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Original Article

The relationship between breast cancer and Krebs cycle

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ABSTRACT

Background: Cancer is a disease with uncontrollable growth in which cells gain some genetic changes to have unusual proliferation and growth. The tumor cells rely on glycolysis for ATP production. *SDH* and *FH* are practical in TCA cycle and ETC with production of intermediate sitrate (for macromolecules synthesis) and ROS (for signaling). Therefore, mitochondria participate in needs for signaling, biosynthesis and bioenergetics in cancer cells. The development of tumor cells damages mitochondrial functions therefore glycolysis is an essential mechanism against the decrease of ATP production from oxidative phosphorylation. **Research Method:** The related resources were searched and reviewed, and mutations in sites like Ensemble, and meta-analysis results in related references were identified. **Findings:** The analysis of the date showed that mitochondrial dysfunctions occurred due to the loss-of-function mutations in the TCA cycle enzymes (*SDH*, *FH* and *IDH*). Both of the *SDH* and *FH* were housekeeping genes, and had bioenergetics roles. *IDH1* and *IDH2* are heterodimer enzymes in cytoplasm and mitochondria; respectively, and produce NADPH by conversion of isositrate to α-ketoglutarate. It has been found that same mutations in *IDH1* and *IDH2* were linked with tumorigenesis. This mutation causes the *IDH* to achieve NADPH dependent enzymatic activity, and converses α-ketoglutarate to 2-hydroxi glutarate. In fact, this change causes the mutant enzymes to be redirected from NADPH production to NADPH consumption. **Conclusion:** It can be concluded that mutations in genes related to the conversion of C4 to C4 and C6 to C5 have a significant correlation with tumorgenesis.

Keywords: krebs cycle, cancer, mitochondria.

Introduction

Breast cancer is one of the most common cancers among women worldwide. Nearly one of every nine women will be diagnosed with breast cancer in their lifetime.[1] Cancer is uncontrolled cell division as a result of environmental factors and genetic disorders. Four classes of genes have the key role in cancer cells: Oncogenes, Tumor suppressor genes, DNA repairing genes and Apoptosis genes. [2] Contrarily, functional mitochondria exist in all proliferative cells in our body (including all tumors), and they modify various nutrients existing in cells to the essential building blocks needed for cell growth. These organelles perform countless functions in cancer cells to improve tumor growth and survival in reaction to stress.[3]

Acetyl-CoA production of catabolic pathways are oxidized to CO_2 in three carboxylic acid cycle (TCA). The principal place of Krebs cycle enzymes is mitochondria. In TCA cycle, electrons are transferred to FAD or NAD, NADH or FADH is produced, then ATP is generated with mitochondrial electron transport chain (respiratory chain) and oxidative phosphorylation. The enzymes of electron transport chain and respiratory chain are in the mitochondria. In the first step, asetyl CoA is with oxaloasetate (C4) synthesizesitrate (C6), then with sitrategenetates $2CO_2$ and 2NADH+H and succinate (C4) and 1GTP with two reactions of oxidative phosphorylation. 1FADH, 1NADH+H and 1 oxaloasetate are produced after the other two oxidative reactions.[4]

The high proliferation of cancer cells needs much energy. According to the role of TCA cycle in energy generation, maybe there is relationship between TCA cycle and cancer. The purpose of this study was finding the relationship between TCA cycle genes and cancer.

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Materials and Method

At first, 22 articles about krebs cycle's genes were gathered. Meta-analysis was done based on the gene expression changes. The results of meta analysis were examined by using a network pathway.

Results and Discussion

The results of the descriptive analysis demonstrated that krebs cycle's enzymes had a role in deferent cancers, including: 90% *succinate Dehydrogenase*,31% *isocitrate dehydrogenase* and 50% *fumarate hydratase*. Among the genes involved, it was reported that *SDH* had 60% role in Paraganglioma, 50% in Pheochromocytoma, 20% in renal cell tumor, and 20% in thyroid cancer (Tables 1 & 2).

Table1. The impact of *SDH*, *FH*, and *IDH* in different cancers.

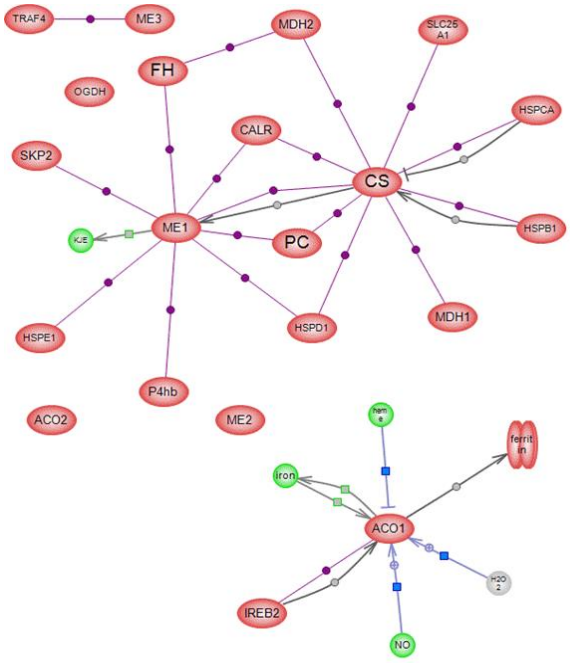
Gene	Number of articles	Percentage
SDH	20	90%
FH	11	50%
IDH	7	31%
	22	

Table 2. The impact of *SDH*, *FH*, and *IDH* in some disorders

Gene	Disorder	Percentage
SDH	Tumorigenesis	65%
	Li-Fraumeni Syndrome	60%
	Pheochromocytoma	50%
	Renal cell cancer	20%
	Thyroid cancer	20%
FH	Hereditary Tumors	45%
	Tumorigenesis	36%
	Leiomyoma	18%
	Leiomyosarcoma	36%
	Renal cell carcinoma	36%
IDH	Tumorigenesis	42%
	Glioblastoma	85%
	Acute myeloid leukemia	71%

Network analysis of krebs cycle genes and cancers showed that genes *FH, CS, MDH, ACO* have been linked to cancer in 27 cases (shape 1).

Although the warburg effect demonstrates the modified cancer metabolism, the changes in metabolic genes that could cause a direct genetic link to altered metabolism were not known until the identification of mutant TCA cycle enzymes that have been associated with familial cancer syndromes. Specifically, mutations in *fumarate hydratase* were discovered to exist in families suffering from leimyomatosis and kidney cancers, and mutations in *succinate dehydrogenase* were discovered to exist in patients with pheochromocytoma and paragangliomas. These mutations would cause a disruption of the TCA cycle with the accumulation of fumarate or succinate, both of which can inhibit *dioxygenases* or *prolylhydrolases* that mediate the degradation of *HIF* proteins. The elevation of *HIF* proteins as a consequence has been likely to be pro-oncogenic, but it has also been notable that these carboxylic acids can also affect dioxygenases that are involved in epigenetic modulation.[5]



Shape 1. Network analysis of the relationship between genes and cancer Krebs cycle

Paraganglioma are typically benign tumours derived from neuronal ectoderm cells along the sympathetic or parasympathetic nervous systems. In 2000, Baysal et al found that the gene which was mutated in a special HPGL syndrome related to the 11q23 locus (PGL1) was in fact *SDHD*.[6] Mutations in the SDH tumour suppressor genes were related not only to the familial syndromes but were also observed in sporadic paraganglioma and in phaeochromocytoma, which has been a subtype of paraganglioma obtained from catecholamine-secreting chromaffin cells, usually in the adrenal medulla. The point that the loss of function of the *SDH* complex was greatly related to paraganglioma, despite the *SDH* subunit involved, indicated that due to these mutations, tumorigenesis was generated from a common biochemical pathway. This point can be admitted by the observation that mutations in either *SDHB* or *SDHD* would cause the *SDH* complex to be disintegrated and *SDH* enzymatic activity to be completely lost. However, a closer examination of the genotype–phenotype link revealed several differences between the different *SDH* genes. *SDHC* mutations or deletions have been rare, and have so far been associated only with familial and sporadic head and neck paraganglioma. In addition, two thorough comparison studies of tumours with *SDHB* or *SDHD* mutations were conducted and various discernible differences were found. It can be noted that *SDHD* mutations have been majorly associated with head and neck paraganglioma, whereas *SDHB* mutations can be observed at higher frequencies in adrenal and extra-adrenal

phaeochromocytoma as well as in non-paraganglioma tumours. *SDHB* mutations have also been related to higher occurrence of malignant and metastatic tumours like malignant phaeochromocytoma and, in some cases, renal cell carcinoma.
The molecular mechanisms by which *IDH1* and *IDH2* mutations contribute to tumorigenesis are still under the investigation, as there is a possibility that these mutant enzymes may be useful targets for therapy. However, *IDH1* and *IDH2* mutations are vividly strong drivers of glioma and AMl, they sound to be rare or absent in other tumour types.

Results

The result of meta analysis demonstrated that *SDH* gene had the greatest influence on tumorigenesis and they also had the most important role in cancers. It seems that the role of krebs cycle genes is high in cancer, because of their high energy needed for growth and cell proliferation.

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