Mitochondrial Pathways in Cancer

Cancer is considered to primarily be the result of multiple driver genetic lesions.[1] Nevertheless, emerging evidence suggests that non-genetic mechanisms may be involved in phenotypic plasticity and cellular adaptation in tumor microenvironment. Cell-intrinsic and -extrinsic factors, such as epigenetic modifications, hypoxia, crosstalk with surrounding cells and metabolic state of the cells, contribute to metabolic heterogenicity.[2-4] Recently, there is a renewed interest to explore mitochondrial mechanisms as a promising target for novel anticancer treatment, especially in tumor types with higher mitochondrial mass and respiratory activity such as leukemia.[5,6]

Mitochondria are essential for various metabolic and cellular processes linked to oncogenesis and phenotypic plasticity.[4,7] One of the hallmarks of cancer cells is their ability to adapt to unfavorable environments to support their rapid growth and supply their energy needs.[8] Selective inhibition of bioenergetic pathways would limit the ability of leukemic cells to derive energy for their growth.[5] However, cells with high tumorigenic potential were reported to display an increased dependence on the cytoplasmic process of aerobic glycolysis, instead of the more efficient mitochondrial process of aerobic respiration (the Warburg hypothesis).[9] This was initially attributed to a defective mitochondrial function (aerobic respiration) in cancer cells. However, an increasing body of evidence suggests that impaired mitochondrial metabolism is not a general feature of cancer cells.[10] For example, leukemia stem cells and progeny cells depend on mitochondrial oxidation for energy production.[6] Glycolytic shift in cancer cells can be used to support cellular growth and maintain the redox state of the cell.[11] Alternatively, an emerging theory, known as the reverse Warburg effect, emphasized the supporting role of stromal cells in the tumor microenvironment. Crosstalk from surrounding cells is believed to play a role in promoting adaptive resistance and glycolytic shift.[10] This was supported by evidence suggesting that the dominance of aerobic glycolysis in some cancer cells is due to alterations in signaling pathways that govern carbon fuel uptake and utilization.[4,7] Moreover, the mutations and alterations affecting various oncogenes and tumor suppressor genes play a role in activating signaling pathways that drive the metabolic phenotype of tumor cells.[12] For example, oncogenes can induce the expression of hypoxia-inducible factor, a transcription factor that regulates genes involved in metabolism, angiogenesis, cell stress response and survival.

Furthermore, cancer cells were reported to be resilient based on their ability to escape apoptosis.[8] Mitochondria are involved in the defining event of the apoptotic process.[13] Mitochondria also produce reactive oxygen species as a byproduct of the electron transport chain, which can promote oxidative stress-induced damage to the mitochondrial and nuclear DNA. Oxidative stress can also induce autophagy.[14]

Understanding mitochondrial mechanisms involved in promoting neoplastic phenotype may help in the development of new therapeutic strategies that allow specific and coordinated modulation of mitochondrial function in tumor cells. Recent evidence suggests that targeting mitochondrial pathways may provide a promising and effective therapeutic target for some tumor types.[5,15] This can be specifically promising in hematologic malignancies such as acute myeloid leukemia, which is characterized by an increased mitochondrial mass and heightened sensitivity to inhibitors of the electron transport chain.[16]

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