Investigation of Manganese Cellular Transport Mechanisms During Cancer-Associated Metallomic Imbalance

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Metallomic imbalance impacts tumor malignancy. Previous work developed by Stelling, and collaborators demonstrated that manganese is accumulated in tumors in vivo and that tumor cells in vitro present an invasive behavior when exposed to Mn. Therefore, in order to elucidate Mn cellular transport pathways in cancer, we considered DMT1 (Divalent Metal Transporter 1) as a target of interest due to its possible contribution to cancer metallomic imbalance. In order to investigate if DMT1 plays an important role in Mn transport in cancer I simulated in vitro conditions a tumor cell could face in vivo. Briefly, murine Lewis lung carcinoma (LLC) cells were exposed to 5μM $MnCl_2$ for 24hs and the metallome was analyzed by X-ray fluorescence (XRF) and Inductively Coupled Plasma Optical Emission spectroscopy (ICP-OES). DMT1 gene expression was performed by semi-quantitative PCR. XRF analysis of the cellular metallome revealed alterations in Mn, Fe and Cu. Meanwhile, the analysis of tumor cell-derived extracellular vesicles revealed Mn as the only altered element. ICP-OES analyses also revealed that Mn is the only altered metal in the cell cytoplasm. These data showed that the tumor cell is capable of retaining Mn, Fe and Cu, but only internalizes and, consequently, secretes Mn, reinforcing its potential for modulating tumor metallomics. In addition, decreased expression of DMT1 indicates a tumor cell protective mechanism against high Mn levels-associated cytotoxicity. In conclusion, these data shows that Mn promotes malignancy, while DMT1 is probably involved in tumor cell resistance mechanisms, putting this molecule under discussion as a new therapeutic target.

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