ABSTRACT

A role for the ATP7A copper transporter in Cisplatin resistance, tumorigenesis and metastasis

Copper is an essential yet potentially toxic nutrient. It is required as a co-factor by many enzymes. However, an overabundance of copper leads to toxicity due to its ability to form damaging reactive oxygen species (ROS). A delicate balance of copper in a living cell is maintained by copper binding proteins and transporters. ATP7A is one such copper transporter localized in the trans-Golgi network (TGN). It delivers copper to newly synthesized cuproenzymes in the Golgi and also traffics to the plasma membrane to export excess copper from the cell. We report that deletion of the ATP7A gene in RAS-transformed mouse embryonic fibroblast (MEF) cells not only confers sensitivity to cisplatin chemotherapy drug in vitro and in vivo but markedly prevents tumor formation in the absence of chemotherapy agent. Deletion of ATP7A in the breast cancer cell line, 4T1, was also found to suppress tumorigenesis and markedly reduce the spread of cancer to the lungs. The ATP7A knockout cells accumulated excess copper and exhibit reduced survival as compared to the 4T1WT cells in the presence of hydrogen peroxide or hypoxia, suggesting that hyper-accumulation of copper sensitizes these cells to ROS production. The ATP7A knockout cells lack activation of copper-dependent Lysyl Oxidase (LOX) and exhibit reduced phosphorylation of focal adhesion kinase (FAK): a pro-cancer protein that is regulated by LOX activity. Taken together, these findings identify roles for the ATP7A copper transporter at the nexus of platinum-drug resistance, tumorigenesis, and metastatic pathways, underscoring its potential as a therapeutic drug target at multiple stages of carcinogenesis.