTHROPOIETIN PROMOTES TUMOR GROWTH VIA THE ALTERNATIVE RECEPTOR EPHB4

Erythropoietin (EPO) is a cytokine involved in multiple cellular functions, including erythropoiesis, angiogenesis, cytoprotection, and proliferation. Recombinant human EPO (rhEPO) has been used to treat chemotherapy-induced anemia in cancer patients; however, rhEPO has been reported to reduce the overall survival of cancer patients, indicating that it may enhance tumor growth. The expression of the canonical EPO receptor EPOR largely fails to explain the tumor-promoting effects of EPO, suggesting the possibility of an alternative EPO receptor. Pradeep, Huang, Mora, and colleagues used in silico strategies to identify EPHB4 as a potential alternative EPO receptor, and confirmed the ability of rhEPO to bind to EPHB4, albeit less strongly than to EPOR. Stimulation of the EPHB4 receptor by rhEPO resulted in the activation of SRC and STAT3, whereas rhEPO stimulation of EPOR resulted in JAK2/STAT5 activation. Additionally, the rhEPO-induced increases in proliferation, migration, and invasion of cancer cells required EPHB4-mediated SRC/STAT3 signaling, but not EPOR. These results were confirmed in vivo in mouse models of ovarian and breast cancer, in which EPO-induced tumor growth was dependent on EPHB4. Furthermore, in human patients with breast or ovarian cancer, increased expression of EPHB4, but not the canonical receptor EPOR, was associated with a poor clinical outcome in patients treated with erythropoiesis-stimulating agents such as rhEPO. Taken together, these findings indicate that EPHB4 is an EPO receptor that functions through the activation of SRC and STAT3 to promote tumor growth in response to treatment with rhEPO. These results explain the harmful effects of EPO treatment on the survival of patients with cancer, and suggest that inhibition of EPHB4 may be a promising therapeutic strategy to reduce the tumor-promoting effects of EPO treatment.

Major finding: EP HB4 is an erythropoietin (EPO) receptor associated with poor survival in rhEPO-treated patients.

Mechanism: rhEPO signals through EPHB4 to activate downstream SRC and STAT3, leading to tumor progression.

Impact: Anti-EPHB4 therapies have the potential to reduce the tumor-promoting effects of rhEPO treatment.