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REVIEW

The Impact Of *Succinate Dehydrogenase* Gene (SDH) Mutations In Renal Cell Carcinoma (RCC): A Systematic Review

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Introduction: Renal cell cancer (RCC) syndrome is linked to Krebs cycle compartments and their coding genes' alterations like *succinate dehydrogenase* genes (*SDHx*). Here we present a systematic review of the SDH genes' mutations and their impact on both RCC diagnosis and prognosis.

Methods: This systematic review includes any study in which tissue samples of RCC are considered in correlation with the SDHx mutations, microsatellite instability (MSI), and protein expression. For this purpose, a systematic search of MEDLINE (PubMed), Scopus, Embase, and Web of Science databases was conducted and finally 5384 articles were recruited. All studies' content was checked to find the related ones which were 145 articles, which with data extraction were limited to nineteen.

Results: The final selected nineteen studies investigating the *SDHx* role in RCC tumor genesis were included, among which fifteen were mutation analysis, three were just *SDHx* protein expression, and two were MSI and mutation analysis studies. A total of 432 RCC patients were reported by *SDH* mutations, and 64 patients with MSI and *SDH* expression change were reported in 514 surgically resected renal epithelial tumors. The most common mutation was the single nucleotide variant rs772551056 (c.137G>A) of *SDHB*. For *SDHC*, *c.380A>G* presented in 48 RCC patients, and for *SDHA* a novel germline mutation c.2T>C: p.M1T in an occasional case of gastrointestinal stromal tumor intricate with RCC.

Conclusion: RCC as an aggressive type of kidney cancer needs some biomarkers to be diagnosed exactly. It was shown recently that the succinate dehydrogenase gene variations can provide this diagnostic and prognostic biomarker. For this purpose, SDHB rs772551056 associated with its protein expression alterations can be taken into account. It is possible that a novel mutation of SDHA (c.2T>C: p.M1T) can provide evidence of GIST associated with RCC as well.

Keywords: renal cell cancer, RCC, succinate dehydrogenases, mutation, expression, MSI

Introduction

Kidney cancers with different genetic changes have different histology and clinical significance. The genes relating to kidney cancer are usually involved in metabolic stress or nutrient stimulation pathways including *Von Hippel-Lindau*(*VHL*), *mesenchymal–epithelial transition factor*(*MET*), *Folliculin*(*FLCN*), *Tuberous sclerosis*(*TSC1* and *TSC2*), *Microphthalmia-associated transcription factor*(*MITF*), *Phosphatase* and *tensin homolog*(*PTEN*), *fumarate hydratase*(*FH*), and *succinate dehydrogenase* (*SDH*).[1,2] One of the usual forms of kidney cancers is RCC that initiates in the lining

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of the proximal convoluted tubule responsible for about 90–95% of kidney cancer cases.[3–6] It commonly is described by an absence of early-warning signs (which outcomes in an extraordinary proportion of patients with metastases), various medical manifestations, and fighting radiotherapy and chemotherapy with a possible impact on immunomodulation in the tumor growth suppression.[7–9] RCC has the highest mortality rate of the genitourinary cancers and its prevalence has ascended steadily over the past few decades.[10] Some recent research has proved the benefit of genomic data, principally gene expression hallmarks, as medical predictive factors in personalized cancer managements.[11–13] *Succinate dehydrogenase* (*SDH or SQR*) is an enzyme complex of the inner mitochondrial membrane that contributes to the citric acid cycle as well as the electron transport chain.[14] Succinate dehydrogenase is made of four protein subunits (*SDHA*, *SDHB*, *SDHC*,and *SDHD*) having a role in the TCA cycle and electron transport chain in mitochondria.[15,16] Patients with mutations in the *SDH* genes are under the risk of autonomic nervous system tumors like pheochromocytomas and paragangliomas (PPGLs), both head and neck, and in the thorax and abdomen, gastrointestinal stromal tumors (GISTs), and renal cell carcinoma (RCC). The evaluation of protein expression by immunohistochemistry routinely is used to find a discriminative biomarker of benign and malignant tumors including RCC.[17–19] Succinate dehydrogenase mutation in PPGL and GIST tumor cells had a microscopic result of predominantly epithelioid morphology, and epithelioid morphology, but not in RCC.[20] In fact, renal tumors are usually known with typical morphology of identical cells with eosinophilic or oncocytic cytoplasm that have cytoplasmic vacuoles or flocculent inclusions.[21–23] RCCs with additional histologic presence have been described in patients with germline mutations of succinate dehydrogenase genes, contrary to some limited histological types of RCCs with no succinate dehydrogenase mutation.[24,25]

In recent years the genetic basis of RCC has been known and both genetic and epigenetic alterations of succinate dehydrogenase have been discussed. Interestingly, germline mutations of the genes coding for the succinate dehydrogenase subunits (*SDHB*, *SDHC*, and *SDHD*) have been identified in patients with a combination of gastrointestinal stromal tumors (GISTs) and paraganglioma (PGL).[26,27] The co-occurrence of RCC with paraganglioma or pheochromocytoma suggested a succinate dehydrogenase gene mutation presence.[28,29] A newly characterized specific subtype of RCC is in the new World Health Organization (WHO) classification and was published in 2016.[30–32]

In spite of the fact that recently the focus of scientists is on RCC genetic and epigenetic modifications, knowledge of the clinical features and management of patients associated with the SDH mutations is limited. The current systematic review study is run with the purpose of delivering the first meticulous summary of all the available primary research over the *SDH* mutations, expression, and microsatellite instability (MSI) in RCC management and screening recommendations.

Research Design And Methods

Search Strategy

The study was based on an international prospective register of systematic reviews with PROSPERO 2018 code CRD42018087806 available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087806. All linked works were searched from four targeted databases including: MEDLINE (PubMed), Scopus, Embase, and Web of Science. Publication dates of relevant articles were limited from 1st January 1990 to 30th March 2018. Our search syntax were "*Succinic Dehydrogenase*", "*SDH* mutations", "Succinic Oxidase", "*succinate-coenzyme Q reductase", " (SQR)*", "respiratory Complex II" combined with "Collecting Duct Carcinoma", "RCC", "Renal Cell Adenocarcinoma", "Kidney adenocarcinoma", and "kidney Cancer" (Supplementary materials). In order to decrease the selection bias, two separate investigators (FK and RH) individually reviewed titles, abstracts, and available full-text articles to choose the related ones with SDH and RCC. Additional related papers were documented above searching the reference lists of selected studies. Disagreements were solved by the third independent investigator (SMKA).

Eligibility Criteria

All chosen studies were studied by two authors individually and based on their English full text were included or excluded. The considering inclusion criteria were: 1) participants included kidney cancer patients pathologically classified as RCC, renal epithelial tumors, or renal tumors; 2) all *SDHx* alteration detection techniques such as immunohistochemistry (IHC), DNA sequencing, western blotting, PCR-based methods, SNaPshot Assay, and PCR-RFLP were included; and 3) *SDHx* alterations were composed mutations, MSI, and protein expression. Studies were excluded if they: 1) analyzed *SDHx* mutations or expression in animals (in vivo studies); 2) studied them in cell culture (in vitro studies); or (3) did not have an appropriate explanation of selected case groups.

Data Extraction And Quality Assessment

All data on population characteristics and *SDHx* deficiency results were extracted in the Excel file. One investigator completed the data extraction step (SPD), which was established via another investigator (FK). Due to the insufficient quantity of studies relevant to *SDHx* deficiencies and RCC, together with the significant variations in targeted genetic variations and study population characteristics, a meta-analysis for the current data was not applicable. The study team used the Newcastle–Ottawa Scale (NOS) scale assessment tools to assess the quality of all selected final studies.[33,34] The methodologies of studies scoring 6/8 or more on the NOS were categorized as "high quality", whereas those that scored 5/8 or lower were reported as "low quality".

Results

Study Selection And Characteristics

The selection flow chart and results of the study selection procedure are presented in Figure 1. A total of 5384 articles was retrieved and after duplication deletion 3964 remained, in which there were 2905 from PubMed, 559 from Scopus, 325 from Web of Science, and 130 from Embase. When the review articles, in vivo/in vitro studies, and book or conference papers were deleted the total number of nineteen articles was chosen for advance considerations. A total of sixteen studies were mainly focused on *SDHx* mutations, three studied the *SDHx* protein expression without mutation analysis, and two targeted *SDHx* MSI with or without mutation (Table 1).

In sixteen studies, *SDHB* was checked for mutation, and protein expression. In these studies, *SDHB* was evaluated alone or simultaneously with other candidate genes like *FH*, *TFE3 gene rearrangement*, *TMEM127*, *MAX*, *HIF1a*, *Cathepsin*, *PAX8*, *Cathepsin, CK20*, and *EMA*. In these studies, several mutations of *SDHB* were checked including exonic mutations (c.137G>A), splice site acceptor or donor mutations (c.72+1G→T), exon 1 splice acceptor site or c.268C>T (p. Arg90X) in exon 3 splice site mutation, and (*c.136C>T Stop*) mutation of stop codons which are resulting in truncated inactive forms of the protein. Five studies were mainly focused on *SDHC* in which loss of heterozygosity (LOH) in two telomeric regions (D3S369, D3S1597) and five centromeric regions (D3SVHL3, D3S1337, D3SVHL7, D3SVHL8, D3S3611) more than c.380A>G mutations were tested. Especially, in an aggressive example of the Warburg Effect in succinate

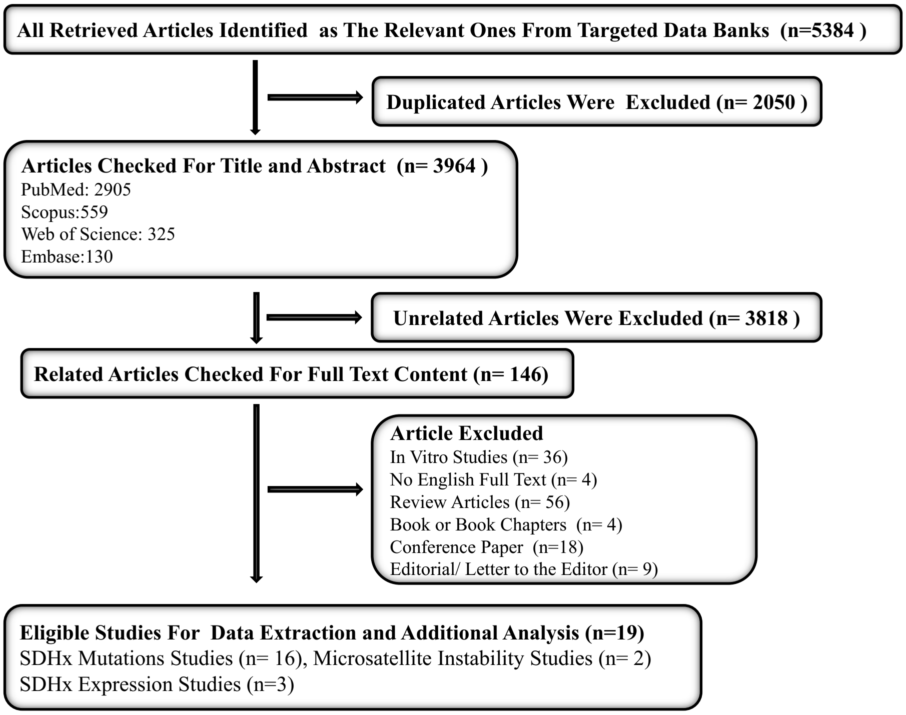

Figure 1 Flow chart of study selection.

Table 1 Characterization Of Nineteen Related Studies To *SDHx* Genetic Modifications And Protein Expression In RCC Patients

Target SDH	Title	First Author	Publication Year	Country	Sample Size	Age	Type Of Study	Detected Mutation
SDHB	Renal carcinoma with giant mitochondria associated with germ-line mutation and somatic loss of the succinate dehydrogenase B gene[39]	Sarah L Housley	2010	UK	1 RCC	58	Case report	c.72+1G→T exon 1 splice acceptor site
	Germline *SDHB* mutations and familial renal cell carcinoma[21]	Christopher Ricketts	2008	UK	68 RCC	50	Case series	c.137G>A, c.32G>A, c.136C>T Stop
	Early-onset renal cell carcinoma as a novel extraparaganglial component of *SDHB*-associated heritable paraganglioma[36]	Sakari Vanharanta	2004	Finland	60 sporadic RCCs	15–34	Case series	e R27X mutation (N8168)
	Succinate dehydrogenase (*SDH*)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients[40]	Anthony J Gill	2014	Australia	36 tumors from 27 patients	37	Cohort	c.137G>A c.725G>A c.423+1G>A SDHB exon 3 deletion c.423+1G>A c.338G>A c.423+1G>A c.749C>A SDHC c.380A>G
	Renal cell carcinoma with *TFE3* translocation and succinate dehydrogenase B mutation[41]	Anna Calió	2017	USA	4 RCCs	From 19 to 65	Case series	c.423+1G 4A p.V140F c.72+1G 4T
	Immunohistochemical characterization of *f*Fumarate hydratase (FH) and succinate dehydrogenase (SDH) in cutaneous leiomyomas for detection of familial cancer syndromes[42]	Cody S Carter	2017	USA	96 consecutive specimens of cutaneous leiomyomas from 87 RCC patients		Case/control	SDHB expression

(*Continued*)

Table 1 (Continued).

Target SDH	Title	First Author	Publication Year	Country	Sample Size	Age	Type Of Study	Detected Mutation
	Clinical and molecular features of renal and phaeochromocytoma/ paraganglioma tumour association syndrome (RAPTAS): case series and literature review[43]	Ruth T Casey	2017	UK	22 probands with non-VHL RAPTAS	30	Case series	N/A
	Succinate dehydrogenase B: a new prognostic biomarker in clear cell renal cell carcinoma[37]	Kristine M Cornejo	2015	USA	420 surgically resected renal epithelial tumors	62.6 (33–92)	Case series	SDHB expression
	Utility of the succinate: fumarate ratio for assessing *SDH* dysfunction in different tumor types[44]	Edward Kim	2017	Australia	11 RCCs 18 PPGLs, 10 GISTs	–	Case/control	c.380T>G, p.Ile127Ser
	Increased *HIF1α*in *SDH* and *FH* deficient tumors does not cause microsatellite instability[45]	Heli J Lehtonen	2007	Finland	11 RCCs, 12 ULMs 1 ULMS		Case series	N/A
	Renal cell carcinoma occurring in patients with prior neuroblastoma[46]	Sara M Falzarano	2016	USA	7 RCCs	40–64	Case series	SDHB expression
	Renal tumors associated with germline *SDHB*mutation show distinctive morphology[20]	Anthony J Gill	2011	Australia	4 renal tumors	32	Case reports	c.166-170delCCTCA in exon 2 c.72+1G>T c.268C>T (p.Arg90X) in exon 3 splice site mutation (c.423 +1G>A)
	SDHB-associated renal oncocytoma suggests a broadening of the renal phenotype in hereditary paragangliomatosis[47]	Alex Henderson	2009	UK	11 Renal tumors	16–73	Case series	c.136C>T c.137G>A c.79C>T c.715_718 delTCTC c.32G>A c.141G>A c.3G>A c.600G>T

(*Continued*)

Table 1 (Continued).

Target SDH	Title	First Author	Publication Year	Country	Sample Size	Age	Type Of Study	Detected Mutation
	Molecular genetic analysis of *FIH-1*, *FH*, and *SDHB* candidate tumour suppressor genes in renal cell carcinoma[35]	M R Morris	2004	UK	29 RCCs	–	Case series	IVS2+33 A R G IVS2+35 G R A c.18 A R C; A6A D1S2697
	Renal carcinoma associated with *succinate dehydrogenase B* mutation: a new and unique subtype of renal carcinoma[48]	Julie Y Paik	2014	Australia	A unique case RCC	27	Case report	c.88delC (p.Gln30ArgfsX47) in exon 2
	Papillary renal cell carcinoma with cytologic and molecular genetic features overlapping with renal oncocytoma: analysis of 10 cases.[49]	Kvetoslava Michalova	2018	Czech Republic	147 PRCCs	67	Case series	N/A
SDHC	Clinical and molecular features of renal and phaeochromocytoma/paraganglioma tumour association syndrome (RAPTAS): case series and literature review[43]	Ruth T Casey	2017	UK	22 probands with non-VHL RAPTAS	30	Case series	N/A
	Increased HIF1α in SDH and FH deficient tumors does not cause microsatellite instability[45]	Heli J Lehtonen	2007	Finland	11 RCCs, 12 ULMs 1 ULMS		Case series	N/A
	Biallelic inactivation of the *SDHC* gene in renal carcinoma associated with paraganglioma syndrome type 3[24]	Angelica Malinoc	2012	Germany	35 head and neck paragangliomas	–	Case series	LOH at SDHC: 2 telomeric D3S3691 D3S1597 5 centromeric D3SVHL3, D3S1337, D3SVHL7, D3SVHL8, D3S3611;
	Succinate dehydrogenase *(SDH)*-deficient renal carcinoma: a morphologically distinct entity a clinicopathologic series of 36 tumors from 27 patients[40]	Anthony J Gill	2014	Australia	28 tumor samples	37	Cohort	SDHC c.380A>G

(*Continued*)

Table 1 (Continued).

Target SDH	Title	First Author	Publication Year	Country	Sample Size	Age	Type Of Study	Detected Mutation
	Succinate dehydrogenase kidney cancer (SDH-RCC): an aggressive example of the Warburg Effect in cancer[50]	Christopher J Ricketts	2012	USA	14 patients from SDHB mutation families	47	Case series	R133X
SDHA	A novel germline mutation in *SDHA* identified in a rare case of gastrointestinal stromal tumor complicated with renal cell carcinoma[38]	Quan Jiang	2015	China	A case of GIST RCC	23	Case report	c.2T>C: p.M1T
	Early-onset renal cell carcinoma as a novel extraparaganglial component of *SDHB*-associated heritable paraganglioma[36]	Sakari Vanharanta	2004	Finland	60 sporadic RCCs	15–34	Case series	N/A
SDHD	Germline *SDHB* mutations and familial renal cell carcinoma[21]	Christopher Ricketts	2008	UK	68 RCC	50	Case series	N/A
	Early-onset renal cell carcinoma as a novel extraparaganglial component of *SDHB*-associated heritable paraganglioma[36]	Sakari Vanharanta	2004	Finland	60 sporadic RCCs	15–34	Case series	N/A
	Clinical and molecular features of renal and phaeochromocytoma/paraganglioma tumour association syndrome (RAPTAS): case series and literature review[43]	Ruth T Casey	2017	UK	22 probands with non-VHL RAPTAS	30	Case series	N/A
	Biallelic inactivation of the *SDHC* gene in renal carcinoma associated with paraganglioma syndrome type 3[24]	Angelica Malinoc	2012	Germany	35 head and neck paragangliomas	–	Case series	N/A
	Increased *HIF1α* in *SDH* and *FH* deficient tumors does not cause microsatellite instability[45]	Heli J Lehtonen	2007	Finland	11 RCCs, 12 ULMs 1 ULMS		Case series	N/A

Abbreviations: RAPTAS, pheochromocytoma/paraganglioma tumor association syndrome; SDH, succinate dehydrogenase; PPGLs, pheochromocytoma and paraganglioma; GISTs, gastrointestinal stromal tumors; RCCs, renal cell carcinomas; HLRCC, hereditary leiomyomatosis and renal cell cancer; ULM, benign uterine leiomyomas; ULMS, uterine leiomyosarcoma; HPGL, hereditary paragangliomatosis; NB, neuroblastoma; GIST RCC, gastrointestinal stromal tumor complicated with renal cell carcinoma; PRCC, papillary RCC; ccRCC, clear cell RCC; LOH, loss of heterozygosity; OPRCC, oncocytic variant of papillary renal cell carcinoma; HIF, hypoxia inducible factor; FH, fumarate hydratase; N/A, not available.

dehydrogenase kidney cancer (SDH-RCC), the germline SDHC mutation (R133X) (NM_003001.3-c.397C>T (p. Arg133Ter)) was identified. Two studies were related to SDHA (c.2T>C: p.M1T/rs864622194) resulting in substitution of Methionine with Threonine in a NM_006493.2: c.2T>C missense variant that change the amino acid sequence in protein and resulted in non-functional protein (https://www.ncbi.nlm.nih.gov/clinvar/variation/219649/).

Five studies concerned *SDHD* with no exact determined targeted mutations. Except for one study in sporadic RCC indicating no mutations in the three *FH*, *FIH-1*, and *SDHB*, others mainly suggested early-onset RCC with unusual histology (e.g., solid) must be observed to take an extended family history and *SDHB* mutant-related RCC in the way of better diagnosis and prognosis.[35,36] In fact the weak staining, particularly in clear neoplasms, usually can be interpreted as negative by mistake.[37] A total of 432 RCC patients were reported by *SDH* mutations, and 64 patients with MSI and *SDH* expression change were reported in 514 surgically resected renal epithelial tumors. The most common mutation was the single nucleotide variant rs772551056 (c.137G>A) of *SDHB* with genomic location Chr1: 17044824 resulting in protein change *R46Q* which was reported in 106 RCC patients. After that, two mutations of c.32G>A and c.136C>T Stop were the most with 79 reported RCC patients. The mutation of *c.423+1G>A* was in 44 RCC patients and c.72+1G→T in 20 patients. The *SDHC* c.380A>G (p. His127Arg) was in 48 RCC, 18 PPGLs, and 11 GIST. The rs786201095 (c.380T>G (p. Ile127Ser)) with chromosome location Chr1: 17028643 is the common mutation found in RCC in addition to GIST and PPGL. *SDHB* expression in ccRCCs with high nucleolar grade (G3–G4) was considerably linked to patient's low survival so it can be an excellent candidate biomarker for RCC diagnosis and prognosis.[37] The novel germline mutation of chromosome X rs864622194 (c.2T>C: p.M1T) with genomic locus ChrX: 103776997 in *SDHA* was recognized in a rare case of gastrointestinal stromal tumor complicated with RCC.[38]

Discussion

RCC arises from the cells of the proximal renal tubular epithelium and has two subtypes: sporadic (non-hereditary) and hereditary.[51] Inherited predisposition to RCC is dependent on cellular metabolism responsible genes.[52,53] RCC is basically a metabolic disease so metabolism involving genes like SDH can trigger the cellular transformation of renal cells in reaction to sensing oxygen, iron, nutrients, and energy.[1,54] The SDH enzyme is a very conserved heterotetrameric protein made up of four subunits (*SDHA*, *SDHB*, *SDHC*,and *SDHD*) in which *SDHA* and *SDHB* are catalytic subunits and *SDHC* and *SDHD* are anchored to the inner membrane.[55] Recently the importance of SDH subunit mutations has been highlighted in different malignancies including RCC.[56,57] There is a rare and aggressive type of RCC which is called SDH-deficient RCC (abbreviated SDH-RCC) that lately has been added to the WHO classification of renal neoplasia.[58] The incidence of SDH-deficient RCC is assessed among 0.05–0.2% of all renal carcinomas and among SDH-deficient RCCs, *SDHB*-mutated RCC is the most frequent,[59] followed by *SDHC* and *SDHD*-deficient RCC.[24,40] Moreover, a patient case with *SDHA*-deficient RCC has been reported currently.[60] Early age of onset for RCC has been observed in patients with SDHB germline mutations.[20,61,62]

Common genetic alterations of SDHB consist of a nonsense mutation (c.268C>T p.Arg90X), four missense mutations (c.137G>A p.Arg46Gln, c.286G>A p.Gly96Ser, c.379A>C p.Ile127Leu, c.689G>A p.Arg230His), two splice site altering mutations (c.286+2T>A, c.541-2A>G), and three complete deletions of the first exon of *SDHB*.[50] The mutation c.72+1G→T which is in the exon 1 splice acceptor site resulting in production of a truncated inactive form of the protein was in RCC with giant mitochondria.[39] *SDHB* mutation results in distinctive morphology of RCC and these RCCs have a respectable prognosis subsequently of whole excision unless there is sarcomatoid dedifferentiation.[20] The involvement of *SDHB* mutations in RCC recommends that *SDHB* mutations must be checked when renal tumors are presented in families with other tumors consistent with hereditary paraganglioma syndrome.[47] The two mutations c.541-2A>G (Splice) and *c.689G>A (pArg230His)* have a role in impairing iron–sulfur cluster delivery and are highlighted in several cancers.[63,64] According to our result the most common *SDHB* mutation was the single nucleotide variant rs772551056 (c.137G>A). *SDHB* is the Fe–S subunit of mitochondrial complex II including extremely consensus L(I)YR motifs essential for gaining of Fe–S clusters by recruiting the Fe–S transfer machinery.[65,66] Importantly, the c.137G>A (*p.Arg46Gln or R46Q*) mutation occurs in the first L(I)YR motif of *SDHB* and can be detected in familial paraganglioma/pheochromocytoma/GIST/renal cell carcinoma tumor syndromes.[67,68] KDM4/JMJD2 proteins are demethylases that target histone H3 on lysine 9 and 36, and histone H1.4 on lysine 26, and are key epigenetic regulators of several cancer cells.[69–71] However, succinate-mediated competitive suppression of 2-oxoglutarate-dependent dioxygenases, histone demethylases (JMJD), and the ten–eleven translocation (TET) family of 5-methyl cytosine (5-mC) family of hydroxylases are important in SDH-deficient tumor phenotypes.[72] Possible succinate-induced modifications contain stabilization of HIF-α propyl hydroxylase and hypermethylation of histones and DNA.[73–75] The morphological study of SDH-deficient renal carcinoma represents a distinct and rare renal neoplasm, which is defined by loss of IHC staining for *SDHB*.[40] It was in 2000 that the first germline mutation of *SDHD* was reported in HOGL families and then in link with familial PCC.[76,77] Moreover, the *SDHD* mutations together with SDHB mutations were reported in familial PCC and HPGL.[78,79] SDH-deficient PPGLs, GISTs, and RCCs keep a considerably advanced succinate:fumarate ratio versus their SDH-sufficient equivalents so metabolomic analysis is essential to directly measure SDH dysfunction linking to the numerous types of malignancies.[44]

Germline mutation c.380A>G (p.His127Arg) of *SDHC* is the important mutation of this gene which is reported as a recurrent biomarker of SDH-deficient GIST and renal carcinoma.[80,81] This variant was described in two brothers with head and neck paragangliomas and in a patient with papillary thyroid cancer, renal cell cancer, and GIST; both the renal tumor and GIST demonstrated absence of *SDHB* by IHC.[40] This mutation was not detected in about 6,500 persons from Europeans and African Americans in the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP), showing that it is not a public benign alternative in these people.[82] Subsequently, the amino acids of Histidine and Arginine share analogous characteristics; this is measured as a conservative amino acid substitution mutation. *SDHC c.380A>G* happens at a conserved protein region through different species and is located at the metal attachment site for iron and in the helical transmembrane topological domain.[83] In silico analyses predict that this polymorphism can perhaps change the protein structure and function, and suggested novel mutations in sporadic head and neck paraganglioma and familial paraganglioma and/or pheochromocytoma.[84–86] Based on the currently available evidence, *SDHC c.380A>G* can be considered the RCC pathogenic variant. These are conflicting because germline *SDHC* mutations are comparatively uncommon, so it was supposed that carriers of mutations of the *SDHC* gene have aspecial risk for head and neck paragangliomas more than a risk for adrenal pheochromocytoma.[87] Therefore, not only the *SDHC* mutations but also the LOH and MSI were taken into consideration in RCC patients.[24] Two telomeric (D3S3691, D3S1597) and five centromeric (D3SVHL3, D3S1337, D3SVHL7, D3SVHL8, D3S3611) were evaluated and renal carcinoma. It was reported by Malinoc et al that for the clear cell renal carcinoma LOH was established in *D3S3691* and, D3S1597 as the telomeric ones and in two centromeric signs (D3SVHL3 and D3S3611) in comparison with undesirable controls so it might be a new molecular indicator for the pathogenesis of RCC and ought to be checked in both heritable and sporadic forms.[24]

A report about *SDHA* by Jiang et al in 2015 diagnosed a rare case as a wild-type gastrointestinal stromal tumor (WT GIST) intricated with renal chromophobe cancer cells and distinguished an innovative germline mutation chromosome X rs864622194 (c.2T>C: p.M1T) in the position of a transcription initial codon within the SDHA gene sequence.[38] There was another described patient of an RCC linked with an *SDHA* mutation.[88] As the main catalytic subunit of *SDH* complex, the (c.2T>C: p.M1T) mutation certainly deactivates the entire *SDH* complex. It has been presented that *SDHA* homozygous deletion mutation of *SDHA* and *SDHB* following altered protein expression evident by IHC and decreased gene expression of *SDHA* noticeable by IHC faultlessly can be coordinated with *SDHA* mutation.[60] Nevertheless, *SDHA* mutation does not result in loss of *SDHA* protein expression, which directs that the role of the other allele is normal, so *SDHA* in addition to *SDHB* have been recommended as diagnostic biomarkers for screening for potential *SDH* mutations in RCC cases.[89,90]

More than genetic change there are some epigenetic modifications that change the gene expression with no change in the DNA sequences. In fact, epigenetics acts as an interface between environmental/exogenous factors, cellular responses, and pathological processes.[91] Epigenetic signatures (DNA methylation, mRNA and microRNA expression, etc) can be biomarkers for risk stratification, early detection, and disease classification, as well as targets for therapy and chemoprevention.[92] To better understand the interplay between etiological factors, cellular molecular characteristics, and disease evolution, the field of “molecular pathological epidemiology (MPE)” has emerged as an interdisciplinary integration of “molecular pathology” and “epidemiology”. The widespread application of epigenome (e.g., methylome) analyses will increase our understanding of disease heterogeneity, epigenotypes (CpG island methylator phenotype, LINE-1 (long interspersed nucleotide element-1; also called long interspersed nuclear element-1; long interspersed element-1; L1) hypomethylation, etc), and host–disease interactions.[93]

Conclusion

Succinate dehydrogenase is an important metabolic enzyme in the TCA cycle and electron transport chain. Germline mutations in *SDHB*, *SDHC*, *SDHA*, and *SDHD* are associated with RCC. To our knowledge, as the first systematic review on the succinate dehydrogenase genetic alterations, we can say that the most frequently detected mutation is SDHB rs772551056 and its protein expression. Moreover, the *c.380A>G* mutation with four MSI markers (D3S3691, D3S1597, D3SVHL3, D3S3611) of *SDHC* can bring a morphologically distinct entity of RCC and be a predictor of its recurrence and aggressive behavior. The newly suggested mutation of *SDHA* (*c.2T>C: p.M1T*) can provide evidence of GIST associated with RCC as well.

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Disclosure

The authors report no conflicts of interest in this work.

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