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Mapping of Diabetes Susceptibility Loci ina Domestic Cat Breed with an Unusually HighIncidence of Diabetes Mellitus

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Tumor cells display metabolic alterations when compared to non-transformed cells. These characteristics are crucial for tumor development, maintenance and survival providing energy supplies and molecular precursors. Anaplerosis is the property of replenishing the TCA cycle, the hub of carbon metabolism, participating in the biosynthesis of precursors for building blocks or signalling molecules. In advanced prostate cancer, an upshift of succinate-driven oxidative phosphorylation via mitochondrial Complex II was reported. Here, using untargeted metabolomics, we found succinate accumulation mainly in malignant cells and an anaplerotic effect contributing to biosynthesis, amino acid, and carbon metabolism. Succinate also stimulated oxygen consumption. Malignant prostate cells displayed higher mitochondrial affinity for succinate when compared to non-malignant prostatecells and the succinate-driven accumulation of metabolites induced expression of mitochondrial complex subunits and their activities. Moreover, extracellular succinate stimulated migration, invasion, and colony formation. Several enzymes linked to accumulated metabolites in the malignant cells were found upregulated in tumor tissue datasets, particularly NME1 and SHMT2 mRNA expression. High expression of the two genes was associated with shorter disease-free survival in prostate cancer cohorts. Moreover, in-vitro expression of both genes was enhanced in prostate cancer cells upon succinate stimulation. In conclusion, the data indicate that uptake of succinate from the tumor environment has an anaplerotic effect that enhances the malignant potential of prostate cancer cells.

Biography

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