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Metabolic Drivers in Hereditary Cancer Syndromes

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Abstract
Cancer is a multifaceted disease in which inherited genetic variants can be important drivers of tumorigenesis. The discovery that germline mutations of metabolic genes predispose to familial forms of cancer caused a shift in our understanding of how metabolism contributes to tumorigenesis, providing evidence that metabolic alterations can be oncogenic. In this review, we focus on mitochondrial enzymes whose mutations predispose to familial cancer, and we fully appraise their involvement in cancer formation and progression. Elucidating the molecular mechanisms that orchestrate transformation in these diverse tumors may answer key biological questions about tumor formation and evolution, leading to the identification of new therapeutic targets of intervention.

Keywords
mitochondria, cancer, metabolism, oncometabolites, inherited, syndrome
1. INTRODUCTION

Cancer is a set of different disorders with 18 million new cases per year worldwide (GCO 2019). While somatic mutations of oncogenes and tumor suppressors contribute to the majority of cancer, 5–10% of cancers are hereditary (Lu et al. 2014, Okur & Chung 2017). Recent progress in human cancer genetics has led to the identification of the genetic basis of rare familial cancer syndromes and, through genome-wide association studies, of common genetic variants that are individually associated with small increases in cancer risk (Stadler et al. 2010). Thanks to this effort, it has been possible to identify a wide spectrum of heterozygous mutations in metabolic genes that may predispose to hereditary cancer. The first hint that metabolic dysregulation could predispose to cancer came when it was shown that asymptomatic carriers of heterozygous mutations of components of the enzymes succinate dehydrogenase (SDH) and fumarate hydratase (FH) were at increased risk of cancer development (Astuti et al. 2001b, Baysal et al. 2000, Tomlinson et al. 2002). Interestingly, besides SDH and FH, it was later shown that other mutations affecting mitochondrial enzymes may predispose to familial cancer. In all these cases, patients inherit one copy of the mutated gene, and loss of the wild-type allele [loss of heterozygosity (LOH)] by a somatic event [e.g., chromosomal deletion or gene mutation, as per Knudson’s two-hit hypothesis (Hethcote & Knudson 1978, Knudson 1971)] leads to cancer. Despite recent progress in understanding how metabolism influences tumorigenesis, the precise molecular mechanisms by which metabolic alterations support cellular transformation remain elusive. Therefore, these hereditary metabolic disorders represent a unique opportunity to identify novel oncogenic mechanisms that link disorders of metabolism to neoplasia. In this review, we provide an overview of hereditary cancers caused by mutations of metabolic enzymes, with a particular focus on mitochondrial enzymes.

2. GERMLINE MUTATIONS OF METABOLIC GENES AND CANCER

2.1. Succinate Dehydrogenase and Fumarate Hydratase

Although Otto Warburg described metabolic abnormalities in cancer cells almost a century ago (Warburg 1924), the first metabolic drivers of tumorigenesis were identified only 20 years ago, when it was shown that mutations in SDH subunit genes (SDHX) (Astuti et al. 2001b, Baysal et al. 2000, Niemann & Müller 2000) and FH (Tomlinson et al. 2002) predispose to familial cancers. Below we discuss which mutations affect SDHX and FH genes, as well as their involvement in human diseases. Moreover, we describe how the metabolic dysfunction generated by SDH and FH loss in cancer cells activates pro-oncogenic signals that ultimately favor cellular transformation, identifying possible overlapping cascades.

2.1.1. Succinate dehydrogenase. SDH is a hetero-oligomer enzyme localized to the inner mitochondrial membrane (IMM). This enzyme has dual functions; the first is to oxidase succinate to fumarate in the TCA (tricarboxylic acid) cycle and the second is to transfer electrons to the ubiquinone pool [coenzyme Q (CoQ)], contributing to cellular respiration (Rasheed & Tarjan 2018, Rutter et al. 2010). From a structural point of view, SDH consists of four subunits (SDHA, SDHB, SDHC, and SDHD) and two assembly factors (SDHAF1 and SDHAF2) (Rutter et al. 2010, Van Vranken et al. 2015), all encoded by nuclear DNA (Bourgeron et al. 1995). SDHA is the flavoprotein subunit responsible for conversion of succinate to fumarate and is exposed toward the mitochondrial matrix, while SDHB is an iron-sulphur (Fe-S) subunit, partially embedded within the IMM. In contrast, both SDHC and SDHD are transmembrane subunits and they are directly involved in binding CoQ (Rasheed & Tarjan 2018, Rutter et al. 2010).
Table 1  Germline mutations of metabolic genes and human diseases

| Gene  | Disease caused by biallelic variants | Disease caused by monoallelic variants | Common mutations found in cancer |
|-------|-------------------------------------|----------------------------------------|---------------------------------|
| SDHX  | Complex II deficiency, Leigh syndrome | PPGL, HNPGL, wtGIST, RCC                | Multiple                        |
| FH    | Fumaric aciduria                     | HLRCC, PPGL                             | Multiple                        |
| MDH2  | Unknown                              | PPGL                                    | c.429+1G>T, p.Arg104Gly, p.R140Q/G, T495M |
| IDH2  | Unknown                              | 2-HGA, myeloid neoplasia               | T495M, R261H                     |
| IDH3A | Unknown                              | Myeloid neoplasia, PPGL                | R360C                           |
| IDH3B | Unknown                              | Myeloid neoplasia, PPGL                | R359W, R334W, c.128_138del      |
| SLC25A11 | Unknown                   | PPGL                                    | Multiple                        |
| GOT2  | Unknown                              | PPGL                                    | c.357A>T                        |
| DLST  | Unknown                              | PPGL                                    | p.Gly374Glu                      |
| OGDHL | Unknown                              | PPGL                                    | c.750G>T                        |

Summary of the mutations of mitochondrial enzymes that predispose to familial cancer, as described in the review. The table includes a distinction between diseases caused by monoallelic or biallelic mutations for the same mitochondrial genes. Abbreviations: 2-HGA, 2-hydroxyglutaric aciduria; HLRCC, hereditary leiomyomatosis and renal cell cancer; HNPGL, head and neck paraganglioma; PPGL, pheochromocytoma/paraganglioma; RCC, renal cell carcinoma; wtGIST, wild-type gastrointestinal stromal tumor.

SDH gene mutations and human disease. SDH-related human diseases may be divided into those that result from biallelic pathogenic variants (inherited as an autosomal recessive trait) and those caused by a heterozygous SDH subunit gene (SDHX) variant (Table 1). Carriers of biallelic mutations in SDHX genes are affected by an autosomal recessive disorder called complex II (CII) deficiency [OMIM (Online Mendelian Inheritance in Man) #252011], a rare infantile mitochondrial disease that targets the respiratory chain with around 36 cases reported in the literature (Jain-Ghai et al. 2013).

Patients affected by CII deficiency may display a multisystem failure in early years of life that leads to untimely death or, in milder cases, may present as adult onset, myopathy or cardiomyopathy, and optic atrophy (Jain-Ghai et al. 2013, Taylor et al. 1996). In more severe cases, specific brain abnormalities such as leukencephalopathy and cerebellar atrophy may be detected by brain imaging (Grønberg et al. 2016, Ochoa-Rapáraz et al. 2010). CII deficiency disorders have been reported with biallelic mutations in SDHA, SDHB, SDHC, SDHD, and SDHAF1 (Alston et al. 2012, Grønberg et al. 2016, Helman et al. 2016, Jackson et al. 2014).

Individuals with heterozygous loss-of-function SDHX mutations do not have any symptoms of mitochondrial CII deficiency but are at increased risk of developing a range of rare tumors. Monoallelic mutations in SDHA, SDHB, SDHC, SDHD, and SDHAF2 have all been associated with tumor susceptibility. All tumors that develop in mutation carriers demonstrate loss of SDH function as a consequence of an additional somatic event that inactivates the wild-type allele of the relevant subunit (as in the Knudson two-hit model for retinoblastoma) (Hoekstra & Bayley 2013, van Nederveen et al. 2009). Given the shared effect on SDH function, as might be expected, there are significant overlaps in the spectrum of tumors associated with mutations in individual SDHX genes, but there are also important clinical differences in overall tumor risks, tumor-type-specific risks, and inheritance patterns. Growing recognition of this clinical heterogeneity has resulted in moves to adopt gene-specific protocols for the management of affected patients and their relatives. In 2000, Baysal et al. (2000) reported for the first time the presence of germline heterozygous mutations in the gene encoding the D subunit of SDH (SDHD) in familial head and neck paraganglioma (HNPGL) kindreds. HNPGL is a type of neuroendocrine...
tumor that arises from parasympathetic ganglia in the head and neck [depending on their location, they may be called carotid paragangliomas, jugulotympanic paragangliomas, etc., or chemodec-tomas (Taïeb et al. 2014, Williams 2017)]. Another form of paraganglioma (PGL) is derived from sympathetic ganglia; these typically occur in the abdomen and thorax (Tischler 2008). Previously known as extra-adrenal pheochromocytomas (PCC), these tumors now known as PGL are, like PCC (which arise in the adrenal medulla) but unlike HNPGL (which are usually nonsecretory), usually accompanied by cardiovascular symptoms (e.g., hypertension) caused by catecholamine secretion (adrenaline, noradrenaline, etc.) (Taïeb et al. 2014, Tischler 2008, Williams 2017). An unusual aspect of SDHD-related familial HNPGL is that although the heterozygous mutations that predispose to the development of disease have high penetrance, their inheritance is atypical for an autosomal dominant disease since, in general, an individual will only develop disease after inheriting a pathogenic variant from their father, while the risk of clinical disease after maternal transmission is very low (Baysal 2013, Baysal & Maher 2015, Burnichon et al. 2017, Vandermey et al. 1989). This type of parent-of-origin effect is typically seen with disorders in genes subject to genomic imprinting (Monk et al. 2019). However, there is no evidence that SDHD is imprinted; on the contrary, it has been suggested that the parent-of-origin effect may be related to the colo-ocation of SDHD (11q23.1) with an imprinted cluster of genes (11p15, including IGF2, CDKN1C, and H19) on chromosome 11 (Baysal et al. 2011, Hensen et al. 2004). After the demonstration that germline SDHD mutations cause familial HNPGL, it was reported that germline mutations in SDHD or other components of the SDH complex may also predispose to PCC/PGL (PPGL) (Astuti et al. 2001a, Gimm et al. 2000). For instance, germline SDHC mutations were found to cause familial HNPGL (Niemann & Müller 2000), while germline SDHB mutations were found to cause inherited PPGL or HNPGL and PPGL (Astuti et al. 2001a), and later, SDHA and SDHAF2 were reported as rare causes of PPGL and HNPGL, respectively (Bayley et al. 2010, Burnichon et al. 2010). The range of tumors associated with germline pathogenic variants in SDHX genes has now expanded beyond HNPGL and PPGL to include renal cell carcinoma (RCC), wild-type gastrointestinal stromal tumors (wt GISTs), and, less frequently, neuroblastoma and pituitary tumors (Boikos et al. 2016, Dénes et al. 2015, Janeway et al. 2011, Schimke et al. 2010). While tumors from patients with germline SDHX mutations typically demonstrate LOH, inactivation of SDHX genes by biallelic somatic events is rare in sporadic HNPGL, PPGL, etc. (Baysal & Maher 2015). However, the silencing of SDHC through promoter methylation, which can occur as a somatic event in the absence of a germ line mutation called epimutation, is well documented in a subset of SDH-deficient (dSDH) wt GISTs (Haller et al. 2014, Urbini et al. 2015). In conclusion, a wide spectrum of mutations affecting the SDH complex have been identified in different types of familial cancers. Based on the subunits targeted by the mutation, it is possible to identify both shared features and clinical differences. Below we give a detailed description of the correlation of genotype/phenotype in dSDH tumors and of the common oncogenic signaling activated by SDH loss.

**Genotype-phenotype correlation in SDHX-related tumorigenesis.** Germline SDHX mutations are the most important causes of inherited HNPGL and PPGL. The latter has been termed the most heritable of human tumors, as up to 40% occur in individuals with a mutation in an inherited PPGL gene. Interestingly, although mutations affect different subunits, there is overlap between the clinical phenotypes associated with heterozygous mutations in SDHX genes. For instance, immunostaining of SDHX-related tumors usually shows loss of SDHB expression irrespective of the subunit harboring the germline mutation (Papathomas et al. 2015, van Nederveen et al. 2009), and all SDHX-mutated tumors are characterized by succinate accumulation. However, despite these shared features, there are also important clinical differences associated with germline mutations.
in specific subunits, implying that the clinical management of individual families should be tailored toward the specific SDHX gene involved (Wong et al. 2019). Thus, while germline SDHAF2 and SDHD mutations display a similar parent-of-origin inheritance pattern, germline mutations in SDHB, SDHC, and SDHA are all associated with no parent-of-origin effects, following a conventional autosomal dominant tumor predisposition inheritance pattern (Baysal & Maher 2015, Wong et al. 2019).

The most commonly mutated subunits of SDH in HNPGL/PPGL are SDHD and SDHB. Initially, mutations affecting both subunits were thought to be associated with a high clinical penetrance (for SDHD after paternal transmission) (Astuti et al. 2001a, Baysal et al. 2000). However, more widespread genetic testing has led to a reduction in penetrance estimates, particularly for SDHB mutations, which are thought to have a lifetime penetrance of tumor development of 20–25% (Andrews et al. 2018, Benn et al. 2018). Germline mutations in SDHB and SDHD both predispose to PPGL and HNPGL, with higher risks to develop PPGL and HNPGL associated with SDHB and SDHD mutations, respectively. Compared to other major inherited PPGL genes such as VHL (Von Hippel–Lindau), RET, and NF1, SDHX mutations are associated with a higher risk of PGL than PCC and predispose to multiple primary tumors (NGSnPPGL et al. 2017). Around 10% of all PPGL cases are malignant, but the risk of malignant disease with germline SDHB mutations is much higher than with mutations in other SDHX subunit genes or other inherited PPGL genes (Andrews et al. 2018). Following reports of SDHB and SDHD involvement in HNPGL and PPGL, germline mutations in SDHB were linked with predisposition to RCC in patients with PPGL and RCC and in those with only inherited RCC (Ricketts et al. 2008, Vanharanta et al. 2004). Mutations in other SDHX genes have also been linked with RCC, but the best-defined association is with SDHB. Of note, dSDH RCC has now been defined as a specific pathological entity with typical histological features (e.g., eosinophilic cytoplasm and cytoplasmic inclusions) that can be used to refer the patients for a genetic test relative to germline SDHX mutation (Wang & Rao 2018). The involvement of SDHA in HNPGL and PPGL was documented sometime after that of SDHB, SDHC, and SDHD, and although there is limited information available on SDHA-related neoplasia, the clinical penetrance of germline SDHA mutations appears to be low (e.g., ≤10%). However, in patients with wt GISTs, SDHA is the most commonly detected germline SDHX mutation (Boikos et al. 2016). Interestingly, these tumors are often associated with inherited disease (either neurofibromatosis type 1 or germline SDHX mutations causing dSDH wt GISTs) (Boikos et al. 2016). The early diagnosis of dSDH wt GISTs is important, as cases do not usually respond to the standard therapy for GIST, such as treatment with imatinib (Boikos et al. 2016).

Following the detection of a SDHX gene mutation in an individual, it is standard practice to identify other family members who might also harbor the mutation and to discuss genetic testing and (if they test-positive) lifelong surveillance to detect SDHX-related tumors at an earlier stage (Wong et al. 2019). Currently there are differences between centers regarding the nature of ongoing surveillance protocols (which must balance the potential benefits of early detection against the inconvenience, economic burden, etc.), but there is a growing movement for tailoring specific management strategies for patients according to which SDHX germline mutations they carry and their relative tumor risks. Finally, the results of surveillance should be collected and audited to enable refinement of existing practice (Wong et al. 2019). Despite the need for a more personalized approach in the management of patients harboring germline SDHX mutations, further effort should also be put into the development of early detection tools for unique markers linked to SDH loss, such as the accumulation of succinate within tumors. Indeed, all dSDH tumors are characterized by the accumulation of succinate (Cardaci et al. 2015, Pollard et al. 2005a) and succinyl-coenzyme A (CoA) (Smestad et al. 2018), which have been shown to activate
oncogenic signaling cascades and reprogram chromatin structure. How accumulation of succinate and succinyl-CoA contribute to tumorigenesis is discussed below.

**Oncogenic signaling activated by SDH loss.** The most striking biochemical feature of dSDH cells is the accumulation of succinate (Cardaci et al. 2015, Pollard et al. 2005a). It has been widely demonstrated that succinate not only is a TCA cycle intermediate but also has different biological functions. The first pro-oncogenic signaling associated with succinate accumulation in dSDH tumors was the stabilization of hypoxia-inducible factor 1 alpha (HIF1α) (Pollard et al. 2005a, Selak et al. 2005) due to the succinate-dependent inhibition of HIF prolyl-hydroxylases (PHDs), a group of proteins that belongs to the family of α-ketoglutarate (αKG)-dependent dioxygenases (aKGDDs). However, the impact of aKGDD inhibition goes far beyond hypoxia. Indeed, succinate was shown to inhibit another class aKGDDs, the DNA demethylases called ten-eleven translocation (TET) proteins (Hoekstra et al. 2015, Laukka et al. 2016, Xiao et al. 2012), leading to CpG (5′−C−phosphate−G−3′) island hypermethylation, a phenotype later termed CIMP (CpG island methylator phenotype) (Letouze et al. 2013). The CIMP has been observed in different types of tumors harboring SDH mutations, including GIST tumors (Killian et al. 2013), PCC, and PGL (Letouze et al. 2013), independent of which subunit of SDH complex was affected. It has been proposed that in PPGL, the DNA hypermethylation phenotype may directly contribute to transformation through the suppression of key genes involved in neuroendocrine differentiation, catecholamine production, and epithelial differentiation (Letouze et al. 2013), whose silencing is part of the epithelial-to-mesenchymal transition (EMT) observed in these tumors (Loriot et al. 2015). Consistent with the biological significance of the CIMP, mouse Sdhb−/− chromafin cells display increased migration properties that are impaired by treatment with 5-azacitidine, a compound that inhibits DNA methyl transferases (Letouze et al. 2013). Furthermore, PGL that display a CIMP have a worse prognosis than those that do not (Letouze et al. 2013). Similarly, the impairment of TET-dependent demethylation of miR200 also induces EMT in Sdhb−/− mouse renal epithelial cells (Sciacovelli et al. 2016), supporting the hypothesis that the epigenetic remodeling caused by SDH loss affects the malignancy of these cells. Despite the link between the CIMP and cancer-associated phenotypes such as the EMT, the consequences of DNA hypermethylation on other malignant features of these tumors are largely unexplored. Through the accumulation of succinate, other key components of the epigenetic machinery are affected. First, dSDH cells exhibit higher methylation levels of lysine 27 of histone H3 (H3K27me3 and H3K27me2) and lysine 9 of H3K9me3 (Letouze et al. 2013) due to inhibition of the Jumonji-containing histone lysine demethylases (JmjC-KDMs). Consistent with these results, dSDH PGL exhibit increased methylation of H3K9me3 (Hoekstra et al. 2015). Second, another aKGDD, the fat mass and obesity-associated protein (FTO) (Gerken et al. 2007), an enzyme involved in the removal of N6-methyladenosine from messenger RNA (mRNA) (Jia et al. 2011), is inhibited in vitro by high levels of succinate (Gerken et al. 2007). Whether these two components affect cell behavior and tumor aggressiveness is still unknown. Finally, the biallelic loss of SDH leads to the accumulation of not only succinate but also succinyl-CoA, the metabolite converted by succinyl-CoA synthase to succinate in the TCA cycle (Smestad et al. 2018). Succinyl-CoA is a source of acylation of proteins (Weinert et al. 2013); consequently, dSDH cells exhibit increased nucleosome succinylation, which overall favors gene transcription but also results in a defect of the DNA repair machinery that sensitizes cells to treatment with genotoxic agents (Smestad et al. 2018). Despite the effort in fully understanding the biological meaning of protein succinylation, the effect of this posttranslational modification on cellular transformation is still largely unexplored and requires further investigation. In conclusion, succinate accumulation plays a key role in the biology of dSDH tumors. However, it remains to be determined which of
these signaling cascades, or other succinate-independent processes, actively contribute to cellular transformation.

### 2.1.2. Fumarate Hydratase

FH is a TCA cycle enzyme that catalyzes the hydration/dehydration of fumarate to L-malate within mitochondria. In eukaryotes, FH is an homotetramer protein present in a cytosolic and a mitochondrial variant (Yogev et al. 2011).

**FH mutations and human disease.** As with SDH-related human disease, FH-related disorders may be divided into those caused by biallelic pathogenic variants (inherited as an autosomal recessive trait) and those caused by heterozygous FH gene variants (Table 1). FH deficiency, also known as fumaric aciduria (OMIM #606812), causes failure to thrive, developmental delay, hypotonia, and cerebral atrophy, as well as lactic, pyruvic, and fumaric acidemia. Prenatal features can include intrauterine growth retardation and brain ventricular enlargement. Postnatally, the most common features are neurologic abnormalities (lethargy or impaired consciousness, hypotonia, epilepsy, developmental delay, and microcephaly), failure to thrive with poor weight gain, and dysmorphic features (e.g., frontal bossing, depressed nasal bridge, and widely spaced eyes) (Allegrì et al. 2010, Kerrigan et al. 2000, Maradin et al. 2006, Ottolenghi et al. 2011, Phillips et al. 2006, Whelan et al. 1983). The prognosis is generally poor with progressive worsening of the neurological state, and many children die in the first decade of life. By 2000, the clinical features of only 21 patients had been described (Kerrigan et al. 2000); today, FH deficiency remains a very rare condition with less than 100 cases known (Ewbank et al. 2006).

Heterozygous mutations in FH predispose to hereditary leiomyomatosis and renal cell cancer (HLRCC). HLRCC is a rare (approximately 1 in 200,000 individuals) autosomal-dominantly inherited tumor predisposition syndrome caused by monoallelic germline loss of function mutations in the FH gene. The major clinical features of HLRCC are cutaneous leiomyomas, uterine leiomyomas in females, and aggressive RCC. The association of familial multiple cutaneous and uterine leiomyomas (MCUL) was described more than four decades ago (Reed et al. 1973) and is sometimes called Reed syndrome. Subsequently the association of MCUL with renal cancer was described in families from Finland (Launonen et al. 2001) and the term “HLRCC” was adopted. Cutaneous leiomyomas have been estimated to occur in about 70% of cases, and these benign smooth muscle tumors present as brownish nodules, which may be painful when exposed to the cold. On average they occur in the third decade (but may occur as early as 10 years of age) and often appear in groups of lesions. Uterine leiomyomas (fibroids) appear in most women and at an earlier age (mean 30 years) than women with noninherited fibroids. If not detected by screening, fibroids usually present with menorrhagia and pain and may require hysterectomy at a young age. Although uterine leiomyosarcomas have been reported in some patients with HLRCC (Lehtonen et al. 2006), this appears to be a rare complication. The most worrisome complication of HLRCC is RCC, which is often highly aggressive, can metastasize at an early stage of development, and has a poor prognosis. Classically, HLRCC-associated RCC has been classified as the type 2 papillary RCC histological subtype, although other histological subtypes also occur (Chen et al. 2014, Launonen et al. 2001, Merino et al. 2007). The overall frequency of RCC in HLRCC is ~15% and the tumors tend to be unifocal (c.f. von Hippel–Lindau disease, in which multicentric and bilateral disease is common), but because of the aggressive nature of the tumors and the possibility of very early onset (the mean age at diagnosis of RCC is 41 years but ranges from 11 to 90 years), it has been recommended that annual renal MRI screening might be offered beginning at 10 years of age (Menko et al. 2014). If a small RCC is detected, then immediate partial nephrectomy is indicated. PPGL and RCC are well-described complications of germline SDHB mutations, and more recently, PPGL has been associated with germline FH mutations, albeit rarely (Clark et al. 2014,
The detection of a germline pathogenic FH variant enables a definitive diagnosis to be made in patients in whom the clinical diagnosis is uncertain. However, pathogenic missense substitutions are a common cause of HLRCC, and the pathogenicity of rare missense substitutions may be difficult to interpret. To date, there are no clear differences in the FH mutation spectra of heterozygotes who are diagnosed because of a personal or family history of HLRCC and of those who are detected because their child had been diagnosed with FH deficiency. Also, no clear genotype-phenotype correlations have been described in HLRCC; therefore, carriers of FH heterozygous mutations should generally be considered at risk of RCC and offered surveillance. Importantly, tumors from patients with HLRCC show loss of the wild-type FH allele leading to full FH inactivation. Therefore, FH-deficient tumors and cells are characterized by increased intracellular fumarate levels (Ashrafian et al. 2010, Frezza et al. 2011, Sciacovelli et al. 2016, Zheng et al. 2013). Fumarate accumulation has recently been the focus of research relative to HLRCC tumors. How fumarate contributes to both cellular transformation and tumor evolution is discussed below.

**Oncogenic signaling triggered by FH loss.** A distinctive signature of both FH-deficient cells and tumors is the accumulation of fumarate (Ashrafian et al. 2010, Frezza et al. 2011, Sciacovelli et al. 2016, Zheng et al. 2013), which has been proposed to contribute to cellular transformation. The protumorigenic effect of fumarate is due to its capacity to interfere with the activity of proteins involved in a variety of signaling cascades (Figure 1). Part of the fumarate-dependent signaling is due to its chemical reactivity: Fumarate is a mild electrophile, and based on the cellular environment and pH (Kulkarni et al. 2019), it can bind cysteine residues of proteins, leading to a posttranslational modification called succination (Alderson et al. 2006, Bardella et al. 2011, Yang et al. 2014). Notably, protein succination represents a biochemical signature of FH-deficient tumors and is proportional to fumarate levels (Yang et al. 2014). Various proteins have been identified as targets of succination; however, the biological significance of this modification is not immediately obvious and may vary based on the target. For instance, succination of glutathione (GSH) (Sullivan et al. 2013, Zheng et al. 2015) and the Kelch-like ECH-associated protein 1 (KEAP1) (Adam et al. 2011) are both involved in the regulation of redox balance in FH-deficient cells. However, while succination of GSH depletes an important antioxidant molecule, leading to increased oxidative stress (Sullivan et al. 2013, Zheng et al. 2015), the succination of KEAP1, a negative regulator of the transcription factor nuclear factor erythroid 2–like 2 (NRF2), favors the activation of a powerful antioxidant response (Adam et al. 2011, Ooi et al. 2011). Which of these two opposing effects prevails is unclear, even though it has been hypothesized that overcoming ROS (reactive oxygen species)-induced senescence may be an oncogenic event required to obtain full transformation in FH-deficient cells (Zheng et al. 2015). Another important group of proteins targeted by succination is involved in iron metabolism and Fe-S cluster biogenesis. For instance, Kerins et al. (2017) showed that IRP2 (iron regulatory protein 2) is succinated in FH-deficient cells, leading to depletion of freely available iron. Moreover, succination of multiple family members of the Fe-S cluster assembly proteins including the Fe-S cluster scaffold 1 (NFS1) has been proposed to contribute to the respiratory chain defect observed in FH-deficient cells (Tyrakis et al. 2017). Finally, it has been demonstrated that a key component of the SWI–SNF (switch/sucrose nonfermentable) tumor-suppressor complex, the SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily C member 1 (SMARCC1), is succinated by fumarate (Kulkarni et al. 2019). Even though the impact of the modification on SMARCC1 activity is uncertain (Kulkarni et al. 2019), it is possible that it may affect both the chromatin structure and the tumorigenic properties of FH-deficient tumors.

Another component of the pro-oncogenic signals elicited by fumarate is the inhibition of aKGDDs, with outcomes similar to those observed in dSDH tumors. For instance, the inhibition
Figure 1

The oncogenic signals activated upon SDH and FH loss via the accumulation of fumarate (green) and succinate (blue), respectively. These signals are activated through posttranslational modification of proteins (succination/succinylation) or inhibition of aKGDDs such as PHDs, FTOs, KDMs, and TETs. As a result of this multilayer cellular reprogramming, SDH- and FH-deficient tumors undergo cellular dedifferentiation and EMT, inhibition of DNA repair, and inhibition of senescence. Abbreviations: Ac, histone acetylation; aKG, α-ketoglutarate; aKGDDs, aKG-dependent dioxygenases; CIMP, CpG island methylator profile; CoA, coenzyme A; EMT, epithelial-to-mesenchymal transition; FH, fumarate hydratase; FTO, fat mass and obesity–associated protein; HIFs, hypoxia-inducible factors; KDMs, lysine histone demethylases; Me, methyl group; NRF2, nuclear factor, erythroid 2–like 2; PHDs, prolyl-hydroxylases; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SMARCC1, SWI/SNF-related, matrix-associated, actin–dependent regulator of chromatin subfamily C member 1; Suc, succinylated histone; TCA, tricarboxylic acid; TETs, ten-eleven translocation proteins.
of PHDs leads to the stabilization of HIF1α (Isaacs et al. 2005), giving rise to a hypoxic response. However, the role of HIF1α activation in FH-dependent tumorigenesis is still debated. On the one hand, HIF activation may drive angiogenesis, metabolic reprogramming, and cross-activation of other oncogenic signaling (Pollard et al. 2005b, Tong et al. 2011). On the other hand, mouse genetic data indicate that HIFs are dispensable for renal cyst formation (Adam et al. 2011). Other aKGDDs disrupted by fumarate are DNA and histone demethylases (Hoekstra et al. 2015, Laukka et al. 2016, Xiao et al. 2012). As for dSDH tumors, FH-mutant cancers are characterized by a distinctive CIMP, which distinguishes these tumors from other renal cancers (Cancer Genome Atlas Res. Netw. 2016, Letouze et al. 2013, Ricketts et al. 2018). The biological relevance of this phenotype is not fully understood. It is possible that through the hypermethylation of tumor-suppressor genes, fumarate can drive tumor progression bypassing the need for additional somatic lesions. Consistent with this hypothesis, it has been demonstrated that the tumor suppressor CDKN2A (cyclin dependent kinase inhibitor 2A), whose silencing is linked to cell cycle alterations, senescence impairment, and metastasis (Zhao et al. 2016), is hypermethylated in FH-deficient renal cancers (Cancer Genome Atlas Res. Netw. 2016). Another biological consequence of the aberrant DNA methylation observed in these tumors is the suppression of a family of antimetastatic micro RNAs, miRNA200, and the activation of an EMT (Sciacovelli et al. 2016), a signature associated with poor clinical outcome and metastasis (Brabletz et al. 2018). As a consequence, FH-deficient cells show a global histone hypermethylation, and RNA methylation is predicted to be increased (Gerken et al. 2007, Xiao et al. 2012). Unlike DNA hypermethylation, the role of both histone and RNA modification in FH-dependent tumorigenesis is largely unexplored. In conclusion, similarly to succinate, fumarate accumulation is responsible for the main biochemical features observed in HLRCC. However, additional experiments are required to identify which oncogenic signaling cascades are sufficient to drive cellular transformation.

2.2. Malate Dehydrogenase

Malate dehydrogenase (MDH) is a dimeric NAD+-dependent enzyme that catalyzes the reversible oxidation of malate to oxaloacetate (Minarik et al. 2002, Musrati et al. 1998). Two main isoforms have been characterized in eukaryotic cells, one mitochondrial, encoded by the MDH2 gene, and one cytosolic, encoded by MDH1, with distinct metabolic functions (Minarik et al. 2002, Musrati et al. 1998). Indeed, MDH2 is part of the TCA cycle, while cytosolic MDH1 is involved in the malate-aspartate shuttle. So far, no inherited mutations in MDH1 have been identified in cancer, whereas MDH2 was recently found mutated in PPGL (Table 1) (Cascon et al. 2015). In this study, the authors reported a heterozygous germline mutation of MDH2 (c.429+1G>T) accompanied by LOH, which causes the suppression of MDH2 at both mRNA and protein levels, in a patient with multiple malignant PGL (Cascon et al. 2015). Surprisingly, these tumors do not accumulate malate at high levels but instead have an increased ratio of fumarate to succinate, which could suppress aKGDDs (Figure 2). Consistently, MDH-deficient tumors have lower 5-hmC (5-hydroxymethylcytosine) staining, a transcriptional profile compatible with a CIMP-like phenotype, and a higher staining for H3K27me3 in immunohistochemistry (Cascon et al. 2015). After this initial report, five new potential pathogenic heterozygous germline variants of MDH2 in PGL were identified (Calsina et al. 2018). Of note, one of these variants (p.Arg104Gly), which was not accompanied by LOH, was shown in vitro to significantly affect MDH2 activity, suggesting a possible dominant negative effect of the mutant on the wild-type protein (Calsina et al. 2018). Even though these works identify a pathogenic role of MDH2 mutations in PGL, the
The oncogenic cascades activated upon genetic loss of the indicated mitochondrial enzymes observed in familial cancer. The loss of function of these enzymes alters the intracellular content of metabolites, including fumarate, succinate, 2-HG, and aKG, dysregulating the activity of multiple aKGDDs, leading to alterations of both histone and DNA methylation status or triggering a pseudo-hypoxic response. Abbreviations: 2-HG, 2-hydroxyglutarate; Ac, histone acetylation; aKG, α-ketoglutarate; aKGDDs, aKG-dependent dioxygenases; CIMP, CpG island methylator phenotype; CoA, coenzyme A; GOT2, glutamic-oxaloacetic transaminase 2; HIFs, hypoxia-inducible factors; IDH, isocitrate dehydrogenase; KDMs, lysine histone demethylases; Me, methyl group; MDH2, malate dehydrogenase 2; OGC, 2-oxoglutarate; OGDC, 2-oxoglutarate/malate carrier; PHDs, prolyl-hydroxylases; TCA, tricarboxylic acid; TETs, ten-eleven translocation proteins.

mechanisms by which MDH2 loss drives tumorigenesis are still unclear. Therefore, it would be important to assess whether the metabolic dysregulation caused by MDH loss or a nonmetabolic function of MDH contributes to transformation.

2.3. Isocitrate Dehydrogenase

Isocitrate dehydrogenase is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to aKG, a reaction involved in the TCA cycle, glutaminolysis, lipid biosynthesis, cellular respiration, and intracellular redox balance (Al-Khallaf 2017). The human genome contains five genes encoding for three different isocitrate dehydrogenase (IDH) isoforms (Al-Khallaf 2017), which present different cofactors, localization, and directionality of the reaction they catalyze. IDH1 and IDH2 are both NADP+-dependent homodimeric complexes that reversibly convert
isocitrate into αKG in different subcellular compartments. Differently, IDH3, a NAD⁺-dependent heterotetrameric protein within the TCA cycle, catalyzes the conversion of isocitrate to αKG, a reaction tightly controlled by Ca²⁺, ADP, ATP, citrate, NADH, and NADPH (Al-Khallaf 2017). Recent sequencing efforts unveiled somatic mutations of both IDH1 and IDH2 in different tumor types including low-grade gliomas, glioblastoma, chondrosarcomas, and acute myeloid leukemia (Dang & Su 2017). Importantly, all of these IDH-mutant tumors accumulate high levels of d-2-hydroxyglutarate (D2-HG) (Dang & Su 2017), a metabolite that, similar to fumarate and succinate, once accumulated can activate pro-oncogenic signaling cascades. Despite a well-established role of IDH somatic mutations in tumorigenesis, the evidence that germline mutations of any IDH gene predispose to cancer is still debated. For instance, it has been shown that IDH2 heterozygous germline mutations (p.R140Q and p.R140G) cause an inborn error of metabolism (IEM) syndrome called D2-HG aciduria type II (Kranendijk et al. 2010), characterized by epilepsy, cardiomyopathy, muscular hypotonia, malformations (Kranendijk et al. 2012), and accumulation of D2-HG in body fluids (Kranendijk et al. 2010). Interestingly, even though these patients accumulate very high levels of pro-oncogenic D2-HG, they do not display signs of cancer (Kranendijk et al. 2012). On the contrary, germline mutations in both IDH2 and IDH3 were identified in some patients with myeloid neoplasias and PGL syndrome (Table 1) (Molenaar et al. 2015). In more detail, eight patients with a history of cancer in their families were found affected by mutations in IDH2 (T495M and R261H), IDH3A (R360C), and IDH3B (R359W and R334W), which seem associated with a higher incidence of myeloid cancer. Interestingly, these lesions seem to be mutually exclusive with somatic TET2 mutations, suggesting the possible involvement of epigenetic reprogramming in tumor development, as observed with IDH somatic mutations. Of note, in a PGL from a patient harboring germline heterozygous truncating mutation in IDH3B, the levels of 5-hmC were decreased and DNA methylation was increased, suggesting that aKGDs were involved in the transformation of this tumor (Figure 2) (Remacha et al. 2017). Even though several lines of evidence suggested that germline mutations in IDHs predispose to cancer, further work is required to uncover the molecular mechanisms activated by IDH loss in these tumors. It would be important first to demonstrate if these cancers accumulate 2-HG and second to understand why heterozygous mutations specifically in IDH2 predispose also to 2-HG aciduria. It is possible that based on the residue affected by the mutations, different types of metabolic reprogramming occur, leading to very diverse clinical outcomes.

2.4. Mitochondrial α-Ketoglutarate/Malate Carrier (SLC25A11)

The αKG/malate carrier [also known as 2-oxoglutarate (OGC)] is a homodimer mitochondrial electroneutral transporter that exchanges αKG for malate and other dicarboxylates (Palmieri 2004). OGC is encoded by the SLC25A11 gene (chromosome 17p13.2) and has a central role in different metabolic pathways such as the malate/aspartate and αKG/isocitrate shuttles, nitrogen metabolism, and gluconeogenesis (Palmieri 2004). Very recently, a cohort was identified of six patients with germline heterozygous mutations in SLC25A11 (two missense and frameshift mutations, one silent mutation, and one intronic mutation) who developed metastatic PGL (Table 1) (Buffet et al. 2018). These tumors were all negative for OGC staining and some of them displayed LOH of the wild-type allele. Surprisingly, these tumors displayed reduced 5-hmC and increased histone H3K9me3 and H3K27me3 staining, a phenotype consistent with a possible inhibition of aKGDs (Figure 2) (Buffet et al. 2018). To validate this hypothesis, the authors explored the effect of SLC25A11 silencing in chromaffin cells. OGC-deficient cells displayed activation of the hypoxia signaling, increased DNA methylation, and enhanced invasive properties (Buffet et al. 2018) compatible with aKGD inhibition probably obtained through reduction of intracellular
levels of aKG rather than accumulation of other oncometabolites. Of note, the discovery of these mutations suggested for the first time that inhibition of aKGDD may be possible through alternative routes that do not involve accumulation of inhibitory metabolites such as fumarate but decrease the availability of the aKGDD reaction substrate.

2.5. Glutamic-Oxaloacetic Transaminase 2

Glutamic-oxaloacetic transaminases (GOTs) are a family of pyridoxal phosphate-dependent enzymes (Ford et al. 1980) involved in the transamination of glutamate to oxaloacetate, producing aspartate and aKG, a reaction involved in different metabolic pathways, including the malate-aspartate shuttle. GOT2 is a specific mitochondrial isoform encoded by the \textit{GOT2} gene (chromosome 16q21), whose germline mutation (c.357A>T) was recently identified in a patient with multiple PGL (Table 1) (Remacha et al. 2017). It is currently unclear how this genetic lesion contributes to tumorigenesis in PPGL, even though this variant does not impair GOT2 activity but instead is associated with stabilization of the protein at both mRNA and protein levels in the tumor. Unexpectedly, this tumor displays a CIMP-like phenotype, as observed for the other familial cancers harboring metabolic gene mutations. Further experiments in vitro suggest that the CIMP of this tumor may be the result of an indirect effect of \textit{GOT2} mutations on the levels of succinate, aKG, and aspartate (Figure 2) (Remacha et al. 2017). However, additional work is required to measure the concentrations of all these metabolites within the tumor tissue and to clarify whether aKGDDs are involved in the tumorigenesis process.

2.6. \textit{α}-Ketoglutarate Dehydrogenase Complex

The aKG dehydrogenase complex (aKGDC), also known as the 2-oxoglutarate dehydrogenase complex (OGDC), is a mitochondrial enzyme and a key component of the TCA cycle, where it catalyzes the conversion of aKG to succinyl-CoA and CO$_2$ (Armstrong et al. 2014). Germline mutations [including a recurrent c.1121G>A (p.Gly374Glu) variant] were found in the dihydrolipoamide S-succinyltransferase (DLST) gene in eight individuals with HNPGL or PPGL (Table 1) (Remacha et al. 2019) and in OGDC component E1–like (OGDHL) gene (c.750G>T) in one patient with PPGL (Table 1) (Remacha et al. 2017). DLST is one (E2) of three subunits of the OGDC (the E1 and E3 subunits are encoded by OGDH and dihydrolipoamide dehydrogenase, respectively) while OGDHL is a protein similar to OGDH E1 (Vatrinet et al. 2017). Interestingly, methylation profiling of \textit{DLST}/\textit{OGDHL}-mutated tumors did not show evidence of the CIMP seen with other PPGL gene mutations, and the gene expression profile of DLST-mutant tumors was most similar to that seen with \textit{HIF2A} (\textit{EPAS1}) and \textit{MAX}–mutated PPGL (Remacha et al. 2019), suggesting possible activation of a pseudohypoxia response (Figure 2). It is possible that mutations of OGDC in PPGL do not show a distinctive CIMP for multiple reasons. First, OGDC impairments may lead to the accumulation of aKG, favoring rather than inhibiting the activity of aKGDDs. Second, it is also possible that accumulation of L-2-HG observed in Hela cells after OGDC loss (Burr et al. 2016) may not be relevant in this tumor type or does not reach the threshold necessary to inhibit TETs in vivo.

3. CONCLUSIONS AND FUTURE PERSPECTIVES

The description provided above indicates that germline mutations of mitochondrial enzymes play a key role in familial cancer, pointing out that mitochondrial metabolism may have a broad impact on tumorigenesis. These apparently diverse hereditary cancers enabled us to identify the
inhibition of aKGDDs as a converging oncogenic mechanism that underpins the general dysregulation of mitochondrial metabolism (Figure 3). Of note, the inhibition of aKGDDs can be achieved either via the accumulation of inhibitors, such as fumarate, succinate, and 2-HG, or through the increase of aKG, the substrate of these enzymes. The biological consequences of the inhibition of aKGDDs are broad, affecting gene transcription through the coordination of epigenetic remodeling and activation of the hypoxic response (Figure 3). It is intriguing to speculate that this converging molecular signature is responsible, at least in part, for the formation of both PCC and PGL, the tumor type that is common among all the metabolic lesions. One possible explanation is provided by evidence that tumor dedifferentiation and DNA methylation patterns are strongly intertwined in inherited PPGL syndromes, a link that may be connected to the neuroendocrine origin of these tumors. Consistently, PGL tumors harboring metabolic germline mutations are characterized by a distinctive CIMP, which is ascribed to TET inhibition,
although this has not been fully proved. Furthermore, at least in some of these tumors, inhibition of DNA methylation impairs the invasive properties of the cancer cells, and patients with CIMP PGL have a worse prognosis than those harboring different mutations. Interestingly, while these signals coexist in most of the tumor types discussed above, tumors harboring mutations of aKGDC seem to display only a partial inhibition of aKGDDs, mainly affecting the stabilization of HIFs. How this selective inhibition is achieved is still unknown and may involve a different sensitivity of aKGDDs to metabolic cues. However, the activation of HIF-mediated signaling in these tumors seems to be a prerequisite to transformation. This hypothesis is also strengthened by evidence that patients harboring inactivating mutations in PHD2 (Ladróu et al. 2008, Yang et al. 2015b) or VHL (Gaal et al. 2009) or gain-of-function mutations in HIF2A (EPAS1) (Yang et al. 2015a) also develop PPGL. Finally, it is important to underline that hypoxia and epigenetic remodeling are not fully independent, and it has been recently proposed that the activation of the hypoxic response requires inhibition of TETs, which are also sensitive to oxygen levels (Thienpont et al. 2016). Therefore, it will be critical to fully assess how the metabolic changes in these hereditary tumors, together with changes in oxygen availability, alter the cell behavior acting on multiple, deeply intertwined cellular layers.

Expanding the analysis of the common features beyond familial cancers, including IEMs, shows that at the molecular basis of transformation, there is the accumulation of a toxic metabolite, which in turn is responsible for an early damage necessary to prime cancer formation. However, why the same metabolic dysfunction leads to different clinical outcomes is still unclear and requires further investigation. It is possible that the early onset of IEMs prevents the development of cancer or that systemic accumulation of metabolites in the body could activate other biological responses in distant organs that contribute to the overall mortality of IEMs in childhood but are not present in familial cancers.

An important consequence of defining the aberrations of the oncogenic signaling triggered by accumulation of fumarate, succinate, and other metabolites is the potential for developing novel therapeutic interventions in patients with metastatic RCC and PGL associated with HLRCC and SDHX mutations. Currently all these tumors are associated with poor prognosis and limited therapeutic options. Thus, interventions to target the HIF pathway and the use of demethylating agents are the subject of increasing interest for clinical trials. Interestingly, it has been recently shown that the accumulation of both fumarate and succinate suppresses homologous recombination via the inhibition of aKGDD histone demethylases involved in DNA repair, making cells sensitive to inhibitors of PARP [poly(ADP)-ribose polymerase], another enzyme involved in DNA repair (Sulkowski et al. 2018).

In conclusion, understanding how metabolic genes are involved in human disease and decrypting the differences between IEMs and familial cancer may unravel new oncogenic mechanisms and therapeutic targets, strongly impacting our understanding of cancer.

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**Errata**

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