PROTEOMIC CHARACTERIZATION OF THE EFFECT OF MANNOSE ON NORMAL AND TRANSFORMED MURINE MELANOCYTE CELL LINES

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Cancer is a set of complex and multifaceted diseases, characterized mainly by uncontrolled growth of cells that replicate abnormally. During oncogenesis, there is a high energetic demand that culminates in important consequences on the metabolism of transformed cells. One of the epimers of glucose, mannose, is absorbed by the same non-specific transporters, which allows for the use of carbohydrates as a source of energy in tumor cells. Recent studies have shown that after mannose enters the cells, its phosphorylated form (M6P) accumulates and does not enter the glycolytic pathway due to low expression of the enzyme mannose phosphate isomerase (PMI), which converts M6P to fructose-6-phosphate, an intermediary of the glycolytic pathway. Our group identified mannose sensitivity in both normal and transformed melanocytes. In this context, the main objective is to evaluate the effects of mannose administration on the proteome of normal and tumoral murine melanocyte cell lines (Melan-A and B16-F10, respectively). We aim to correlate the results obtained with possible relevant biological pathways in the oncogenic process. From a therapeutic standpoint, the results obtained will elucidate fundamental molecular aspects that could support the development of clinical intervention strategies using this hexose (mannose) in conjunction with therapies already used for the treatment of melanoma. To study the effects of mannose on the cell lines, we conducted viability assays, assessed cellular growth, measured lactate formation, analyzed acidic vesicular organelles (AVOs), and performed proteomics. Mannose did not induce a decrease in cell viability but caused a stagnation in the number of growing cells, along with lower levels of lactate in the culture medium. Additionally, mannose led to significant changes in the proportion of phosphorylated proteins in both normal and transformed melanocytes, with higher levels observed in tumor cells and the formation of AVOs. Phosphoproteomics data revealed proteins unique to each condition in both strains, with distinct phosphorylation sites and condition-specific phosphorylation in shared proteins. Moreover, a protein associated with autophagy was more phosphorylated in the presence of mannose. Furthermore, the secretome from the melanoma cell line cultivated with mannose showed increased cell viability in the endothelial cell line. Our results demonstrate that mannose exhibits cytostatic potential in the melanoma cell line and causes significant changes in protein phosphorylation, suggesting interference in energy metabolism and molecular pathways, especially in autophagy. Comprehensive proteome analysis is underway to elucidate the mechanisms and pave the way for new studies and therapeutic strategies.

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