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Succinate as an Oncometabolite in Endocrine, Mesenchymal, and Epithelial Tumors

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Abstract

Succinate dehydrogenase (SDH) is a multifaceted enzyme for the mitochondria of eukaryotes, which is responsible for converting succinate to fumarate as a component in the Krebs cycle. Its dysfunction occurs in several malignancies associated with endocrine and epithelial tumors. SDH is an enzymatic complex made of some subunits. Succinate is recognized as an oncometabolite; therefore, the discovery of SDH mutations can give a straight connection between the changes of succinate and tumorigenesis. Progresses in laboratory technologies made it possible to make profiles of and identify succinate accumulation in several types of cancer. In this study, we reviewed the potential roles of SDH mutation and alteration of succinate in tumorigenesis and as tumor markers for the early detection of malignancies.

Keywords: Endocrine, Epithelial, Neoplasm, Oncometabolite, Succinate, Succinate dehydrogenase

1. Background

Tumorigenesis is a progressive process related to a series of genetic and epigenetic changes in the neoplastic cells (1). It is well recognized that disarrays in mitochondrial function are related to exceptional infancy diseases and maybe to numerous general disorders of the elderly, including Parkinson's disease and dementia. Moreover, there is a large amount of data connecting mitochondrial dysfunction with tumorigenesis (2). Therefore, a deficiency in the cycle of Krebs has been tested to engage the neuromuscular systems and exhibit early phase symptoms. Mitochondrial dysfunction is the reason for neurological impairments and tumors (3). Cancer cells reveal significant changes in some metabolic ways consisting of glucose carrying, a cycle of the tricarboxylic acid (TCA), lysis of glutamine, oxidatiation-phosphorylation in mitochondria, and pentose-phosphate pathway (4). The mitochondrial pathways and succinate dehydrogenase (SDH) functions are important for regulating reserve respiratory capacity, cell survival, and wound healing (5, 6). Typical changes in the metabolism of tumor cells have been shown on energetic pathways mainly on increased lysis of glucose and concealed oxidation-phosphorylation (Warburg effect) (7). Furthermore, neoplastic cells have enlarged metabolic stresses with impaired glucose or glutamine metabolic pathways. Glucose produces glycolytic intermediates, while glutamine produces TCA cycle agents to cooperatively make adenosine triphosphate (ATP) and others (8). It has been found that SDH has a significant function in the cycle of citric acid and carrying electron chain, as well as the most important role in mitochondria. SDH is also critical for oxidative phosphorylation (9) and binds to mitochondria on the inner side of the membrane, which is a multi-metric enzyme (10). Therefore, SDH is recognized as a mitochondrial multifaceted enzyme, which is engaged in the transport of electrons and the cycle of Krebs. SDH includes four units, namely SDHA, SDHB, SDHC, and SDHD, each of which is expressed on three different chromosomes by autosomal genes (11). The products of SDHA and SDHB attach the drives of SDHC and SDHD, which produce the metabolic center in the inner membranes of mitochondria (12). SDH needs two cofactors, including SDHAF1 and SDHAF2, whose function is a NAD-dependent deacetylase sirtuin-3 deacetylation (13). SDHA and SDHB are implicated in the oxidation and transfer of electrons. The *SDHB* gene is placed on the short arm and the *SDHC* gene on the long arm of chromosome 1. The *SDHD* gene is located on the long arm of chromosome 11, and *SDHA* is on the short arm of chromosome 5 (14). Cancer-related FH and SDH mutations, which concentrate fumarate and succinate, respectively, have principal roles in α-ketoglutarate dependent dioxygenases inhibition and methylation of histone and DNA (15). In spite of the fact that genetic and epigenetic alterations in human neoplasms need specific molecular probes, and high throughput molecular sequencing techniques, pathology, and immunohistochemistry (IHC) are still vital components of laboratory testing (16-18). Therefore, SDH and FH mutation cause an increased accretion of

succinate and fumarate resulting in α-ketoglutarate dependent dioxygenases inhibition, composed of demethylases of histone and the hydroxylases of 5-methylcytosine (19). Succinate and fumarate can have concentrations up to milli-molar levels in tumors with SDH and FH mutations of about 400-500 μm (20). Succinate or fumarate concentrated mitochondria will lead to the dysfunction of SDH or FH, release into the cytosol, and is reason of reduction of prolylhydroxylase (PHDs). By the reduction of the PHD, recently known ways that sustain cancer preservation could possibly be followed: no response of cancerous cells to apoptosis signal and active response to hypoxemia condition that increases the lysis of glucose (21). SDH encoded by nuclear and mitochondrial DNA and mutations have been related to tumor predisposing or cancer progress (22). Additionally, modifications after translation, including phosphor and acetyl addition, have been revealed to alter SDH action (23). Krebs cycle enzymes gene mutations are the reason for cell energy dysfunction, chromatin changing, DNA methylation, and the production of species of reactive oxygen (24). In addition, the accretion of these metabolites in cancerous cells can be due to the transition of epithelial cells to mesenchymal cells, even though the precise mechanisms are indescribable (25). Totally, succinate is due to the reduction of demethylase, which is implicated in the demethylation of histone, owing to another epigenetic change (26-28). Moreover, DNA hypermethylation was related to dedifferentiation and amplified progression in SDH-mutated tumors (29). There are insufficient data indicating that mitochondrial dysregulation is the definite reason for the metabolic change in neoplasm and tumorigenesis (30). Therefore, high levels of succinate followed by fumarate on SDH and FH mutations can encourage tumorigenesis in components throughout epigenetic modulation (31). SDH mutation is the reason for the increased concentration of succinate that hinders hydroxylases and the establishment of hypoxia-induced factor 1α (HIF-1α). These outcomes demonstrated the existence of a relationship between SDH mutation and HIF-1α stimulation, causing a clarification for the great tumors with high vascular that extend in the lack of Von-Hipple-Lindau (VHL) mutations (32). The following recognition of mutation in other mitochondrial enzymes, including fumarase in the inherited form of kidney, skin, and uterine, has described the potential function of mitochondrial enzyme mutation in cancers (33). These findings have revealed that SDH dysfunction is oncogenic due to causing the protection of tumor cells from hypoxia (34). Mutations in enzymes, including SDH, that are involved in succinate-related pathways cause a variety of pathologies, including tumor development and innate inflammatory responses (35). Furthermore, it must be noted that succinate by HIF-1α in precise cancers leads to macrophage activation and dendritic cell stimulation (36).

2. Succinate as an important oncometabolite

Recognition of tumors related to genes programming mutation, mainly mitochondrial enzymes, has revealed a straight association between distorted metabolism and tumorigenesis. Furthermore, new advanced technologies have recognized metabolite in tumor cells with high resolutions, which are known as the accretion of metabolites related to defects in specific genes (37). Metabolites whose abnormal accretion is due to mutation in mitochondrial enzymes have a potential change to tumorigenesis, known as "oncometabolite" (37). Oncometabolite is a quite novel word that relates to metabolites, which have plenty of high distinction in tumors. This term is kept for metabolites since there is an obvious mechanism related to a definite mutation in the neoplasms to the accretion of the metabolite, and there are convincing data for the contribution of the metabolite in the development of tumors (38). These mutations are identified by various types of neoplasm consisting of paragangliomas, renal tumors, myomas, gliomas, and acute myeloid leukemia. Due to the accretion of oncometabolite, which acts as a competitor of 2-oxoglutarate-dependent dioxygenases, it was implicated in an extensive variety of pathways including response to hypoxia and reprogramming of epigenetics (39). The succinate can be entered easily into the mitochondria and accretion (40). Therefore, distorted metabolism is commonly recognized as a characteristic marker of tumor cells, and the consequential increase in the level of oncometabolite is due to the dysfunction of metabolism and it has important potential for conversion to cancer (41). In addition to that, metabolites can encourage tumorigenesis by changing the epigenome, which has been recognized. These 'oncometabolites' are composed of succinate, and fumarate increased in certain neoplasms with SDH and FH mutations, respectively (42). Oncometabolites can act as an oncogenic factor by changing cell signaling and stopping cellular differentiation (31). However, mutations in isocitrate dehydrogenases (IDH), SDH, and FH that generate oncometabolites competitively reduce epigenetic instructions (43). Oncometabolite-determined tumorigenesis has recently gained attention with the identifications of SDH, IDH, FH, and malate dehydrogenase mutation that links the mitochondrial enzymes to tumorigenesis (Figure 1). It is supposed that oncometabolite could support the enzymatic pathways reprogramming and the production of neoplastic cells with discriminating compensation (44). Oncometabolites are considered important findings in the relationship between the

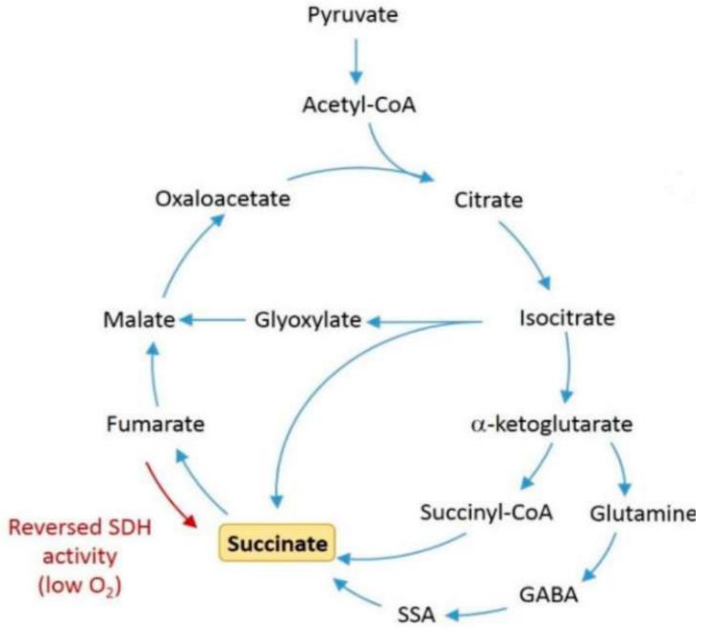

Figure 1. Succinate is an oncometabolite produced from the alteration of succinyl-CoA, oxidization by succinate dehydrogenase to produce fumarate. (SSA: Succinic semialdehyde; GABA: γ-aminobutyric acid)

nucleus and mitochondria. Long-time accretion of this oncometabolite stimulated by hereditary or ecological factors may probably change the epigenetic setting of the cell resulting in oncogenic signaling events (29). As a result, based on these mechanisms of metabolic dysregulations in tumoral cells, owing to the consequences of mitochondria and oncometabolite on tumor metabolism, new adjuvant therapies can be improved to reach better malignancy treatments (44).

3. SDH mutation in cancers

Endocrine neoplasms are arising from endocrine organs consisting of the pituitary gland, thyroid, parathyroid, adrenal, and pancreas (45-47). Furthermore, mutations of genes concerned in the mitochondria, composed of FH, SDH, and IDH, are mainly related to hereditary cancer syndrome or glioma and acute myeloid leukemia (48). Although they are portions of the mitochondrial enzymes, the consequential clinical manifestations are not considered. SDH mutation shows hypoxia pathway activation, and FH and IDH mutations show tumor development by suppressing cellular differentiation (49). Therefore, SDH is one of the first mitochondrial enzymes to be concerned with the tendency of familial cancer as a driver of genetic alteration (50). This finding is unpredicted because it was formerly considered that mitochondrial disorders were the only reason for neurodegenerative diseases composed of Leigh syndrome due to SDHA mutations or other encephalopathies with a variety of intensities and occurrences. It is also recognized that FH mutation, which catalyzes the conversion of fumarate to malate in the Krebs cycle, prompts hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome, which contains skin involvements and leiomyoma of uterine and kidney tumors (39). Outcomes of SDH and FH mutations in a Krebs cycle inhibitor involve atypical accretion of their substrates, including succinate and fumarate, characterized by inhibition of 2OG-dependent dioxygenases and HIF activation, respectively, and by increased angiogenesis and high anaerobic metabolism in tumor cells (51). These tumors initiate from genetic disorders of genes and are important for hypoxia pathways together with VHL and HIF or cellular metabolism including SDH (52). Consequently, Krebs cycle dysfunction with the accretion of oncometabolite is the reason for 5-methylcytosine dioxygenase methylation inhibition (53, 54). SDH inhibition, on the other hand, helps neoplastic progression by HIF (34). Additionally, SDHA and FH mutations can cause encephalopathies with no evidence of malignancy (55). SDHB mutations are commonly found in some cancers and are related to bad outcomes in these patients (56). SDH mutations have been recognized in certain tumors, both hereditary and sporadic, including familial paraganglioma/pheochromocytoma, ovary, kidney, thyroid, and testis tumors, neuroblastoma, and gastrointestinal stromal tumor (57, 58). SDH-mutated pituitary adenomas can have larger sizes, and there is a higher chance for prolactin production than other pituitary tumors (59). Moreover, high levels of succinate have been recognized in patients with malignancy (60). Succinate- or fumarate-mediated inhibition represents new treatment opportunities for the tumors related to the altered

Krebs cycle (61). FH and SDH mutation act as major characteristics in tumorigenesis and consist of pseudohypoxia, dysfunction in mitochondria and apoptosis impairment, oxidative stress, and anabolic ways (62). Immunohistochemistry (IHC) for SDHB is consequently known as a practical means to distinguish these distinctive cancers determined by mitochondrial enzyme mutations and to choose proper genetic testing for the related diseases (63). Therefore, it is crucial to distinguish and characterize SDH-mutated cancers because they have syndromic nature and familial predisposition (64).

4. Neuroendocrine tumors

Pheochromocytomas (PCCs) and paragangliomas (PGLs) are neural crest-originated neoplasms, which happen from VHL, SDHB, SDHC, SDHD, and other gene mutations (65). PGLs are recognized as neuroendocrine tumors originating from chromaffin cells placed close to the root of inferior mesenteric artery. In addition, these tumors develop with mutations predominantly in SDHB, C, and D (66). The identification of these tumors is regularly established by measuring the catecholamines or the levels of their metabolites in blood or urine. The only important and reliable marker for malignancy in PCC is the occurrence of metastasis (67). Nevertheless, based on the fact that PCC is related to the rise of catecholamines in blood or urine, some patients have no symptoms; hence, the diagnosis of PCC may be difficult (68). Mutations in SDHD are the mainly well-known reasons for PGLs in the head and neck, while mutations in SDHB are mainly correlated to adrenal and extra-adrenal PCC as well as malignant disease. In contrast, malignant PGLs have only been related to SDHD mutations (69). SDHB mutated tumors present with a vaguely elevated incidence of bone involvement and operation (70). Moreover, using molecular testing, it is possible to discover SDHB gene deletion in malignant PGLs in whom early recognizable SDHB mutations were faint (71). Furthermore, SDHB-related endocrine neoplasms can be more susceptible to specific adjuvant therapy and may possibly have a better prognosis if this treatment is advised (72).

5. Gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) originate from the pacemaker cells, and 85-90% of patients are determined by tyrosine kinases (*KIT*) or platelet-derived growth factor receptor alpha (PDGFRA) mutations. SDHB mutation and impaired cellular respiration may have essential roles in oncogenesis in GISTs without KIT mutation (73). Genotyping GISTs has turned into an extra significant issue because not all genotypes react similarly to tyrosine kinase inhibitors (74). SDH-mutated GISTs are a recently accepted subtype of GISTs presented with a lack of SDHB staining on IHC (75). However, there is a subtype of GISTs with a lack of KIT or PDGFRA mutations that preserves a nonmutated SDH (76). Furthermore, SDH-mutated GISTs are recognized to be nonmutated KIT or PDGFRA, and most of the patients involved in this subtype of GISTs are juvenile. Some of these patients have shown SDH mutations, which are identified as Carney-Stratakis syndrome mostly accompanied by PGL (77). In addition, the patients with SDH-mutated GISTs who lack SDH mutations are identified by methylation of the *SDH* gene (78). As a result, SDH-mutated GIST is mostly observed in adolescent women with a discrete clinical presentation, commonly recognized by primary tumor site in the stomach, morphological findings of different epithelioid and spindle cells, and disperse IHC positivity for KIT, common lymph node involvement, and distant metastasis, as well as being revealed on gastrointestinal stromal tumors 1 (DOG1) (79). Moreover, SDH-mutated GISTs have distinctive morphologic findings consisting of multi-involvement of the gastric wall, commonly multiple dividing tumors, frequent lymphovascular invasion, and occasional lymph node metastases (80). Furthermore, the SDH-mutated GIST is identified by the increased insulin growth factor 1 receptor expression. Altogether, the main recurrent confident genetic findings discovered in SDH-mutated GISTs are germline mutations or somatic loss of function mutations (76). Patients with metastatic SDH-mutated GISTs containing mutated SDHA show a notably good outcome. These patients must be identified for conservative management and further therapies and followed up over time (81). The incidence of germline mutations might recommend that these involved patients must be evaluated for the possibility of progressing to further malignancies (76).

6. Renal Cell Carcinoma

Renal cell carcinoma (RCC) includes an assembly of tumors associated with their primary location of origin, the kidney (82). SDH-mutated RCC is newly known in the World Health Organization meeting (83). Recently documented epithelial renal cell tumors are classified as HLRCC syndrome-associated RCC, SDH-mutated-RCC, papillary RCC, clear cell RCC, and other types (84). SDH-mutated RCCs are infrequent, with a median age of 38-40 years. Characteristic histological presentations of these tumors include tubular, solid, or nested appearances with different cystic areas. Cells are predominantly eosinophilic cuboidal, have indistinguishable cell margins, and demonstrate inclusions in the cytoplasm (85). Oncocytic tumor cells with a solid structure, as well as intracytoplasmic inclusions admixed with mast cells between tumor cells, must be able to rapidly assess SDH condition, as it probably has clues for selecting the patient and family. The absence of KIT staining on IHC evaluation

and various other epithelial markers are extra consistent presentations (86). Although these tumors are mainly low-grade, some tumors may have progressive features, principally whether they have atypical nuclei and contain extensive necrosis or sarcomatoid discrimination (87). Particularly, it is advised to closely observe patients who are at risk for SDH mutation-related RCC and had undergone extensive resection (88). In addition, germline SDHB mutations are capable of triggering RCC with PGL and provide clues for close observations (89). However, SDHA mutations are due to strong neurology symptoms and cardiomyopathy, and SDHB and SDHD mutations seem to be due to PCC and PGL. About 1-5% of SDHB or SDHD mutation carriers have been established to show RCCs, which is another presentation of Codewn syndrome (11). Moreover, negative IHC for SDHB suggests mitochondrial dysfunction despite the subunit involved (90). The lack of SDHB staining recognizes neuroendocrine tumors linked with mitochondrial enzyme mutations and can be used to select proper patients for further evaluation and follow-up (63, 91). Thus, it is principally suggested that experts carry out molecular evaluations for suspicious PCC/PGL patients with a documented family record, advanced age, unpredictable increased hypertension, tumor recurrence, and especially SDHB and/or SDHD mutations (92). The occurrence of SDH mutations can highlight the fact that these patients must be closely observed for the possibility of progressing to further tumors (81). Germline testing is significant when SDH mutations are revealed because of specific management and observation strategies (90).

7. The oncometabolite succinate as a cancer biomarker

Oncometabolites are introduced as small molecules of standard metabolic pathways, whose accretion is due to signaling deregulation to find a situation that begins carcinogenesis (93). Succinate is critical in mitochondria for ATP production and is an essential metabolite in mitochondrial pathways. It is generally found at about 5 μM concentration in plasma, although in abnormal situations, it is concentrated in extracellular places. Therefore, elevated levels up to 150 μM have been recognized in plasma or urine in metabolic disorders (41). SDH mutation causes a considerable accretion of succinate, performing as an oncometabolite with elevated levels evaluated on surgically resected tissues, an extremely definite marker of SDH-mutated cancers. Finding succinate utilizing molecular tests for SDH-mutation detection is a highly sensitive and specific evaluation, and also a non-invasive approach (94). Medical laboratories have a significant responsibility to participate in the organization of oncometabolite-related tumors through the progression and confirmation of susceptible and precise ways, which determine oncometabolite. These tests can be used to select ways and for a follow-up to evaluate reactions to therapy. It must be noted that they are also used to discover any residual disease and recurrence (95). Succinate to fumarate percentage and other oncometabolites suggest a valuable manner to recognize patients with SDH mutations for genetic testing (96). Possible other benefits include non-invasive diagnosis tools and helping with disease categorization, as well as evaluation of cancer reaction to specific therapies (97). Therefore, metabolite measuring could convert various aspects of surgical care (98). The level of succinate in plasma is higher in patients with SDH-mutated tumors than in normal people (22). SDH mutations are recognized by low fumarate and malate levels as well as elevated succinate levels (99). Present results revealed a considerably high succinate-to-fumarate percentage in SDH-mutated PGLs for the first time, and therefore, it is recommended that this ratio be recognized as a novel oncometabolite indicator for the discovery of SDH-mutated PCCs/PGLs (100). These indicators are mentioned to be more delicate and precise for target therapy and have a better evaluation of the prognosis (101). In vivo revealing of succinate genetic testing could be carried out by describing SDH subunits of indefinite outcomes (in the lack of obtainable cancer section), and even optimizing a choice of correct therapy (102). A huge amount of preclinical information and accumulated clinical pieces of knowledge showed that some metabolic agents could be proficiently targeted to attain anticancer results in vivo. Therefore, an important relationship between the metabolism of the neoplastic cells and a therapeutic method is recognized for treating malignancy (103). Although at present, no therapeutic approaches straightly targeted SDH-mutated neoplastic cells, based on the mentioned explanations, there may be some chances to target SDH-mutated neoplastic cells that consist of the metabolism changes or epigenetics (104).

8. Conclusion

Detection of SDH mutations in endocrine-related tumors in addition to epithelial malignancies can not only highlight the impact of the genetic mutation on tumorigenesis but also indicate the oncogenic role of succinate as an oncometabolite. Advanced molecular technology could offer straight pathophysiological understandings of cancer metabolic pathways and serve as an exceptional means for cancer indicator detection.

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Footnotes

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