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Lipoic acid inhibits radiation-induced EMT and migration in breast cancer cells via inhibition of TGF-β signaling

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Background: Breast cancer metastasis is the second leading cause of cancer related death among women. Radiation therapy is one of the important modes of treatment to breast cancer. However, radiotherapy has certain limitations such as development of radioresistance and cancer recurrence. Radiation also promotes the migration and invasion of breast cancer cells by activating the signaling mechanisms such as TGF-β signaling.

Objective: To study the role of lipoic acid in treatment of radiation-induced TGF-β signaling in breast cancer.

Materials And Methods: The Breast cancer cells, MCF-7 and MDA-MB-231, were treated with different doses of lipoic acid pre and post radiation. The effect of lipoic acid on cell viability, proliferation and clonogenicity were measured. The activity of MMP9 was measured by gelatin zymography. The expression of ANGPTL-4 was measured by qPCR and the expression of EMT markers was analyzed by western blot.

Results: Lipoic acid treatment in combination with radiation in MCF-7 and MDA-MB-231 cells showed a synergistic dose and time dependent increase in cell death. Lipoic acid pre treatment also reduces the migration of breast cancer cells induced by radiation. Further, lipoic acid treatment reduced the activity and expression of matrix metalloproteinase 9 (MMP9). MMP-9 degrades extracellular matrix, thus the inhibition of MMP9 might play a role in preventing invasion and metastasis of breast cancer cells. The radiation induced EMT was evident from the decreased expression of epithelial markers and increased expression of mesenchymal markers; lipoic acid treatment effectively prevented the radiation-induced EMT. Lipoic acid treatment inhibits the TGF-β downstream signaling through the inhibition of Non-Smad pathway. Lipoic acid also reduced the expression of ANGPTL-4, a downstream target of TGFβ in breast cancer cells.

Conclusion: Our findings suggest that lipoic acid increases the sensitivity of breast cancer to radiation and inhibits the radiation-induced migration and invasion of breast cancer cells.

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