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MITOCHONDRIAL CYTOCHROME C OXIDASE AND SUCCINATE DEHYDROGENASE: EMERGING BIOMARKERS IN CANCER

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ABSTRACT: Mitochondria, renowned as the cell's "powerhouse," plays a pivotal role in cellular metabolism, influencing various physiological and pathological processes, including cancer initiation and progression. This review delves into the significance of mitochondrial enzymes, specifically Succinate Dehydrogenase (SDH) and Cytochrome c Oxidase (CcO), in cancer biology. Alterations in these enzymes' activity and expression levels are associated with changes in cellular energetics, oxidative stress and apoptotic pathways, contributing to tumorigenesis. Mutations in SDH subunits are linked to various cancers, particularly paraganglioma, and pheochromocytoma, while decreased CcO activity correlates with cancer development and progression. Experimental evidence, including studies on DBN-treated mice, demonstrates a significant decrease in SDH and CcO activities in cancerous tissues compared to controls, underscoring their potential as diagnostic and prognostic biomarkers. The review also discusses challenges and future directions in utilizing these mitochondrial enzymes as cancer biomarkers, emphasizing the need for further research to enhance their clinical applicability. In conclusion, understanding the roles of SDH and CcO in cancer metabolism offers promising avenues for advancing cancer diagnostics and therapeutics.

INTRODUCTION: The mitochondrion, often dubbed the cell's "powerhouse," generates over 90% of the adenosine triphosphate (ATP) required by cells. Recent research highlights mitochondria's pivotal role in regulating diverse physiological and pathological processes within human cells, including cell survival, proliferation, and migration, as well as their involvement in tumor initiation, progression, and metastasis [1-3].

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Mitochondria serve as targets and feedback hubs for various regulators of energy metabolism. Studies have verified that aberrant amino acid, fatty acid, and glucose metabolism are prevalent during tumorigenesis [4], tightly linking abnormal mitochondrial metabolism to cancer cell proliferation, metastasis and survival.

Additionally, mitochondria serve as the primary source of reactive oxygen species (ROS) within cells, with mounting evidence indicating that ROS dysregulation drives malignant tumor progression [5]. Functioning as crucial regulators of apoptosis, mitochondria bolster cancer cells' antiapoptotic defenses, fueling rapid cancer cell proliferation [6]. Furthermore, as integral components of

intracellular calcium pool regulation, mitochondria govern intracellular calcium homeostasis *via* diverse calcium transport systems on mitochondrial membranes. Disruptions in mitochondrial calcium homeostasis are intricately linked to mitochondrial dysfunction and tumor development [7].

Mitophagy, a selective autophagy process targeting mitochondria, stands out as a vital mechanism for maintaining mitochondrial homeostasis [8, 9]. Its implications extend to various diseases, including cancers, neurodegenerative disorders, and immune conditions [10-12]. Consequently, mitochondria are deeply entwined in processes such as tumorigenesis, proliferation, invasion and metastasis, emerging as a focal point in cancer research.

Cytochrome c Oxidase, the terminal oxidase in the electron transport chain and Succinate Dehydrogenase, a critical enzyme in the Krebs cycle and electron transport, are pivotal for mitochondrial function. This section sets the stage by highlighting the importance of mitochondrial enzymes in cellular metabolism and introduces Cytochrome c Oxidase and Succinate Dehydrogenase as potential cancer biomarkers. In addition to mutations that directly affect mtDNA, mutations in nDNA-encoded mitochondrial enzymes have been found in specific cancers.

Succinate Dehydrogenase in Cancer: This section delves into the role of Succinate Dehydrogenase in cellular energy metabolism and its implications in cancer biology. It discusses studies indicating alterations in SDH activity in cancer cells and how these changes relate to cellular energetics and the Warburg effect. Additionally, it explores the association of SDH mutations with various cancer-related syndromes, highlighting the enzyme's potential as a diagnostic marker. One of the enzymes that play a major role in the citric acid cycle is succinate dehydrogenase, which oxidizes succinate to fumarate. The SDH complex is the connecting enzyme between the TCA cycle and the ETC. It is also known as succinate: ubiquinone oxidoreductase or mitochondrial complex II. With four subunits, the enzyme is heterotetrametric. The hydrophobic membrane-anchoring subunits SDH-C and SDH-D are also implicated in ubiquinone binding for ETC processes, whereas the two catalytic subunits are the flavoprotein SDH-A and the iron-sulfur protein SDH-B [13]. Mutations in SDH subunit A lead to progressive necrotic lesions, which in turn induce ocular atrophy or Leigh syndrome in the elderly. The paraganglioma components B, C, and D are linked to mutations and the pheochromocytoma subunits B and D with significantly decreased tumor SDH activity (B and D are also linked to papillary and medullary thyroid cancer). Two SDH assembly factors, SDHAF1 assembly factor and SDH5 assembly factor, have been linked to further mutations that cause paraganglioma and infantile leukoencephalopathy [14].

Because of the reduced electron flow, increased oxygen toxicity and accumulated succinate, altered SDH activity may contribute to the development of disease and cancer. The regulation of SDH activity plays a crucial role in the buildup of succinate. Notably, the presence of a mutation in the gene responsible for encoding SDH in certain cancer types has been observed to diminish SDH activity, resulting in succinate accumulation and subsequent augmentation of mitochondrial ROS generation [15].

Due to the various subunits within the SDH complex, the difference in functionality can be responsible for these metabolic changes. SDH can be influenced by non-coding RNAs that are regulated by RNA-editing and RNA-modifying enzymes as well as transcription factors that have been found to contribute to various cancers. Early research connected the malfunctioning of the SDH complex with cancer, as demonstrated by studies demonstrating that mutations in the SDHB, SDHC, and SDHD enhanced the generation of superoxide anion (oxidative damage), which caused cells to undergo apoptosis or transformation. The accumulation of succinate leads to increased histone methylation *via* binding directly and inhibiting histone demethylase JumonjiD3, which enhances epigenetic changes and oncogenic transformation [16].

Numerous investigations have demonstrated that succinylation can occur in organisms through both enzymatic and non-enzymatic means. In fact, the majority of is known to occur through non-enzymatic processes, as extensively documented in the literature [17, 18, 19] particularly by Matthew D

Hirschey *et al.*, who have demonstrated the higher chemical reactivity of succinyl-CoA compared to other acyl-CoA species [20]. Two rare tumors in the autonomic nervous system called paraganglioma (PGL) and pheochromocytoma (PCC) have been linked to specific genetic mutations in SDHB [21], SDHC [22] and SDHD [23]. These mutations are known to increase ROS production[24], which causes DNA damage and tumorigenesis [25].

PCC and PGL have been demonstrated to be caused by mutations in all four subunits of SDH-encoding genes, which impede the histone demethylation route [26]. Studies also revealed that SDHB mutations were more effective in blocking histone methylases, hence facilitating elevated levels of hypermethylation [26]. Despite evidence indicating that SDHAF2 does not cause PGL and PCC through the suppression of histone demethylation [26], mutations of SDHAF2 alone have been associated with PGL and PCC [27]. It is noteworthy that PGL and PCC are the tumor types most frequently linked to inheritance and germline mutations, particularly in the SDH subunits [28]. This emphasizes the dynamic role that somatic and germline mutations within the SDH complex play in the development of cancers, and emphasizes the significance of genetic counseling for the former.

While SDH mutations are most frequently linked to PGL and PCC, they can also cause other malignancies through decreased SDH activity or mutations in SDH. As an example, ovarian cancer spread was aided by higher levels of HIF-1α and adenosine monophosphate-activated protein kinase resulting from SDHB silencing [29]. In another case, because of the Warburg effect and increased expression of markers linked to the epithelial-mesenchymal transition, the decrease in SDHB in hepatocellular carcinoma exacerbated its malignancy [30]. Studies have shown and linked SDHB loss in hemangioblastoma [31], SDHB deficiencies in pituitary adenomas [32] and SDHB and SDHD mutations in thyroid malignancies and renal cell carcinoma [33]. The cerebral IR injury results in the ischemic accumulation of succinate, which subsequently induces Cdc42 succinylation and inhibits the proliferation of neural stem cells [34]. The significance of succinate and SDH's involvement in the pathogenesis of IR injury underscores the potential of targeting succinate metabolism as a therapeutic strategy for the prevention and treatment of this condition [35]. The development of pharmaceuticals that specifically target succinate metabolism may offer a novel approach to address the clinical challenge posed by IR injury [15].

The process, known as aerobic glycolysis or the Warburg effect, occurs when cancer cells use this fermentative metabolism more frequently even when oxygen is present. Protumoral signaling pathways are activated, molecules that promote cancer progression are produced, and increased glycolytic rates, which enable cancer cells to obtain higher amounts of total ATP, are the primary characteristics of this alternative metabolism. Succinate, a Krebs cycle intermediate whose concentration is increased in cancer and is considered an oncometabolite. Several protumoral actions have been associated with succinate [36].

In a study carried out by us, the activity of the succinate dehydrogenase (SDH) was determined in N. Nitrosodibutyl amine (DBN) treated mice liver mitochondria and compared with normal control mice liver mitochondria. Swiss albino mice (BALB/c) bred by random breeding at the animal house of the department were kept on basal diet ad libitum in plastic cages at the temperature-controlled animal room (21 ± 2°C) with a 12 hour light and dark cycle. At the start of the experiment, the mice were 6-8 weeks old weighing around 22-25 gm in weight. The sex chosen for the experiment was female. Cancer induction was done by giving a weekly dose of 10 mg per kg body weight of N-Nitrosodibutylamine (DBN) in 5% ethanol was administered intravenously in healthy female mice of 6-8 weeks old weighing around 22-25gm for a period of 16 weeks and sacrificed at the end of treatment as required. Age-matched sham-treated mice served as control. All animal procedures were performed according to the approved protocol and by recommendations for the proper use and care of the laboratory animals. The progress of carcinogenesis was followed by monitoring the level of marker enzyme activities such as GGT, AChE, GST in DBN-exposed mice and the values were compared with untreated normal control mice. Liver function tests i.e. SGOT, SGPT, ALP and histological examination of liver tissues were also carried out.

The results of marker enzyme assays, liver function tests and histological examination of the liver tissues confirm that i.v administration of DBN (10 mg/kg body weight) in 5% ethanol as a promotor may be used to successfully induce liver cancer in Swiss albino mice. After the successful induction of cancer in liver by DBN, our main target of interest was to observe whether DBN inflicts any alteration to the liver mitochondrial enzymes or not or not. Intact liver mitochondria were isolated as per the method described. Briefly, mice were starved overnight, killed by cervical dislocation and liver was rapidly explanted from the peritoneal cavity. The tissue was immersed in 50 ml of ice-cold isolation buffercontaining10 ml of 0.1M Tris–MOPS, 1.0 ml of EGTA/Tris and 20 ml of 1 M sucrose, pH7.4 and washed several times until the blood washed out completely from the tissue. It was minced into small pieces using scissors in an ice bath. Minced tissue was transferred to the glass homogenizer tube and homogenized using a Teflon pestle operated at 1,600 rpm. Homogenate was then transferred to a 20 ml tube and centrifuged at 600 x g for 10 min at 4°C. The supernatant was transferred to another tube and centrifuged at 7,000 x g for 10 min at 4°C. The supernatant was discarded and the pellet re-suspended in 5 ml of ice-cold isolation buffer and centrifuged again at 7,000 x g for 10 min at 4°C. The supernatant was again discarded and the pellet, containing mitochondria was re-suspended in 5 ml of ice-cold fresh isolation buffer and stored on ice.

To check the level of SDH activity in the sample the method described was followed.

In brief, the following reagents

- 0.2M Phosphate buffer pH 7.8
- 0.6 M Succinic acid pH 7.8 (pH adjusted with NaOH)
- 0.0015 M DCIP
- 0.009 M PMS in distilled water
- 0.045 M KCN (freshly prepared)

were taken in a 3ml spectrophotometer glass cuvette.0.75ml of 0.2 phosphate buffer pH 7.8, 0.10ml of 0.045 KCN, 0.2ml of 0.6M succinate, 0.1ml of 0.0015M DCIP and 0 to 6ml of 0.009M PMS. The final volume was made up to 2.95ml with distilled water. The reaction was started by the addition of 0.05ml of the enzyme prepared (isolated mitochondria). The amount of the enzyme that was added such that it produced an absorbance change of between 0.05-0.20 per minute. The change in OD (Δ 600nm) against water blank was recorded after 5 seconds.

A significant decrease in the activity of SDH enzyme was seen in the case of the DBN-treated mice as compared to that of the normal control mice as shown in **Table 1**. The decrease in the activity of this enzyme shows the lack of the SDH enzyme in the mitochondria as the destabilization of the SDH protein complex. As this enzyme plays and important role in ETC and oxidative phosphorylation so decrease in the activity of this enzyme indicates the depleted use of oxidative phosphorylation for ATP synthesis supporting the Warburg hypothesis.

TABLE 1: SUCCINATE DEHYDROGENASE ACTIVITY IN SHAM-TREATED AND DBN-TREATED LIVER MITOCHONDRIA. (**P<0.0001, n=10).**

Groups	Specific Activity (U/mg protein) Mean ± SEM, n=10
Control	2.434±0.05613
Treated	1.2689±0.009215

Cytochrome c Oxidase in Cancer: Here, the focus shifts to Cytochrome c Oxidase and its involvement in mitochondrial energy production and apoptotic pathways. The review discusses research showcasing alterations in Cytochrome c Oxidase activity in cancer cells and its correlation with p53 regulation and mitochondrial physiology. The section also explores how mutations affecting Cytochrome c Oxidase function may contribute to cancer development or progression.

Mitochondrial cytochrome c oxidase (CcO) is a key enzyme involved in the electron transport chain and oxidative phosphorylation within the mitochondria. Emerging evidence suggests that alterations in mitochondrial function, including changes in cytochrome c oxidase activity, are associated with cancer development and progression. Mitochondrial dysfunction and Cancer is one of the most complex and diverse diseases on the planet. It is caused by uncontrolled cell proliferation and

invasion of surrounding tissues. The intricate and varied collection of disorders known as cancer is typified by the uncontrolled proliferation of cells and the capacity to infiltrate surrounding tissues. It is essential to comprehend the molecular processes that underlie the onset and spread of cancer to enhance prognoses, treatment options and diagnostics. The significance of mitochondrial dysfunction in cancer has garnered more attention in recent years, with a particular emphasis on mitochondrial cytochrome c oxidase (CcO) as a newly discovered biomarker. The relevance of mitochondrial CcO in cancer is examined in this essay, along with its potential as a biomarker and its consequences for diagnosis, prognosis, and treatment options. CcO, a key enzyme in the mitochondrial respiratory chain, is responsible for the final step in electron transfer to oxygen, contributing to ATP synthesis and cellular energy production. Recent investigations have highlighted the link between CcO and cancer, suggesting that alterations in its activity and expression levels may play a critical role in carcinogenesis [37].

Extensive study on cyt c throughout the decades has provided essential knowledge not just into mitochondrial respiration [38, 39], but also into apoptosis [40, 41], a type of programmed cell death. Proapoptotic stimuli cause the mitochondrial outer membrane to permeabilize, resulting in the outflow of cyt c from the mitochondrial intermembrane gap to the cytoplasm [42]. In the cytoplasm, cyt c attaches to apoptotic protease-activating factor-1 (Apaf-1) [43] triggering a series of biochemical processes that activate caspases, a type of proteases that carry out apoptosis by destroying cellular components [44, 45].

Apoptosis is a significant mechanism in cancer. First, it is generally inhibited in cancer cells [46]. Second, the induction of cancer cell apoptosis has outstanding therapeutic potential [47]. Cytochrome C (Cyto C) is a critical molecule in mitochondria-induced apoptosis, as well as a key component of energy metabolism and the respiratory chain [48, 49]. Mitochondrial Cyto C has been shown to play a dual role in energy metabolism and apoptosis. Liu *et al.*[50] first proposed that Cyto C has a role in apoptosis. Once released into the cytoplasm, Cyto C interacts with its adaptor molecule Apaf-1 to activate pro-caspase-9 in the presence of ATP or dATP. Caspases-9 and 3 are triggered by active caspase-9, leading in the intrinsic mitochondrial route to apoptosis [51]. The release of Cyto C from the mitochondria into the cytoplasm is the vital initial stage in the apoptotic process. Cyto C, as a component of the mitochondrial electron transport chain, facilitates electron transfer between complex III (ubiquinol: Cyto C oxidoreductase) and complex IV (cytochrome oxidase) [52]. Cyto C is a mitochondrial biomarker that is released into the extracellular space and blood within 1 hour of apoptosis caused by permeabilization of damaged mitochondria [53]. As a result, Cyto C is recognized as a crucial mediator and biomarker of mitochondria-mediated apoptosis.

A high cytochrome C level of up to 190 ng/mL increases the risk of a heart attack, systemic inflammatory response syndrome, influenza-associated encephalopathy, chronic hepatitis C, and myocardial infarction **Fig. 1** [54]. All of these findings highlight the necessity for determining cyt c quantities in serum samples for the early detection of a variety of illnesses. Reactive oxygen species (ROS) formed as a result of oxidative stress resulted in continuous changes in DNA sequences, responsible for mutations, gene amplifications, deletions, and gene rearrangements, which eventually cause degenerative changes that lead to tissue degradation, responsible for aging, and also acts as a hallmark of cancer. Cyt c provides intense knowledge about apoptosis extent, medical diagnostics, various pathologies, and therapeutic treatment [54].

Detecting changed CcO activities in biological materials (such as blood or tissue) has enormous promise as a biomarker for cancer diagnosis. Monitoring CcO levels can reveal valuable information about the presence of cancer. It can also provide information about the tumor's features, allowing for earlier discovery and tailored therapy.

Similarly, the cytochrome c oxidase activity was monitored after 16 weeks of N, Nitrosodibutyl amine (DBN) treatment and compared to normal control mice. The activity of this mitochondrial enzyme was assayed using the kit from Sigma-Aldrich. This enzyme is located on the internal mitochondrial membrane that divides the mitochondrial matrix from the intermembrane and it has been used for many years as a marker for the

mitochondrial membrane. 0.95ml of 1X Assay buffer was added to a cuvette and the spectrophotometer was zeroed. 30µl of enzyme preparation was added to the cuvette and the final volume was made to 1.05ml with enzyme dilution buffer. The reaction was started by adding 50µl of ferrocytochrome c substrate solution and mixed by inversion. The absorbance was read at 550 nm.

A significant decrease in the level of the activity of the enzyme was observed in the case of DBN-treated mice as compared to that of the age-matched normal control mice as shown **Table 2**. Our study, showed a drastic decrease in the activity of the cytochrome c oxidase in the DBN-treated mice as compared to control mice indicating a resultant decrease in the activity of this enzyme due to change in cytochrome c oxidase subunits adjustment by the Bcl-2 during carcinogenesis stress brought by DBN. This change had a significant impact on the decrease of the cytochrome c oxidase activity and maintenance of mitochondrial ROS levels.

TABLE 2: CYTOCHROME C OXIDASE ACTIVITY IN SHAM-TREATED AND DBN-TREATED LIVER MITOCHONDRIA (**P<0.0001, n=10)**

Groups	Specific Activity (U/mg protein) Mean ± SEM, n=10
Control	0.35058±0.007748
Treated	0.077996±0.000588

The significant decrease in the enzyme activities of SDH and COX in DBN-treated liver mitochondria compared to sham-treated control relates to the proliferation of tumor formation and depleted use of oxidative phosphorylation in ATP production.

Implications for Cancer Biomarkers: Bringing the discussion together, this section consolidates the findings on Cytochrome c Oxidase and Succinate Dehydrogenase alterations in cancer. It emphasizes their potential as biomarkers, highlighting the significance of measuring their activity or expression levels in cancer diagnosis, prognosis, or therapeutic monitoring. Additionally, it addresses the challenges and future directions in utilizing these mitochondrial enzymes as biomarkers in clinical settings.

CONCLUSION: The conclusion summarizes the key insights gained from exploring Cytochrome c Oxidase and Succinate Dehydrogenase as potential biomarkers for cancer. It underscores their importance in mitochondrial function, their alterations in cancer cells, and the promising avenues for further research and clinical applications in cancer diagnosis and treatment monitoring.

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