Rock the Metals! Investigating Manganese as a Trigger of Malignancy and Metal Transporters as Targets in Cancer Treatment

de Araujo Pereira da Silva, Carolina (School: Instituto Federal de Educacao Ciencia e Tecnologia do Rio de Janeiro)

Metals and their transporters influence cell behavior in cancer, and previous research demonstrated that manganese promotes malignancy. Therefore, if metal transporters are essential in maintaining the metallome, do variations in extracellular Mn alter transporters' expression? To model tumor microenvironment metallome dynamics, lung carcinoma (LLC) cells were incubated in high-Mn culture medium for 24 h, followed by 48 h of recovery in standard medium. Real time-PCR and ICP-OES techniques were applied to analyze cells and medium, respectively. Statistical analyses were performed using GraphPad Prism 5 software. Data obtained are in accordance with previous work, confirming DMT1 transporter's negative regulation in high-Mn medium. It was observed that such regulation negatively correlates with Mn concentration, increasing at low-Mn and decreasing at high-Mn. Other transporters (ZIP8, ZnT1 and FPN1) also showed changes, an interesting finding, since not all are direct Mn transporters. Also, cells previously exposed to Mn-rich environment showed they are capable of secreting this element back into the medium upon return to standard conditions. These data demonstrate that tumor cells oscillate between Mn uptake and secretion, perpetuating a Mn-rich tumor microenvironment that promotes a complex and regulated network. Future experiments will involve cell migration to evaluate the impact of cell-secreted microenvironmental Mn on tumor cell invasion, and analysis of X-ray fluorescence data obtained by the group to unveil Mn subcellular distribution in LLC cells. DMT1 inhibitors will also be tested regarding efficiency in reversing Mn-promoted malignancy. This innovative project presents great potential to the development of new therapeutic targets in cancer treatment.