REVIEW ARTICLE

Succinate Dehydrogenase Mutation and Paraganglioma Syndromes: A Review Article

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Abstract

Pheochromocytomas and paragangliomas are rare tumours of both sympathetic and parasympathetic origin. Pheochromocytomas are derived from the adrenal medulla whereas paraganglioma arise from extra adrenal sympathetic and parasympathetic tissues. Between a quarter to one-third of pheochromocytomas-paragangliomas have familial aetiology which are heterogenous and include syndromes like on Hippel-Lindau (VHL), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1) and succinate dehydrogenase (SDH) mutation-related tumours. SDH is a mitochondrial complex involved in both Kreb's cycle and electron transport chain consisting of different subunits (A-D). Different mutations in various sub-units SDH leads to significant phenotypic heterogeneity, hence has been classified as different paraganglioma syndromes. Herein we review the pathogenesis, inheritance, clinical presentation, diagnosis and management of SDH related paragangliomas.

Keyword: Paraganglioma, Pheochromocytoma, Succinate dehydrogenase, Endocrine surgery.

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Introduction

Neuroendocrine tumors arising from the sympathetic or parasympathetic ganglia are commonly referred to as paragangliomas (PGLs). Paragangliomas arising from the parasympathetic ganglia are usually nonsecretory and are commonly located in the head and neck called head and neck paragangliomas (HNPGLs). Catecholamine-secreting paragangliomas arise from the sympathetic trunk and are commonly located in the abdomen and thorax. There is a possible close embryological and physiological relationship between HNPGL and paragangliomas associated with the sympathetic ganglia. Mutations in the *VHL, RET,* and *NF1* genes were closely associated with pheochromocytomas and paragangliomas (PPGLs) prior to the year 2000. Familial paraganglioma, especially HNPGL, was then reported to be associated with mutations in the succinate dehydrogenase subunit D gene (*SDHD*)[1], which was considered a major breakthrough toward a better understanding of underlying pathology. Subsequently, paraganglioma syndromes were reported to be associated with other subunits of succinate dehydrogenase (*SDH*), and this facilitated better understanding of a role of mitochondrial *SDH* complex and underlying metabolism in tumorigenesis. Presently, approximately 30% of PPGL and HNPGL are associated with inherited mutations.[2]

History

Familial head and neck paragangliomas were first described more than 80 years ago in 1933,[3] and evidence of autosomal inheritance with parent of origin effect was described by Van Der May et al.[4] Baysal et al.[5] reported that certain sporadic and familial paragangliomas and pheochromocytomas were associated with germline mutations in *SDHD* (PGL1).[6] Subsequently, germline mutations in *SDHC* (PGL3) were reported by Niemann et al.[7] to cause HNPGL (autosomal dominant, no parent of origin effect), and mutations in *SDHB* (PGL4) were found by Astuti et al.[8] to cause aggressive pheochromocytomas and paragangliomas. Germline mutations in *SDHAF2* (*SDH*-associated protein) were also reported to cause HNPGL in rare cases[9], and *SDHA* mutations, initially reported in the context of an autosomal recessive juvenile encephalopathy, were demonstrated to be a rare cause of (dominantly inherited) predisposition to PPGL with very low penetrance.[10]

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Structure and Function of *SDH*

Succinate dehydrogenase (*SDH*), also known as Complex II, is a dual-function mitochondrial enzyme involved in both the Kreb's cycle and the electron transport chain (ETC) for efficient energy production. *SDH* is a highly conserved heterotetrameric protein consisting of four subunits (A, B, C, and D) that have different functions (Fig. 1). *SDHA* is a hydrophilic flavoprotein that serves as a substrate-binding site, and together with another hydrophilic *SDHB*, it forms the catalytic part of the enzyme. Hydrophobic *SDHC* and *SDHD* serve as membrane anchors and ubiquinone binding site. *SDHA* carries the binding site for succinate. Upon succinate binding, *SDHA* brings succinate into juxtaposition with the isoalloxazine ring of flavine adenine dinucleotide (FAD), where oxidation to fumarate is catalyzed. *SDHB* contains three Fe–S centers that mediate electron transfer between succinate and ubiquinone. *SDH* differs from other proteins of ETC as it is the only complex which does not span the membrane and does not transfer hydrogen ions into the intermembrane space.[11]

Pathogenesis of *SDH*-mutated PPGLs

Even with the recent advances in biotechnology, the pathogenesis of PPGLs caused by *SDH* mutations remains elusive. *SDH* is responsible for the oxidation of succinate to fumarate in the Kreb's cycle and also responsible for transfer of electron to ubiquinone in the ETC.[12] Various models studying consequences of loss of *SDH* are broadly classified into constitutive hypoxic drive, inhibition of developmental neuronal culling, and histone/genome hypermethylation (Fig. 2).

Constitutive Hypoxic Drive

Hypoxia-induced factor (HIF) has been linked to the pathogenesis of PGL in *VHL*-associated tumors. Studies of the transcriptional overlap between *SDH*- and *VHL*-related PPGL have also implicated HIFs in the tumorigenesis in *SDH*-related PGLs.

The translational products of *VHL* gene (pVHL) form a component of protein complex possessing ubiquitin ligase activity which mediates degradation of HIFs under normal condition.[13] Cellular adaptation to hypoxia is mediated by hypoxia-inducible factors (HIF1, HIF2, and HIF3). During normoxia conditions, hydroxylation of HIF-α subunits is mediated by prolyl/asparaginyl hydroxylase enzymes (PHD1, PHD2, PHD3, and HIF). These subunits are further degraded by ubiquitination. Inhibition of hydroxylase enzymes occurs during hypoxic conditions, which leads to stabilization of HIF-α subunits.[14] *SDH* mutations lead to loss of *SDH* activity and increase in succinate concentrations and reactive oxygen species (ROS). Increased concentration of succinate causes its influx into cytoplasm, which inhibits PHDs, resulting in HIF stabilization. This mechanism of succinate accumulation as trigger molecule for tumor formation was first proposed by Dahia et al.[15] Hence, even in normoxia conditions, HIF degradation does not occur via ubiquitination in *VHL*-gene-mutated individuals. *In vitro* studies using cell lines showed that siRNA-mediated knockdown of *SDH* subunits led to stabilization of HIF1α.[16] However, recent gene expression studies do not provide an unequivocal evidence for involvement of HIFs in pathogenesis of *SDH*-mutated paragangliomas.[12]

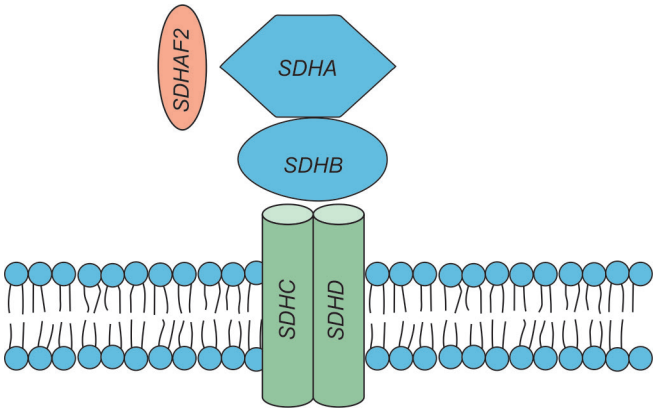

Fig. 1: Schematic structure of *SDH* subunits is shown. *SDH* is comprised of four structural subunits encoded by *SDHA, SDHB, SDHC,* and *SDHD*. The *SDHC* and *SDHD* gene products are hydrophobic, sandwich a heme moiety, and span the inner mitochondrial membrane. The *SDHA* and *SDHB* gene products are cytosolic and contain a covalently bound FAD and three iron–sulfur clusters, respectively. *SDHAF2* (*SDH5*) is a nonstructural assembly protein critical for flavination of the *SDHA* gene product.[12]

Histone/Genome Hypermethylation

The prolyl hydroxylase enzymes (PHDs) are members of Fe(II)/α-ketoglutarate (KG)-dependent dioxygenase family. Succinate accumulation leading to PHD inhibition theoretically raises possibility of *SDH* contribution to PPGL development. Succinate accumulation leads to histone H3 hypermethylation by inhibition of Jumonji-domain histone demethylases (JmjC),[17] and hypermethylation of CpG islands on DNA by inhibition of KG-dependent dioxygenases, including collagen prolyl-4-hydroxylases and ten-eleven translocation (TET) family of 5-methylcytosine (5mC) hydroxylases.[18] Evaluation of histone and DNA hypermethylation in *SDH*-mutated PPGL showed promotor gene hypermethylation due to TET family hydroxylase inhibition

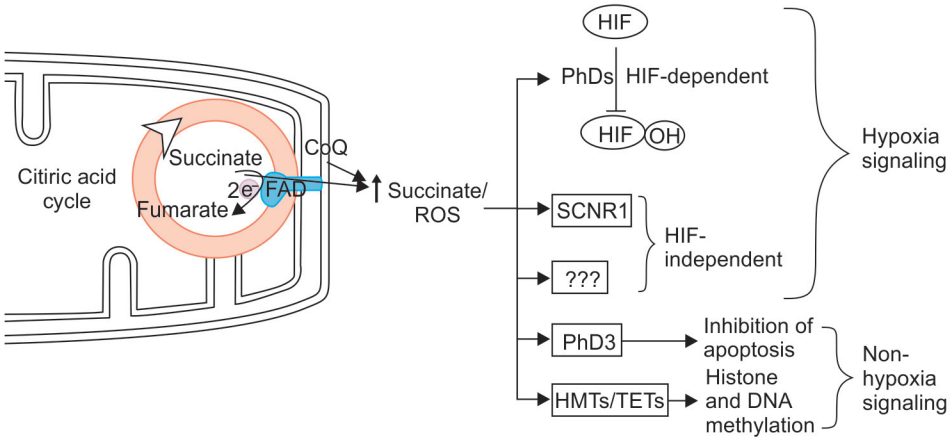

Fig. 2: Overview of the proposed mechanisms of *SDH*-mutated paragangliomas. Mutations in *SDH* subunits (mainly in *SDHB* and *SDHD*) result in loss of Complex II activity and drive paraganglioma formation through accumulation of ROS or succinate. Evidence favors constitutive hypoxia signaling as the initiating mechanism of paraganglioma formation. Role of HIF1α/HIF2α in mediating this hypoxic signaling remains to be confirmed in relevant cell culture and animal models. Succinate may separately stimulate certain biological pathways regulated by succinate receptors (e.g., SCNR1). Alternatively, succinate-mediated inhibition of certain α-KG-dependent enzymes, such as PHD3, histone methyltransferases (HMTs), or TETs, may lead to inhibition of neural apoptosis, histone, and DNA hypermethylation.[12]

leading to downregulation of gene expression of 191 genes, including PNMT and KRT19 which are linked to neuroendocrine differentiation and epithelial-to-mesenchymal differentiation, respectively.[19]

Inhibition of Developmental Neuronal Culling

Prolyl-3-hydroxylase (PHD3) activity is required for neuronal apoptosis after neuronal growth factor (NGF) withdrawal. Accumulation of succinate due to *SDH* mutation has been proposed to be the cause of PHD3 inhibition, and subsequently reduced apoptosis and enhanced survival of sympathetic neurons leading to tumorigenesis.[20]

Inheritance and Screening

Inheritance of *SDH*-related PPGL syndromes differs from other PPGL syndromes such as *VHL* and *NF-1*. *SDHB*- and *SDHC*-linked mutations show autosomal dominant inheritance, while *SDHD* and *SDHAF2* mutations show exclusive paternal transmission.[9] Maternal inheritance of *SDHD* and *SDHAF2* mutations occurs, but tumor formation after maternal transmission is extremely rare.[21] The guidelines for screening in patients with *SDH* mutation or suspected *SDH* mutations are not well established and are based only on the expert opinion. An HNPGL or multifocal/ metastatic PPGL should prompt investigations for *SDH* mutation in the absence of family history. *SDHB*-mutated tumors show similar biochemical profile to *VHL* patients with predominantly normetanephrine secretion; however, they may also have high methoxytyramine secretion along with normetanephrine or isolated elevation of methoxytyramine.[22] Parasympathetic ganglia tumors are usually HNPGL and associated with *SDHC*, *SDHD*, and *SDHAF2* mutations; however, these tumors do not secrete catecholamines. If biochemical testing results show high levels of catecholamine secretion in patients with known head and neck PGL, imaging studies should be done to identify another possible primary tumor, most commonly located in the abdomen or pelvis.

Screening of both affected and unaffected *SDH* mutation carriers should include biochemical evaluation—24-hr urinary and/or plasma metanephrines and catecholamines. In the presence of HNPGLs, which are mostly of parasympathetic origin, catecholamine evaluation should be done, as these tumors may have elevated methoxytyramine or dopamine.[23] The mutation carriers should also undergo regular imaging studies as a part of screening, as parasympathetic origin PPGL may be missed through biochemical evaluation alone in the absence of local symptoms. For unaffected carriers with known *SDHB*, *SDHC*, *SDHD,* and *SDHAF2* mutations, which have normal biochemical evaluation, imaging studies in the form of magnetic resonance imaging (MRI) or computed tomography (CT) scan of neck, thorax, abdomen, and pelvis should be carried out every two years. The frequency of these imaging studies on biochemical evaluation in unaffected carriers should be increased in the presence of elevated metanephrines or catecholamines. Functional imaging studies such as I-123 MIBG scans can also add value in such situations.[23] PPGLs, both benign and malignant, have been reported in children as young as 5 to 8 years old in the presence of *SDHB* and *SDHD* mutations;[24] hence, screening of unaffected mutation carriers should be started between 5 and 10 years of age. Recommendations for affected mutation carriers vary across literature and will depend on location of tumor, multicentricity, type of mutation, and distant metastasis. *SDH* mutation carries the most aggressive course, with higher chances of metastatic and multicentric disease; hence, more frequent follow-up may be warranted in these carriers. A summary of gene, protein function, and syndrome is given in Table 1.

SDHA Mutation

The current significance of *SDHA* in the PPGL syndrome spectrum is still unclear. *SDHA* is the major catalytic site of the complex and is coded by the largest gene. Mutations in both maternal and paternal alleles lead to Leigh's syndrome characterized by early-onset neurodegenerative

Table 1: Summary of gene, protein function, and syndrome

Gene	*Locus*	*Protein function*	*Gene mechanism*	*Syndrome*	*Primary locations*
SDHD	11q23	One of the two transmembrane subunits of Complex II of the respiratory chain	Autosomal dominant with LOH imprinting	Hereditary paraganglioma/ pheochromocytoma PGL1	Head and neck; parasympathetic trunk
SDHB	1p36.1-p35	The iron–sulfur protein catalytic subunit of Complex II	Autosomal dominant with LOH	Hereditary paraganglioma/ pheochromocytoma PGL4	Abdominal/thoracic paraganglia, adrenal; sympathetic trunk
SDHC	1q23.3	One of the two transmembrane subunits of Complex II of the respiratory chain	Autosomal dominant with LOH	Hereditary paraganglioma/ pheochromocytoma PGL3	Head and neck; parasympathetic trunk
SDHAF2	11q12.2	Mitochondrial assembly factor for Complex II—interacts directly with SDHA	Autosomal dominant with LOH imprinting	Hereditary paraganglioma/ pheochromocytoma PGL2	Head and neck; parasympathetic trunk
SDHA	5p15	The flavoprotein catalytic subunit of Complex II	Autosomal dominant with LOH	Hereditary paraganglioma/ pheochromocytoma PGL5	Abdominal paraganglia, sympathetic trunk
SDHA	5p15	The flavoprotein catalytic subunit of Complex II	Autosomal recessive	Mitochondrial encephalopathy/Leigh syndrome	Systemic
SDHAF1	19q13.12	Mitochondrial assembly factor for Complex II. Interacts directly with SDHB	Autosomal recessive	Infantile leukoencephalopathy	Systemic

LOH: loss of heterozygosity

disorder and cardiomyopathy.[25] *SDHA*-associated mutations are mapped to the *SDHA* gene on chromosome 5p15.33 and have shown to have low penetrance. Burnichon et al. identified one of the first heterozygous missense *SDH* mutation associated with abdominal PPGL;[26] subsequently, they also demonstrated that *SDHA* mutation represents approximately 3% of germline mutations in apparently sporadic PPGL.[27] It has been suggested by various authors that low penetrance of *SDHA* mutation may cause most of the carriers to escape from the development of clinical syndrome.

SDHAF2 Mutation

The *SDHAF2* gene is located on the chromosome 11q12.2 and encodes for a protein that facilitates the insertion of FAD group into *SDHA*.[9] Hence, mutations may lead to indirect loss of *SDH* activity. There are 15 reported cases of *SDHAF2*-associated PPGL, with 100% penetrance by age of 45.[28] The mutation maybe maternally imprinted and carriers usually develop parasympathetic tumors.[29]

SDHB Mutation

SDHB is mapped to chromosome 1p36.1-p35 with eight exons spanning 40 kb and encodes the iron sulfur subunit of the *SDH* complex. *SDHB* gene has been demonstrated to have tumor suppressor activity, with two-hit hypothesis as the proposed mechanism for loss of heterozygosity (LOH).[30] The mutation types are as follows: missense mutations (46%), frameshift mutations (23%), and splicing mutations (12%). The resulting syndrome from *SDHB* mutation usually affects the sympathetic ganglia of the abdomen and appears to be the most aggressive familial PPGL syndrome associated with *SDH* mutation.[31] Although the sympathetic ganglia of the abdomen and pelvis are most common site of affection, most tumors are extra-adrenal (about two-thirds) with rare cases in the head and neck as well. About one-third of the patients present with multifocal disease. The mean age at initial diagnosis varies from 28.7 to 36.7 years (range 6–77 years), with penetrance reaching 100% by 70 years of age.[24] The largest study to date, including 295 patients with *SDHB* mutations, found that the lifetime risk by age 60 of an *SDHB* mutation carrier developing a non–head and neck PGL was 52% with a mean age of diagnosis of 27 years old; the risk of developing a head and neck PGL was 29% with a mean age of diagnosis of 42 years old.[32] The estimated risk of malignancy in *SDHB*-mutation-associated PPGL ranges from 31 to 71%. The presence of metastasis has been observed in patients even after 20 years of initial PPGL diagnosis, making the calculation of absolute risk of malignancy difficult.[31,32] *SDHB* mutation carriers are also susceptible to other cancers, namely gastrointestinal stromal tumors (GIST), papillary carcinoma thyroid, neuroblastoma, and clear cell and papillary renal cell carcinoma.[31–33] The risk of renal cell carcinoma development in *SDHB* mutation carriers has been reported to be as high as 14%, compared to 1.49% lifetime risk in general population.[31] Mutations in *SDHB, SDHD*, and *SDHC* have also been demonstrated to be associated with Carney–Stratakis syndrome (GIST and PGL), but not with Carney's triad.[34]

SDHC Mutation

PPGLs associated with *SDHC* mutations are rare and account for less than 1% of patients.[35] *SDHC* mutations show autosomal dominant inheritance, with no parent of origin effect. The gene is located in chromosome 1q23.3. Reported *SDHC* mutations include nonsense mutations (47%), splicing mutations (33%), and large deletions (7%).[7] The mean age of initial diagnosis is 38 years, with a range of 17–70 years.[24] *SDHC* mutation carriers usually develop PGL in the head and neck region, although PPGL can rarely occur at other sites.[36]

SDHD Mutation

SDHD-related PPGL syndrome was first reported in Dutch population and was the first *SDH* mutation to be found.[37] *SDHD* is located at gene locus 11q23. *SDHD* mutations show high penetrance (87–100%) and are maternally imprinted. *SDHD* mutations include frameshift mutations (40%), nonsense mutations (25%), and splicing mutations (9%).[38] *SDHD* mutations are associated with both sympathetic (adrenal and extra-adrenal PPGL) and parasympathetic (HNPGL) tumors. These tumors are usually benign although shown multicentricity. Malignant transformation and metastasis is rare, but may occur. A German–Polish cohort of 34 patients with *SDHD* mutations showed predominantly HNPGL (79%), with 53% patients showing adrenal pheochromocytoma.[31] *SDHD*-related PPGLs express more genotype–phenotype correlation, with reports of nonsense and splicing mutations being associated with earlier disease development.[39]

Other Tumors Associated with SDH Gene Mutations

Two additional autosomal dominant hereditary syndromes are associated with *SDH* mutations—gastrointestinal stromal tumors (GISTs) and Carney–Stratakis dyad (GIST with paraganglioma).

GISTs are mesenchymal stromal tumors found predominantly in stomach and small intestinal tract. *SDH* mutation is implicated in about 7.5% of GISTs; however, majority are caused by *KIT* or platelet-derived growth factor α (*PDGF*α) mutations. These mesenchymal tumors are found in multiple locations along the gastric and intestinal wall and often metastasize to regional lymph nodes. It is believed that the pathogenesis of *SDH*/GISTs starts from germline mutations and epigenetic silencing of *SDH* genes. To date, *SDHA* mutations are most common, reported in 28% of *SDH*-deficient GIST. *SDHB, C,* and *D* mutations together made up 20 to 30% of all *SDH*-deficient GISTs.[40]

The Carney–Stratakis dyad (GISTs with paraganglioma) occurs due to mutations in *SDHB, SDHC,* or *SDHC,* and shows incomplete penetrance.[41]

Diagnosis and Management of SDH-related Tumors

PPGLs in *SDH*-associated syndromes pose a diagnostic challenge. *SDH* PGLs are preferential norepinephrine- or dopamine-secreting tumors due to lack of PMNT enzyme in the tissue. *SDHB*-mutated tumors may also be biochemically silent due to predominant dopamine secretion and/or lack of tyrosine hydroxylase.[42] HNPGLs are parasympathetic tumors, which are usually biochemically silent/dopamine-secreting, and may present with loco-regional compressive complaints as the leading symptom. Based on the expert recommendations from the International Symposium on Pheochromocytoma, initial biochemical testing should include measurement of fractionated metanephrines in urine or plasma or both. Chromogranin A can be used as a secondary diagnostic and follow-up marker in both sympathetic and parasympathetic tumors. Genetic testing is mandatory in family members of patients with *SDH*-related tumors and recommended in all cases

of malignant PPGL, early-onset or multifocal disease, and all cases of HNPGL.[43]

Imaging and localization studies carried out in *SDH*-related tumors are similar to sporadic cases. Both CT and MRI are sensitive modalities. In patients with suspected multifocal disease, especially *SDHB*-related, functional imaging is recommended. ^{123}I-metaiodobenzylguanidine (MIBG) (isotope uptake by cell membrane norepinephrine transporters), ^{18}F-fluorodopamine scintigraphy (isotope uptake by cell membrane norepinephrine transporters), ^{18}F-fluorodihydroxyphenylalanine positron emission tomography (PET) (catecholamine-production-related amino acid uptake), ^{18}F-fluorodeoxyglucose PET (isotope uptake through glucose transporters and hexokinase activity), and SST receptor scintigraphy are various functional imaging modalities that can be utilized depending upon the local availability.[44]

The mainstay of *SDH*-related PPGL is surgical resection whenever feasible, either conventional or laparoscopic. Pre- and perioperative management is aimed at control of catecholamine excess and associated complications. Pharmacological agents—α- and β-adrenergic blocking agents—can be used for preparation, along with others such as calcium channel blockers, similar to those used in sporadic cases. Operative mortality, both in sporadic and in familial cases, is less than 1% with the use of adequate pharmacological preparation.[45] Follow-up postsurgery should include regular measurement of blood pressure (biannual) and annual plasma or urinary metanephrines, along with the imaging studies such as CT or MRI or neck, thorax, abdomen, and pelvis. This follow-up should continue indefinitely, although time period for follow-up can be individualized. Patients with large tumors of >5 cm should be followed up initially every 3 months. The recurrence rates of *SDH*-mutation-related tumors remain unknown; however, *SDHB* mutations have shown to have a higher recurrence rate as compared to sporadic cases. The significance of chromogranin A as a follow-up marker is still debated; however, in the presence of significant pre-operative values, it can be used as a prognostic and follow-up marker.[46]

The management of metastatic cases is difficult and is same as that of sporadic metastatic cases. Metastasis in malignant PPGL can occur via both hematogenous and lymphatic route, although there exist disparities based on mutated genes. The most common sites of involvement in patients who have an *SDHB* mutation are the bone (78%), the lungs (45%), the lymph nodes (36%), and the liver (35%). In patients with sporadic PPGL, the most common sites of metastasis are the bones (64%), the lungs (47%), the lymph nodes (36%), and the liver (32%).[47] Presently, most therapies are palliative in the setting of a metastatic PPGL. The role of debulking surgery is not well established. Other treatment modalities include cytoreductive techniques, radiopharmaceuticals, chemotherapy, radiotherapy, and experimental therapies. Radiopharmaceuticals (like MIBG) and chemotherapy (cyclophosphamide, vincristine, and dacarbazine [CVD]) have an overall response rate of less than 40%; however, overall survival rate is poor as all patients usually develop progressively fatal disease.[47] Catecholamine excess itself causes debilitating and life-threatening symptoms and can be controlled with α-adrenergic blockers and metyrosine. Targeted therapies for *SDH*-related metastatic PPGL including anti-angiogenic therapies, HIF inhibitors, immunotherapy (nivolumab + ipilimumab, and pembrolizumab), temozolomide, and PARP inhibitors (Olaparib), which targeted the pseudohypoxic/cluster I gene products, have been used with varying success. Therapies targeting the kinase and Wnt pathway like mTOR inhibitors may not be as effective in this clinical scenario but may be tried. The clinical benefit of peptide receptor radionucleotide therapy (PRRT) is still unclear and requires further studies. The prognosis after diagnosis of metastatic PPGL is highly variable, with an estimated five-year survival rate between 34 and 74%.[48]

Conclusion

SDH contains multiple subunits participating in both Kreb's cycle and ETC. Mutation in any of the components leads to a pseudohypoxic response and increased tumorigenesis. Although most PPGLs and HNPGLs associated with *SDH* mutation are benign, those associated with SDHB mutations are aggressive, multifocal, and often malignant. Screening protocols are not well established and should be individualized based on the clinical presentation and genetic workup. Management does not differ from sporadic cases; however, postoperative follow-up should continue indefinitely.

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