Conclusions

• Inhibition of glutathione reductase (GR) induced intracellular thiol oxidative stress and suppressed the multi-step of metastasis of murine melanoma cells in vitro and in vivo.
• GR inhibition-induced oxidative stress suppressed epithelial-to-mesenchymal transition (EMT) by upregulation of E-cadherin and downregulation of Snail and Vimentin.
• Actin S-glutathionylation was found under thiol oxidative stress and it may contribute to the F-actin rearrangement.
• Induction of oxidative stress is a promising approach to suppress melanoma metastasis.
• GR can be a potential target in inhibition of melanoma cell metastasis through regulation of thiol oxidative stress.

Introduction

Malignant melanoma is a highly metastatic and life-threatening cancer. It has been reported that oxidative stress spontaneously generated in circulating melanoma cells was able to suppress distant metastasis in vivo. Reduction of GR activity is able to generate reactive oxygen species (ROS), which play important roles in cancer initiation and progression. It was found that melanoma cell metastasis was suppressed by inhibition of GR. However, little is known regarding the effects and mechanism of GR inhibition-induced oxidative stress in regulation of melanoma metastasis. This study was aimed to explore the effects of GR inhibition on tumorous behaviors, including metastasis and EMT, of murine melanoma cells and investigate the mechanism of action.

Results

Figure 1. GR-inhibition-induced oxidative stress inhibited B16F10 cell subcutaneous growth and lung metastasis in vivo. (A) Isograft mice and tumors. (B) Number of mice bearing isograft tumors. (C) Tumor volumes. (D) Lungs of C57BL/6J mice with intravenous injection of B16F10 cells. (E) Number of metastatic foci of B16F10 cells formed in mice lungs. The data are presented as mean ± SEM of three independent experiments.

Figure 2. Inhibition of GR-induced ROS production and thiol oxidative stress in B16F10 cells.

Figure 3. GR inhibition-induced oxidative stress suppressed cell migration, invasion and adhesion in vitro. The data are presented as mean ± SD of three independent experiments.

Figure 4. GR inhibition-induced oxidative stress inhibited EMT and induced S-glutathionylation on β-actin in B16F10 cells.

Figure 5. GR inhibition-induced oxidative stress induced actin cytoskeleton rearrangement in B16F10 cells.

Future work:
To investigate molecular basis of the correlation between melanoma stemness, EMT and GR-induced oxidative stress, whether protein S-glutathionylation is involved in this processes.

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