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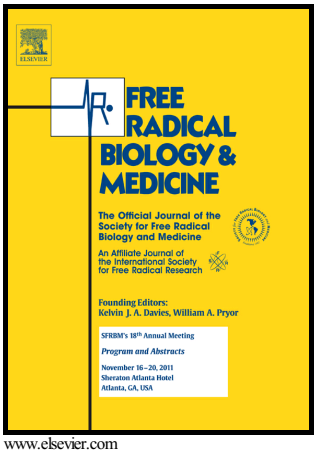

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Glutathione Reductase-mediated Thiol Oxidative Stress Suppresses Metastasis of Murine Melanoma Cells

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ABSTRACT

Malignant melanoma is a highly metastatic and life-threatening cancer. Reactive oxygen species (ROS) play important roles in cancer initiation and progression including metastasis. It has been reported that the oxidative stress spontaneously generated in circulating melanoma cells was able to suppress distant metastasis *in viv*o. However, little is known regarding the effects and mechanism of glutathione reductase (GR) inhibition-induced oxidative stress in regulation of melanoma metastasis. Here, we demonstrate that GR inhibition generates oxidative stress and suppresses lung metastasis and subcutaneous growth of melanoma *in vivo*. In addition, inhibitory effects by GR activity reduction were observed on cell proliferation, colony formation, cell adhesion, migration and invasion in melanoma cells *in vitro*. GR inhibition-induced oxidative stress was also found to block epithelial-to-mesenchymal transition (EMT) by decreasing the expression of Vimentin, ERK1/2, transcription factor Snail and increasing the expression of E-cadherin. In addition, actin rearrangement, a key element involved in cell motility, is also affected by GR-mediated oxidative stress possibly through protein *S*-glutathionylation on actin. In conclusion, this study identifies GR as an effective regulator of oxidative stress that affects the multistep processes of metastasis in melanoma cells, and it becomes a potential target for melanoma therapy.

Graphical Abstract: