Current views on cell metabolism in SDHx-related pheochromocytoma and paraganglioma.

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Abstract

Warburg's metabolic hypothesis is based on the assumption that a cancer cell's respiration must be under attack, leading to its damage, in order to obtain increased glycolysis. Although this may not apply to all cancers, there is some evidence proving that primarily abnormally functioning mitochondrial complexes are indeed related to cancer development. Thus, mutations in complex II (succinate dehydrogenase (SDH)) lead to the formation of pheochromocytoma (PHEO)/paraganglioma (PGL). Mutations in one of the SDH genes (SDHx mutations) lead to succinate accumulation associated with very low fumarate levels, increased glutaminolysis, the generation of reactive oxygen species, and pseudohypoxia. This results in significant changes in signaling pathways (many of them dependent on the stabilization of hypoxia-inducible factor), including oxidative phosphorylation, glycolysis, specific expression profiles, as well as genomic instability and increased mutability resulting in tumor development.
Although there is currently no very effective therapy for SDHx-related metastatic PHEOs/PGLs, targeting their fundamental metabolic abnormalities may provide a unique opportunity for the development of novel and more effective forms of therapy for these tumors.


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