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REVIEW

The impact of mitochondria on cancer treatment resistance

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Abstract

Background The ability of cancer cells to develop treatment resistance is one of the primary factors that prevent successful treatment. Although initially thought to be dysfunctional in cancer, mitochondria are significant players that mediate treatment resistance. Literature indicates that cancer cells reutilize their mitochondria to facilitate cancer progression and treatment resistance. However, the mechanisms by which the mitochondria promote treatment resistance have not yet been fully elucidated.

Conclusions and perspectives Here, we describe various means by which mitochondria can promote treatment resistance. For example, mutations in tricarboxylic acid (TCA) cycle enzymes, i.e., fumarate hydratase and isocitrate dehydrogenase, result in the accumulation of the oncometabolites fumarate and 2-hydroxyglutarate, respectively. These oncometabolites may promote treatment resistance by upregulating the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, inhibiting the anti-tumor immune response, or promoting angiogenesis. Furthermore, stromal cells can donate intact mitochondria to cancer cells after therapy to restore mitochondrial functionality and facilitate treatment resistance. Targeting mitochondria is, therefore, a feasible strategy that may dampen treatment resistance. Analysis of tumoral DNA may also be used to guide treatment choices. It will indicate whether enzymatic mutations are present in the TCA cycle and, if so, whether the mutations or their downstream signaling pathways can be targeted. This may improve treatment outcomes by inhibiting treatment resistance or promoting the effectiveness of anti-angiogenic agents or immunotherapy.

Keywords Mitochondria · Treatment resistance · Mitochondrial transfer · Fumarate · 2-Hydroxyglutarate

1 Introduction

The ability of cancer cells to develop resistance to treatment is a major contributing factor to recurrence and mortality. Current treatment approaches involve administering the maximum tolerated dose (MTD) of any given therapy to eradicate the tumor. Although this approach is associated with initial positive effects, it often acts as an environmental selection mode favoring resistant cancer cells. As a result, cancer often relapses after treatment. Cancer recurrence is especially common when a heterogenous tumor is treated with the MTD [1]. It has been observed that 30–55% of patients with non-small cell lung cancer relapse after treatment and ultimately die from the disease [2]. Furthermore, recurrence in glioblastoma has been regarded as inevitable as most patients develop recurrences 6–9 months after primary treatment [3]. The recurrence rate in patients with ovarian cancer is 85% [4] and in patients with soft tissue carcinoma 15-40% [5, 6]. Additionally, Fischer and co-authors found that 37% of patients with pancreatic cancer suffered from tumor recurrence after resection and adjuvant therapy with a two-year survival rate of only 13% [7]. These results indicate that treatment resistance and cancer recurrence are significant obstacles that need to be considered before and during treatment [8–10]. Accumulating evidence indicates that mitochondria are main facilitators of treatment resistance. However, the involvement of mitochondria in mediating treatment resistance has not yet been fully elucidated. In this review, we explore the genetic changes that modify mitochondrial functioning in cancer cells and the effect thereof on cell signaling pathways. Furthermore, we describe how these mitochondrial alterations promote tumor progression and treatment resistance and how mitochondria can be targeted to combat treatment resistance and improve treatment outcomes.

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2 Mitochondrial functioning in the context of cancer

Mitochondria, predominantly known for their role in supplying energy in the form of adenosine triphosphate (ATP), also regulate a myriad of critical physiological processes such as cell signaling, apoptosis, epigenetics, stemness, differentiation and bioenergetics [11, 12]. Mitochondria have, therefore, been denoted as central cellular hubs that regulate various cellular outputs. Since mitochondria regulate numerous complex physiological processes, it is not surprising that alterations in mitochondrial utilization are involved in cancer initiation and/or progression [13]. It was Otto Warburg who first discovered altered mitochondrial utilization by cancer cells when he found that these cells derive energy from fermentation rather than from oxidative phosphorylation (OXPHOS), even in the presence of sufficient oxygen [14]. Warburg proposed that the altered metabolism results from mitochondrial damage. However, a more in-depth understanding of cancer metabolism has indicated that the mitochondria are not damaged but rather reprogrammed, giving cancer cells a survival advantage that also enables treatment resistance.

The role of mitochondria in facilitating treatment resistance is particularly relevant in cancer stem cells (CSCs). CSCs, also called tumor-initiating cells or stem-like cancer cells, comprise approximately 1–2 % of the total tumor mass [15]. The relative abundance of CSCs is a predictor of treatment outcome [16]. CSCs can self-renew and initiate tumorigenesis. Additionally, these cells have a low proliferation rate and are the only tumorigenic cells able to give rise to tumor cells with different characteristics [17]. CSCs are resistant to commonly used chemotherapeutic agents. As such, these agents primarily select for CSCs, and thus increase the CSC population. Consequently, a more aggressive tumor recurs [18–20]. The role of mitochondria in mediating resistance in CSCs is becoming increasingly evident [17]. Mitochondria promote CSC resistance through altering metabolism, inhibiting apoptosis and promoting cell survival [17]. Bidirectional communication exists between the mitochondria and the nucleus. Mitochondrial-to nucleus signaling (retrograde signaling) is an essential mechanism by which the mitochondria communicate with the cell to influence its dynamics and promote treatment resistance. Five mechanisms by which the mitochondria influence retrograde signaling include the release of cytochrome c, the activation of AMP-activated protein kinase (AMPK), the production of reactive oxygen species (ROS), the release of mitochondrial DNA (mtDNA) and the release of tricarboxylic acid (TCA) cycle metabolites [21]. TCA metabolites that are shuttled from the TCA cycle can regulate cell fate functions as they are involved in epigenetic regulation, post-translational protein modification and cell signaling [21].

TCA metabolites are often upregulated in cancer due to mutations in mitochondrial enzymes. These upregulated metabolites are referred to as oncometabolites, i.e., metabolites that accumulate to abnormal levels and cause metabolic and non-metabolic dysregulation with the potential to promote cell transformation and tumorigenesis [22]. Two well-known oncometabolites that may play a role in promoting treatment resistance are fumarate and 2-hydroxyglutarate (2-HG). Fumarate is a standard product of the TCA cycle. Loss of function mutations in the enzyme fumarate hydratase (FH) inhibits its ability to convert fumarate to malate. Consequently, fumarate accumulates to abnormal levels. Additionally, gain of function mutations in the TCA enzyme isocitrate dehydrogenase (IDH) enable it to reduce α-ketoglutarate to the oncometabolite 2-HG [23]. FH and IDH mutations have been well-documented in cancer and result in oncometabolite accumulation, as illustrated in Fig. 1 [24–35].

3 The oncometabolite fumarate may promote treatment resistance through Nrf2 upregulation

Fumarate accumulation may promote cancer treatment resistance in a nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent manner. The Nrf2 cell signaling pathway is typically viewed as beneficial, as it is involved in cyto-protection by promoting the transcription of genes involved in antioxidant defense, redox homeostasis and cell survival [36]. Activation of Nrf2 and the subsequent expression of its target genes is vital for eliminating carcinogens and conferring protection from cell transformation. For example, Nrf2 knockout mice have been found to be more susceptible to carcinogens, such as cigarette smoke and diesel exhaust, than their wild-type counterparts [37, 38]. Furthermore, Nrf2 knockout mice showed increased tumor formation after exposure to the carcinogen N-nitrosobutyl(4-hydroxybutyl)amine [39]. Therefore, Nrf2 has conventionally been deemed as a tumor suppressor. Subsequent studies, however, revealed increased Nrf2 levels in a wide array of cancer types, including prostate, lung, gallbladder, esophageal and skin cancer [40–44]. Elevated Nrf2 levels result in the upregulation of cytoprotective genes that encode detoxification and antioxidant enzymes, which endows cancer cells with a survival advantage against anti-cancer drugs. Nrf2 exerts cytoprotective effects in both non-cancerous and cancerous cells, implying that it prevents cell transformation, but that once a cell has become cancerous, it confers a survival advantage by upregulating detoxification processes [45]. Therefore, established tumors can use Nrf2 as a self-protective factor that promotes malignant cell survival, cancer progression and treatment resistance [46–51].

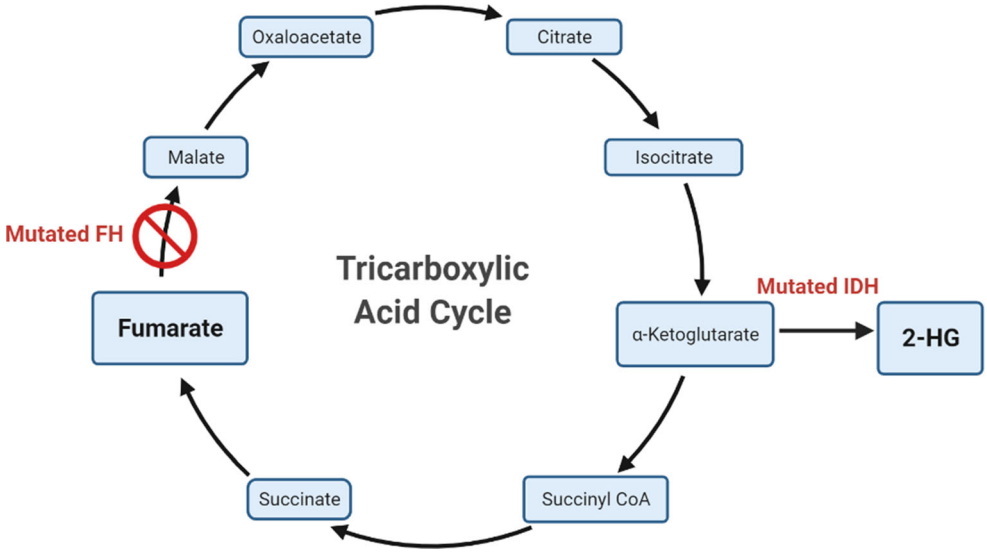

Fig. 1 Mutations in fumarate hydratase or isocitrate dehydrogenase result in the accumulation of fumarate and 2-hydroxyglutarate, respectively. Abbreviations: FH (fumarate hydratase), IDH (isocitrate dehydrogenase), 2-HG (2-hydroxyglutarate). Figure created using BioRender

Under homeostatic conditions, Nrf2 is bound to a repressor protein Kelch ECH associating protein 1 (Keap1), which promotes the ubiquitination and proteasomal degradation of Nrf2. The Keap1-Nrf2 pathway is a significant regulator of a cell's antioxidant defense in response to ROS and electrophiles [52]. Keap1 contains several cysteine residues that are redox-sensitive and can be modified by free radicals. Elevated ROS can compromise the conformation of Keap1 through oxidizing its cysteine residues. Consequently, the interaction between Keap1 and Nrf2 is abrogated and Nrf2 is liberated to translocate to the nucleus [53]. Additionally, several protein kinase pathways have been shown to regulate the interaction between Keap1 and Nrf2. For example, Huang et al. found that protein kinase C promotes the dissociation of Nrf2 from Keap1 by phosphorylating Nrf2 at Ser40 [53]. Furthermore, the phosphatidylinositol 3-kinase (PI3K)/Akt, ERK and JNK mitogen-activated protein kinase pathways have been shown to act upstream of Nrf2 and to regulate its activation and nuclear translocation [54–57]. Once in the nucleus, Nrf2 heterodimerizes with MAF proteins and promotes the transcription of genes harboring antioxidant response elements (AREs) in their promoter regions to maintain redox homeostasis [58].

Literature indicates that accumulation of the oncometabolite fumarate can disrupt the homeostatic regulation of the Nrf2 pathway, thereby increasing Nrf2 activation and nuclear translocation. It is, therefore, possible that elevated levels of fumarate in fumarate hydratase (FH) mutant tumors may promote treatment resistance by upregulating Nrf2. As mentioned, fumarate accumulation results from loss of function mutations in FH that prevent the conversion of fumarate to malate [59]. Adam et al. found that fumarate can target and succinate Keap1 on specific cysteine residues in FH deficient cells [60]. Subsequently, the interaction between Keap1 and Nrf2 is abrogated, and Nrf2 can translocate to the nucleus to promote the expression of genes that facilitate treatment resistance [60].

3.1 Mechanisms by which Nrf2 promotes treatment resistance

The protective mechanisms activated by Nrf2 that facilitate treatment resistance include inhibition of apoptosis, increased antioxidant responses and expression of drug efflux proteins. These mechanisms enable cancer cells to resist treatment by evading cell death, tolerating high levels of chemotherapy-induced ROS and promoting drug efflux [51].

Nrf2 has been shown to regulate apoptosis by promoting the transcription of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) by binding to its ARE. Subsequently, it was found that elevated Bcl-2 attenuated the levels of the pro-apoptotic protein Bax. Bax, in turn, reduced cytochrome c release from the mitochondria and diminished caspase activation *in vitro* [61]. Additionally, Zhang et al. found that Nrf2 inhibition promoted an apoptotic cellular phenotype and that Nrf2 expression positively correlated with the anti-apoptotic protein B-cell lymphoma-extra large (Bcl-xL) in hepatocellular carcinoma Bel-7402 and HepG2 cells [61, 62]. These results indicate that Nrf2 may inhibit apoptosis by promoting the expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL.

Nrf2 also directly affects ROS and reactive nitrogen species (RNS) homeostasis through regulating antioxidant defense systems. Once Nrf2 translocates to the nucleus, it promotes the transcriptional activation of antioxidant components such as heme oxygenase-1, NAD(P) H:quinone, and oxidoreductase 1, as well as antioxidant enzymes such as catalase and superoxide dismutase [63]. It has been observed that Nrf2 is involved in conferring treatment resistance to a wide range of chemotherapeutic agents, including cisplatin, fluorouracil, oxaliplatin, paclitaxel, doxorubicin and gemcitabine, through

attenuating ROS [64–70]. Excessive cellular levels of ROS cause severe damage to macromolecules that can lead to cell death through apoptosis [71]. Indeed, chemotherapeutic agents and radiotherapy have been shown to increase intracellular ROS levels to facilitate apoptosis [72, 73]. Excessive ROS levels can promote apoptosis via both the intrinsic and extrinsic apoptotic pathways. For example, elevated ROS has been shown to activate the intrinsic apoptotic pathway by oxidizing cardiolipin and disrupting the mitochondrial membrane potential (MMP) [74, 75]. Subsequently, cytochrome c is released from the mitochondria to initiate apoptosis. Furthermore, ROS can promote activation of the extrinsic apoptotic pathway through transmembrane death receptors such as Fas and TRAIL [76, 77]. ROS's activation of these death receptors leads to recruitment of proteins to form the death-inducing signaling complex (DISC), which promotes the activation of initiator and effector caspases to trigger apoptosis [78]. These results indicate that elevated Nrf2 may protect FH mutant cancer cells from chemotherapeutic assaults by upregulating intracellular antioxidant defenses that inhibit ROS induced apoptosis.

Furthermore, Nrf2 can promote treatment resistance by regulating the expression of drug efflux transporters, including multidrug resistance associated proteins (MRPs) and breast cancer resistance proteins (BCRPs) [79, 80]. These proteins enhance drug efflux, thereby preventing the intracellular accumulation of chemotherapeutic drugs and maintaining the intracellular drug concentration below toxic levels. These proteins are overexpressed in various tumor types, such as breast, lung, bladder and ovarian cancer, and are associated with treatment resistance [81].

An additional mechanism by which Nrf2 may promote treatment resistance is by restoring metabolic flexibility in FH mutant cancers. FH mutant tumor cells and elevated fumarate levels are associated with impaired OXPHOS [82]. Nrf2, however, plays a crucial role in supporting the structural and functional integrity of the mitochondria. It has been found that Nrf2 knockout mouse embryonic fibroblasts and primary glioma neuronal cells exhibit impaired complex I activities compared to their wild type counterparts [83]. Furthermore, Nrf2 upregulation restores mitochondrial membrane potential and ATP production [84]. Therefore, upregulation of Nrf2 by fumarate may decrease impaired OXPHOS in FH mutant tumors, thereby at least partly restoring metabolic flexibility.

Although the Warburg effect and high glycolytic rates can promote cancer progression, the ability of cancer cells to switch from glycolysis to OXPHOS may promote treatment resistance [85]. It has been found, for example, that the ability of glioma cells to switch from glycolysis to OXPHOS promoted resistance to PI3K inhibition [86]. Furthermore, oncogene ablation in pancreatic cancer cells was found to select for a subpopulation of cells that rely on OXPHOS [87]. Similar results have been observed in breast cancer cells after MYC/KRAS or MYC/ERB2 ablation [88]. Therefore, metabolic plasticity can serve as a protective mechanism that promotes treatment resistance in cancer. Impaired OXPHOS characterizes FH mutant cancers. However, upregulation of Nrf2 by fumarate may partly restore metabolic flexibility during stress and serve as a mechanism by which FH mutant tumor cells can resist treatment.

Taken together, these results indicate that elevated levels of Nrf2 can promote treatment resistance through inhibiting apoptosis, upregulating antioxidant defense systems, facilitating drug efflux and, possibly, through restoring OXPHOS as illustrated in Fig. 2. Since fumarate can enhance Nrf2 activation, it can be speculated that FH mutant tumors may have an increased ability to resist treatment.

4 The oncometabolite 2-hydroxyglutarate may promote resistance to immunotherapy

The adaptive immune system is critical for the identification and eradication of cancer cells. Therefore, stimulation of the adaptive immune system through immunotherapy is a promising avenue in cancer research. The oncometabolite 2-HG serves as a paracrine immune regulator that inhibits the antitumor immune response. Gain of function mutations in IDH1 and IDH2 are common in cancer and result in 2-HG accumulation. Interestingly, intracellular accumulation of 2-HG negatively affects cellular functions as it inhibits ATP production, promotes apoptosis and inhibits cell proliferation [89, 90]. It seems as if IDH mutant tumors can overcome this challenge by exporting 2-HG to the extracellular environment, since this oncometabolite has been detected in sera of cancer patients with IDH mutations [91, 92]. Once in the extracellular environment, 2-HG has been shown to inhibit the anti-tumor immune response, which may confer resistance to immunotherapy [90]. Bunse and co-workers found that the extracellular 2-HG levels were 5-fold higher in IDH mutant gliomas compared to the intracellular levels [90]. Additionally, the authors found that extracellular 2-HG was imported by tumor infiltrating lymphocytes via sodium-dependent dicarboxylate transporter 3 (SCL13). After internalization 2-HG suppressed T-cell activity by interfering with the nuclear translocation of nuclear factor of activated T-cells (NFAT) and by preventing polyamine biosynthesis.

Mechanistically, 2-HG interferes with NFAT nuclear translocation by promoting the phosphorylation of phospholipase C-gamma 1 (PLC-γ1) [90]. Unphosphorylated PLC-γ1 usually hydrolyses phosphatidylinositol (PI)-4,5-bisphosphate (PIP_2) to inositol-1,4,5-trisphosphate (IP_3) [93]. Subsequently, IP_3 binds to IP_3 receptors on the endoplasmic reticulum (ER) to promote the release of Ca^{2+} from the ER. Thereafter, the ER Ca^{2+} sensor, stromal interaction molecule 1 (STIM1), senses the decrease in ER luminal Ca^{2+} levels and is translocated to the plasma membrane to interact with and

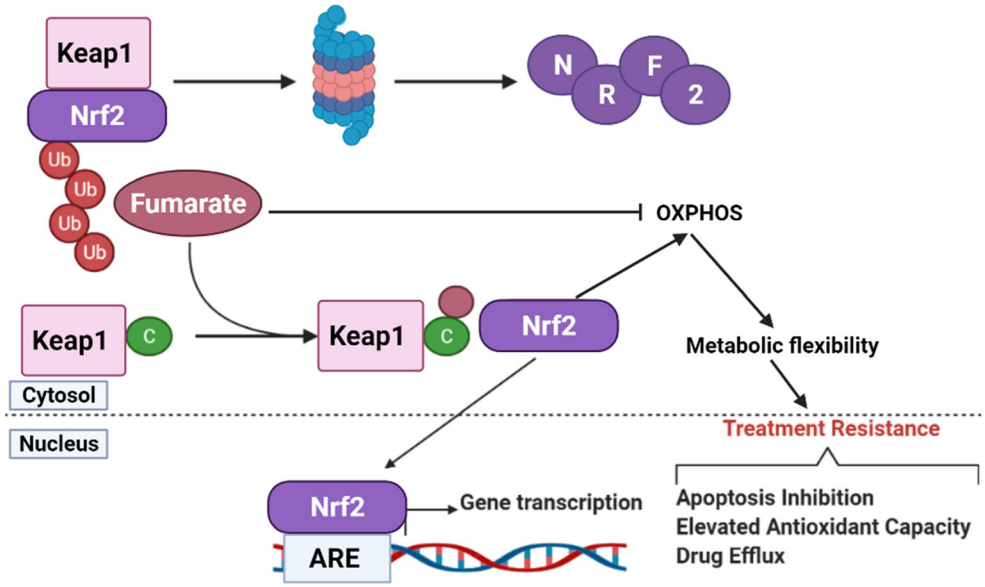

Fig. 2 Fumarate promotes treatment resistance through Nrf2 upregulation. Under homeostatic conditions, Keap1 binds to Nrf2 and promotes its ubiquitination and proteasomal degradation. Fumarate can abrogate the interaction between Keap1 and Nrf2 by modifying cysteine residues on Keap1. Subsequently, Nrf2 is translocated to the nucleus to promote the transcription of genes that inhibit apoptosis and promote drug resistance. Additionally, Nrf2 promotes OXPHOS which may restore metabolic flexibility. Abbreviations: Keap1 (Kelch ECH associating protein 1), Nrf2 (nuclear factor erythroid 2–related factor 2), ARE (antioxidant response element), OXPHOS (Oxidative phosphorylation). Figure created using BioRender

activate calcium channels, i.e., calcium release-activated calcium channel protein 1 (Orai1) and calcium release-activated channels (CRACs) [94–98]. Activation of Orai1 and CRAC promotes the influx of extracellular Ca^{2+} into the cytosol, which activates calcineurin. Calcineurin, in turn, dephosphorylates and activates NFAT to promote its nuclear translocation [99]. Bunse and co-workers found that phosphorylation and inhibition of PLC-γ1 by 2-HG in T-cells inhibited NFAT transcriptional activity. NFAT regulates the expression of immune response-related genes, and its inactivation results in T-cell inhibition [90]. Additionally, 2-HG repressed NFAT activity by inhibiting ATP synthase subunit beta (ATP5b). The inhibition thereof resulted in a reduction in ATP generation and a subsequent activation of AMPK. AMPK has been shown to inhibit NFAT and the rate-limiting enzyme involved in polyamine synthesis, ornithine decarboxylase 1 (ODC1). ODC1 usually converts ornithine to putrescine, which is important for cellular growth and proliferation [100]. In summary, 2-HG, which accumulates because of IDH mutations, can be exported from cancer cells and can enter tumor infiltrating lymphocytes (TILS) to suppress T-cell functionality as illustrated in Fig. 3. 2-HG accumulation in T-cells promotes a cascade of cell signaling events that converge at NFAT inhibition and a subsequent inhibition of T-cell activity. Additionally, 2-HG interferes with the production of a polyamine, putrescine, that is important for T-cell growth and proliferation. The ability of 2-HG to interfere with the anti-tumor immune response may confer resistance to immunotherapy in IDH mutant tumors.

5 Involvement of oncometabolites in angiogenesis

Angiogenesis, the formation of new blood vessels from pre-existing ones, is considered a hallmark of cancer and is an essential step in the transformation of a benign tumor into a malignant tumor. The newly formed vasculature assists tumor survival by supplying the necessary oxygen and nutrients and removing waste products [101]. The conversion of a dormant avascular tumor into a highly vascularized tumor refers to the angiogenic switch and results from a shift in the balance of pro- and anti-angiogenic factors towards the latter [102].

Vascular endothelial growth factor (VEGF) is a crucial mediator of angiogenesis and tumor progression [103]. Tumor-derived VEGF exerts its angiogenic function by binding to VEGF receptors on vascular endothelial cells. The binding of VEGF to its receptor induces receptor dimerization and autophosphorylation. Subsequently, intracellular signaling pathways such as the PI3K, mitogen-activated protein kinase (MAPK) and RAS pathways are activated. These pathways regulate angiogenesis by promoting the migration of endothelial cells, as well as cell proliferation, survival and permeability [104].

Hypoxia, often found in a growing tumor, is a significant inducer of VEGF expression. Usually, during normoxic conditions prolyl hydroxylases (PHDs) indirectly inhibit VEGF transcription. PHDs catalyze the

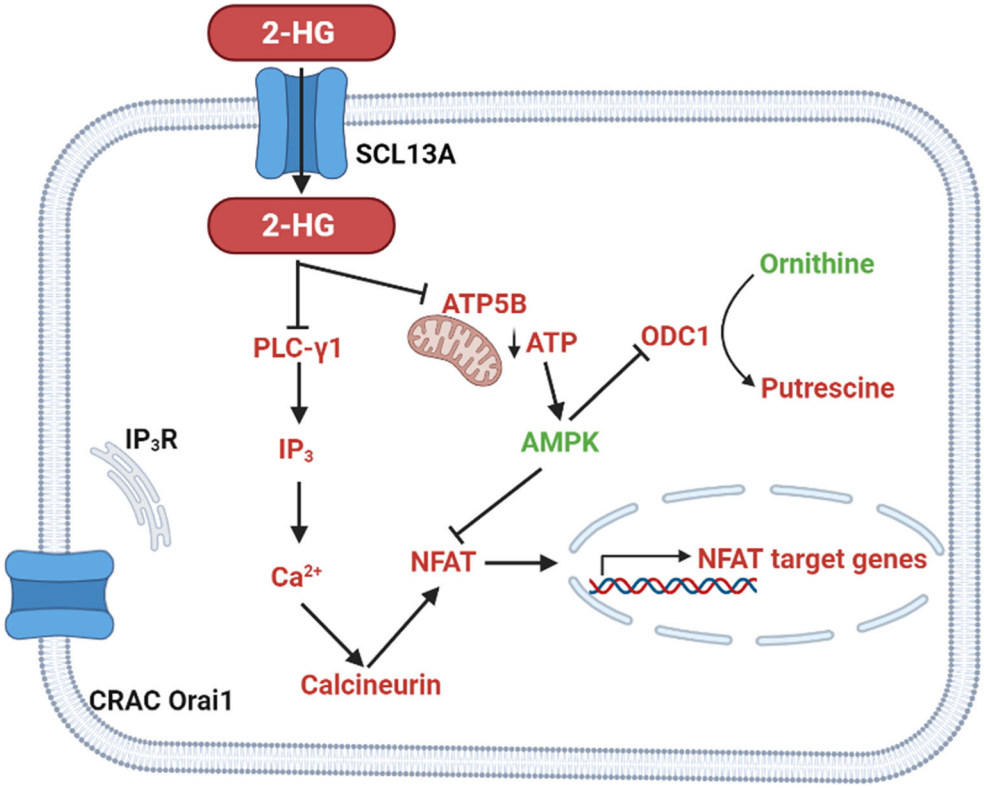

Fig. 3 2-HG inhibits T-cell activity. 2-HG is exported from cancer cells, whereafter it enters T-cells via SCL13A to inhibit T-cell activation and proliferation. 2-HG attenuates NFAT signaling as well as ornithine biosynthesis. Adapted from [90]. Abbreviations: 2-HG ((R)-2-hydroxyglutarate), SCL13A (sodium-dependent dicarboxylate transporter 3), PLC-γ1 (phospholipase C-gamma 1), IP_3 (inositol-1,4,5-trisphosphate), IP_3R (IP_3 receptor), CRAC (calcium release-activated channels), Orai1 (calcium release-activated calcium channel protein 1), NFAT (nuclear factor of activated T-cells), AMPK (5' AMP-activated protein kinase), ATP (adenosine triphosphate), ATP5B (ATP synthase subunit beta), ODC1 (ornithine decarboxylase 1). Figure created using BioRender

conversion of prolyl, oxygen and α-KG to hydroxyprolyl, CO_2 and succinate while using ascorbate and Fe^{2+} as cofactors to hydroxylate hypoxia inducible factor-1 alpha (HIF-1α) on proline residues [105, 106]. Subsequently, the Von Hippel Lindau protein (pVHL) recognizes and binds to hydroxylated HIF-1α, thereby promoting its ubiquitination and subsequent proteosomal degradation. Therefore, under normoxic conditions, PHDs hydroxylate HIF-1α, which ultimately leads to its degradation. In contrast, hypoxia promotes angiogenesis by inhibiting PHD activity as insufficient oxygen is available to be utilized by PHDs. Subsequently, HIF-1α will be stabilized and will form a heterodimer with HIF-1β. Then, this complex translocates to the nucleus, promoting the transcription of genes involved in angiogenesis, such as VEGF, as shown in Fig. 4 [107–109].

In addition to hypoxia, oncometabolites can also inhibit PHDs to promote HIF-1α stabilization and angiogenesis [110, 111]. These oncometabolites can inhibit PHD activity even in the absence of hypoxia, a phenomenon known as pseudohypoxia. Fumarate and 2-HG are structurally similar to α-KG and have been shown to inhibit PHD activity by competing with α-KG [112]. Several studies have indicated that the addition of α-KG was sufficient to combat HIF-1α activation mediated by fumarate [113, 114]. Furthermore, it has been found that 2-HG competes with α-KG for the binding site on PHDs to inhibit its activity [115].

6 Mitochondrial transfer from non-tumor to tumor cells facilitates drug resistance

Besides being maternally inherited, mitochondria can be transferred horizontally between cells [116]. Mitochondrial transfer was first observed in 2006 when Spees and co-workers found that human mesenchymal stem cells (MSCs) transferred their mitochondria to cells with non-functional or deprived mitochondria via tunneling nanotubes (TNTs), exosomes or vesicles [117]. TNTs are nanotubular structures supported by actin and microtubule filaments. The formation of these structures between cells is a main mechanism by which mitochondria are transferred, as illustrated in Fig. 5. Mitochondrial transfer has been observed between multiple cell types, where it plays a vital role in maintaining tissue homeostasis. For example, in immune cells, MSCs have been found to donate mitochondria to innate immune cells to improve their phagocytic activity [118]. Mitochondrial donation has also been shown to promote the regeneration of damaged cells [119, 120]. Additionally, donor cells (MSCs or endothelial cells) have been shown to donate mitochondria to cancer cells after therapy to promote resistance. Cancer cells exhibit extensive phenotypic plasticity, which is unmasked when exposed to different environmental stressors [121]. The ability of cancer cells to receive intact mitochondria implies another level of adaptability that allows cancer cells to maintain mitochondrial functioning, even after exposure to

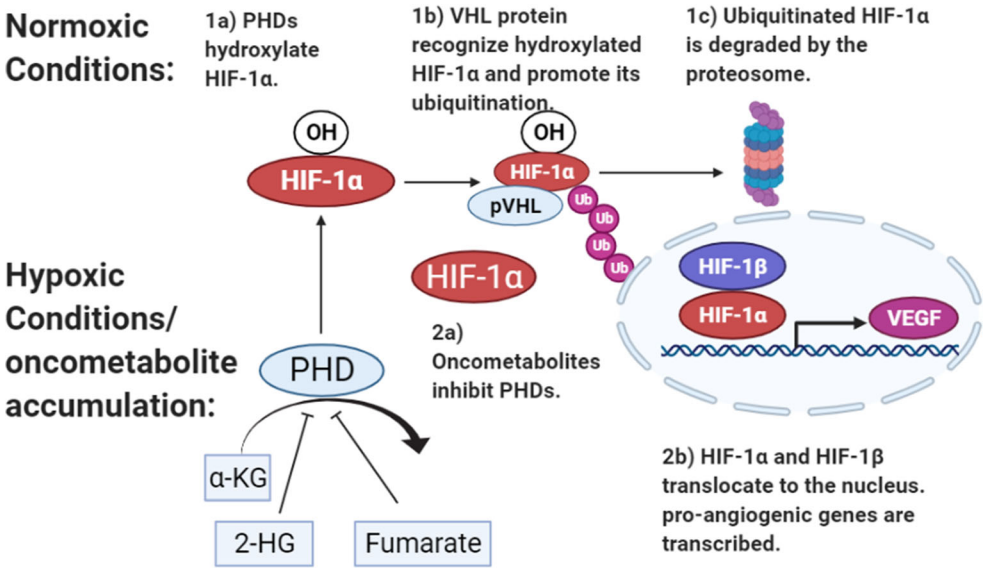

Fig. 4 The oncometabolites, 2-HG and fumarate, inhibit PHD activity to promote angiogenesis. PHDs promote the proteosomal degradation of HIF-1α. Therefore, inhibition of PHDs by oncometabolites results in activation of HIF-1α. Subsequently, HIF-1α forms a heterodimer with HIF-1β whereafter the complex translocates to the nucleus to promote VEGF gene expression. Abbreviations: HIF-1α (hypoxia inducible factor-1 alpha), PHD (prolyl hydroxylase), α-KG (alpha-ketoglutarate), 2-HG (2-hydroxyglutarate), pVHL (Von Hippel Lindau protein), HIF-1β (hypoxia inducible factor-1 beta), VEGF (vascular endothelial growth factor). Figure created using BioRender

chemotherapeutic agents. It has been found that the donation of healthy mitochondria can restore mitochondrial functioning after treatment [122, 123].

Although the exact mechanism of mitochondrial transfer in cancer remains unknown, high OXPHOS demand and severe mitochondrial damage are typical features of recipient cells [117]. To initiate the transfer, the donor cells should possess non-damaged, healthy mitochondria and be specifically activated by the recipient cells. Activators mostly include metalloproteinase-1 (MMP-1), nestin, pro-inflammatory cytokines and ROS [124, 125]. Elevated levels of these activators are common in advanced tumors and may serve as signals that prompt mitochondrial transfer. Interestingly, all these molecules are also associated with drug resistance [126–128]. Although this has not been specifically assessed, it is possible that mitochondrial transfer is one of the mechanisms by which

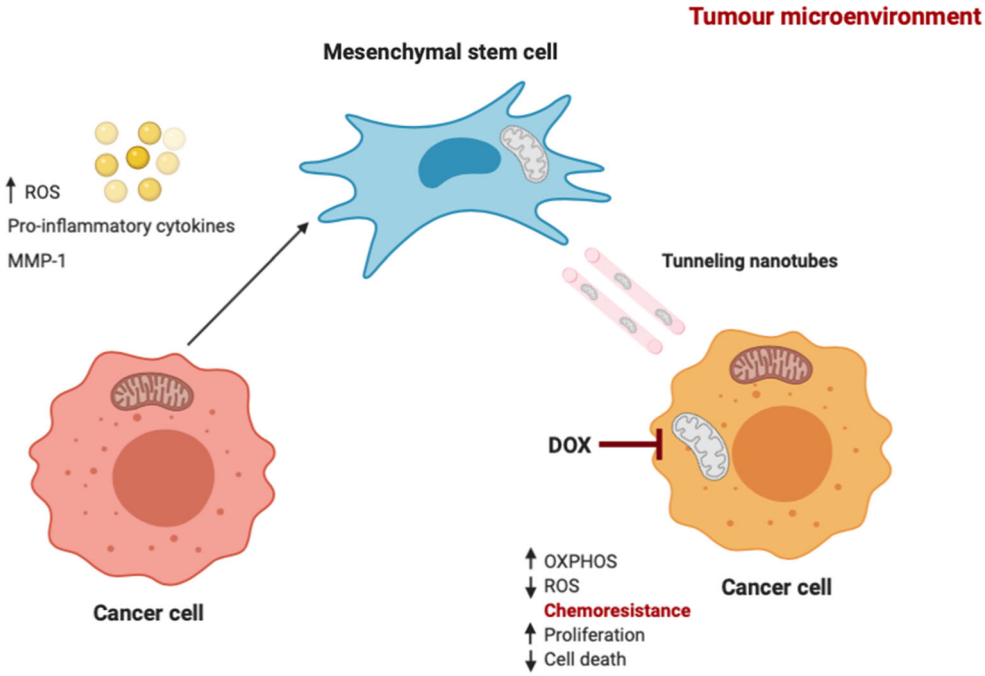

Fig. 5 Mitochondrial transfer in the tumor microenvironment. Cancer cells promote mitochondrial transfer from mesenchymal cells by secreting certain activators. Mitochondria can then be transferred via tunneling nanotubes to cancer cells to rescue OXPHOS and promote chemoresistance. Abbreviations: ROS (reactive oxygen species), MMP-1 (matrix metalloproteinase-1), DOX (doxorubicin), OXPHOS (oxidative phosphorylation). Figure created using BioRender

these molecules regulate treatment resistance in advanced tumors. Furthermore, chemotherapeutic agents have been shown to upregulate ROS production in cancer cells and to serve as additional activators of mitochondrial transfer [129].

The mechanisms of how mitochondrial donation promotes chemoresistance to cancer cells have not been fully elucidated yet. However, it has been observed that recipient cancer cells could maintain their mitochondrial transmembrane potential after chemotherapy as opposed to controls [130]. Furthermore, mitochondrial donation has been shown to rescue mitochondrial integrity and ATP production in neuronal cells after treatment with cisplatin [122]. Similar results have been obtained by Caceido et al. showing that mitochondrial donation restored ATP production in MDA-MB-231 breast cancer cells after treatment [131]. Mitochondrial transfer has also been shown to combat apoptosis in stressed pheochromocytoma-derived PC12 cells after UV radiation [132]. Mitochondrial transfer via TNTs rescued the cancer cells from undergoing apoptosis, indicating a pro-survival mechanism. These results suggest that mitochondrial transfer can promote drug resistance by maintaining mitochondrial transmembrane potential, restoring ATP production and inhibiting apoptosis. However, it is also possible that the transfer of other cytoplasmic components, such as proteins or genetic material, via TNTs may be involved in mediating chemoresistance [123]. Therefore, future studies should aim at further elucidating the mechanisms by which mitochondrial transfer promotes drug resistance. Inhibition of mitochondrial transfer should also be explored as a treatment option to prevent drug resistance.

7 Future recommendations

Resistance to treatment is a significant obstacle that hampers effective cancer treatment. Current approaches to treating advanced heterogeneous tumors with MTDs are ineffective, as they select resistant CSCs and promote recurrence [1]. Mitochondria are among the primary players that mediate treatment resistance. Targeting mitochondria may sensitize cancer cells to therapy and enable the administration of lower treatment doses. Our recommendations agree with those of others who indicated that a tumor's metabolic phenotype should be used to predict its drug response and that pharmacological strategies should be implemented to target multiple mitochondrial metabolic pathways [133, 134].

Mutations in FH and subsequent fumarate accumulation is associated with hereditary leiomyomatosis and renal cell cancer (HLRCC). As mentioned above, fumarate accumulation can activate Nrf2 by abrogating the interaction between Keap1 and Nrf2. Upregulated Nrf2 has been observed in multiple tumor types and has been shown to promote treatment resistance. Therefore, patients with RCC may exhibit increased Nrf2 activation, which may make them resistant to treatment. Sequencing the tumor genome of HLRCC patients may, therefore, provide valuable therapeutic information. Small molecule Nrf2 inhibitors should be considered as adjuvants as they may reduce treatment resistance in FH mutant HLRCC patients.

Examples of clinical drugs that act as Nrf2 inhibitors include glucocorticoids and cardiac glycosides. Choi et al. found that the glucocorticoid clobetasol propionate (CP) prevented nuclear translocation of Nrf2 and promoted its degradation [135]. Furthermore, CP inhibited the *in vitro* and *in vivo* growth of Keap1 mutant tumors. Treatment with CP also upregulated ROS levels in Keap1 mutant tumor cells, suggesting that Nrf2 may interfere with redox homeostasis [135]. Additionally, the cardiac glycoside digoxin has been found to reverse drug resistance by inhibiting Nrf2 in gemcitabine-resistant pancreatic cancer cells by suppressing the PI3k/Akt signaling pathway [136]. Certain natural products such as Trigonelline (an alkaloid occurring in many plants) and Brusatol (a natural product from *Brucea javanica*), and ascorbic acid (vitamin C) have been identified as Nrf2 inhibitors [137]. Treatment with small molecule Nrf2 inhibitors has been shown to reverse drug resistance and sensitize cancer cells to chemotherapeutic agents [136, 138–141]. Therefore, it can be speculated that Nrf2 inhibitors may attenuate drug resistance in FH deficient tumors as well.

IDH1 and IDH2 mutations are associated with hematologic and solid tumors, including acute myeloid leukemia, cholangiocarcinoma, chondrosarcoma and glioma [142–145]. As mentioned above, gain of function mutations in IDH1 and IDH2 result in the accumulation of the oncometabolite 2-HG. This oncometabolite is exported by cancer cells, whereafter it enters T-cells via SCL13A and impairs T-cell activity. The immunosuppressive effect exerted by 2-HG may impair the functionality of immunotherapy. Therefore, patients with IDH mutations may benefit from IDH-mutant inhibitors, especially when combined with immunotherapy. IDH mutant inhibitors have indeed been found to have tumor supressing effects [146, 147]. Enasidenib and ivosidenib are two IDH inhibitors that have recently been approved by the FDA and should be considered as adjuvants for the treatment of IDH mutant tumors [148]. Fumarate and 2-HG are also regulators of angiogenesis. As such, targeting these oncometabolites may indirectly serve as an anti-angiogenic therapy and promote the sensitivity of FH and IDH mutant tumors to anti-angiogenic drugs.

Furthermore, mitochondrial transfer promotes drug resistance by acting as a pro-survival mechanism that allows cancer cells to adapt and survive stress conditions. Targeting TNTs is, therefore, a feasible strategy to inhibit mitochondrial transfer and chemoresistance. Anti-diabetic drugs such as metformin and everolimus have been shown to suppress TNT formation by inhibiting mTOR [149, 150]. The use of

these drugs may improve treatment outcomes in heterogeneous treatment-resistant tumors.

8 Conclusions

The data reviewed here indicate that enzymatic mutations and subsequent accumulation of the oncometabolites fumarate and 2-HG can promote treatment resistance through upregulating Nrf2 and inhibiting the antitumor immune response, respectively. Additionally, both of these oncometabolites are facilitators of angiogenesis. Genomic sequencing may determine whether the relevant mutations are present and, if so, whether they can be used to guide treatment choices. Furthermore, stromal cells can donate intact mitochondria to cancer cells and rescue them from therapeutic onslaught. Targeting Nrf2, mitochondrial mutations and TNTs may serve as feasible strategies for combatting treatment resistance and improving treatment outcomes.

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Declarations

Conflict of interest disclosure None declared.

References

1. R.A. Gatenby, A.S. Silva, R.J. Gillies, B.R. Frieden, Adaptive therapy. Cancer Res. **69**, 4894–4903 (2009)
2. H. Uramoto, F. Tanaka, Recurrence after surgery in patients with NSCLC. Transl. Lung Cancer Res. **3**, 242–249 (2014)
3. S. Mallick, R. Benson, A. Hakim, G.K. Rath, Management of glioblastoma after recurrence: A changing paradigm. J. Egypt. Natl. Canc. Inst. **28**, 199–210 (2016)
4. G. Corrado, V. Salutari, E. Palluzzi, M.G. Distefano, G. Scambia, G. Ferrandina, Optimizing treatment in recurrent epithelial ovarian cancer. Expert Rev. Anticancer Ther. **17**, 1147–1158 (2017)
5. W.G. Kraybill, J. Harris, I.J. Spiro, D.S. Ettinger, T.F. DeLaney, R.H. Blum, D.R. Lucas, D.C. Harmon, G.D. Letson, B. Eisenberg, Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group trial 9514. Cancer **116**, 4613–4621 (2010)
6. M. Chowdhary, A. Chowdhary, N. Sen, N.G. Zaorsky, K.R. Patel, D. Wang, Does the addition of chemotherapy to neoadjuvant radiotherapy impact survival in high-risk extremity/trunk soft-tissue sarcoma? Cancer **125**, 3801–3809 (2019)
7. R. Fischer, M. Breidert, T. Keck, F. Makowiec, C. Lohrmann, J. Harder, Early recurrence of pancreatic cancer after resection and during adjuvant chemotherapy. Saudi J. Gastroenterol. **118**, 18 (2012)
8. X. Wang, H. Zhang, X. Chen, Drug resistance and combating drug resistance in cancer. Cancer Drug Resist. **22**, 141–160 (2019)
9. P. Borst, Cancer drug pan-resistance: Pumps, cancer stem cells, quiescence, epithelial to mesenchymal transition, blocked cell death pathways, persisters or what? Open Biol. **2**, 120066 (2012)
10. C. Holohan, S. Van Schaeybroeck, D.B. Longley, P.G. Johnston, Cancer drug resistance: an evolving paradigm. Nat. Rev. Cancer **13**, 714–726 (2013)
11. I. Vega-Naredo, R. Loureiro, K.A. Mesquita, I.A. Barbosa, L.C. Tavares, A.F. Branco, J.R. Erickson, J. Holy, E.L. Perkins, R.A. Carvalho, P.J. Oliveira, Mitochondrial metabolism directs stemness and differentiation in P19 embryonal carcinoma stem cells. Cell Death Differ. **21**, 1560–1574 (2014)
12. A. Wanet, T. Arnould, M. Najimi, P. Renard, Connecting mitochondria, metabolism, and stem cell fate. Stem Cells Dev. **24**, 1957–1971 (2015)
13. S. Missiroli, M. Perrone, I. Genovese, P. Pinton, C. Giorgi, Cancer metabolism and mitochondria: Finding novel mechanisms to fight tumours. EBioMedicine **59**, 102943 (2020)
14. O. Warburg, On the origin of cancer cells. Science **123**, 309–314 (1956)
15. C.A. O'Brien, A. Kreso, J.E. Dick, Cancer stem cells in solid tumors: an overview. Semin. Radiat. Oncol. **19**, 71 (2009)
16. E. Vlashi, C. Lagadec, L. Vergnes, T. Matsutani, K. Masui, M. Poulou, R. Popescu, L. Della Donna, P. Evers, C. Dekmezian, K. Reue, H. Christofk, P.S. Mischel, F. Pajonka, Metabolic state of glioma stem cells and nontumorigenic cells. Proc. Natl. Acad. Sci. U. S. A. **108**, 16062–16067 (2011)
17. J.M. García-Heredia, A. Carnero, Role of mitochondria in cancer stem cell resistance. Cells **9**, 1693 (2020)
18. S. Ma, T.K. Lee, B.J. Zheng, K.W. Chan, X.Y. Guan, CD133 + HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. Oncogene **27**, 1749–1758 (2008)
19. P. Dey, M. Rathod, A. De, Targeting stem cells in the realm of drug-resistant breast cancer. Breast Cancer Targets Ther. **11**, 115–135 (2019)
20. P. Zhou, B. Li, F. Liu, M. Zhang, Q. Wang, Y. Liu, Y. Yao, D. Li, The epithelial to mesenchymal transition (EMT) and cancer stem cells: Implication for treatment resistance in pancreatic cancer. Mol. Cancer **16**, 1–11 (2017)
21. I. Martínez-Reyes, N.S. Chandel, Mitochondrial TCA cycle metabolites control physiology and disease. Nat. Commun. **11**, 1–11 (2020)
22. M. Yang, T. Soga, P.J. Pollard, Oncometabolites: Linking altered metabolism with cancer. J. Clin. Invest. **123**, 3652–3658 (2013)
23. D. Ye, S. Ma, Y. Xiong, K.L. Guan, R-2-hydroxyglutarate as the key effector of IDH mutations promoting oncogenesis. Cancer Cell **23**, 274–276 (2013)
24. C. Chinopoulos, Which way does the citric acid cycle turn during hypoxia? The critical role of α-ketoglutarate dehydrogenase complex J. Neurosci. Res. **91**, 1030–1043 (2013)
25. E. Dalla Pozza, I. Dando, R. Pacchiana, E. Liboi, M.T. Scupoli, M. Donadelli, M. Palmieri, Regulation of succinate dehydrogenase and role of succinate in cancer. Semin. Cell Dev. Biol. **1**, 4–14 (2020)
26. M.E. Figueroa, O. Abdel-Wahab, C. Lu, P.S. Ward, J. Patel, A. Shih, Y. Li, N. Bhagwat, A. Vasanthakumar, H.F. Fernandez, M.S. Tallman, Z. Sun, K. Wolniak, J.K. Peeters, W. Liu, S.E. Choe, V.R. Fantin, E. Paietta, B. Löwenberg, J.D. Licht, L.A. Godley, R. Delwel, P.J.M. Valk, C.B. Thompson, R.L. Levine, A. Melnick, Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 Function, and impair hematopoietic differentiation. Cancer Cell **18**, 553–567 (2010)
27. B. Ryder, F. Moore, A. Mitchell, S. Thompson, J. Christodoulou, S. Balasubramaniam, Balasubramaniam, Fumarase deficiency: A safe and potentially disease modifying effect of high fat/low carbohydrate diet. JIMD Rep. **40**, 77–83 (2018)

28. J. Zhang, M.F. Walsh, G. Wu, M.N. Edmonson, T.A. Gruber, J. Easton, D. Hedges, X. Ma, X. Zhou, D.A. Yergeau, M.R. Wilkinson, B. Vadodaria, X. Chen, R.B. McGee, S. Hines-Dowell, R. Nuccio, E. Quinn, S.A. Shurtleff, M. Rusch, A. Patel, J.B. Becksfort, S. Wang, M.S. Weaver, L. Ding, E.R. Mardis, R.K. Wilson, A. Gajjar, D.W. Ellison, A.S. Pappo, C.-H. Pui, K.E. Nichols, J.R. Downing, Germline mutations in predisposition genes in pediatric cancer. N. Engl. J. Med. **373**, 2336–2346 (2015)
29. A. Fieuw, C. Kumps, A. Schramm, F. Pattyn, B. Menten, F. Antonacci, P. Sudmant, J.H. Schulte, N. Van Roy, S. Vergult, P.G. Buckley, A. De Paepe, R. Noguera, R. Versteeg, R. Stallings, A. Eggert, J. Vandesompele, K. De Preter, F. Speleman, Identification of a novel recurrent 1q42.2-1qter deletion in high risk MYCN single copy 11q deleted neuroblastomas Int. J. Cancer. **130**, 2599–2606 (2012)
30. J. Hu, J.W. Locasale, J.H. Bielas, J. O'Sullivan, K. Sheahan, L.C. Cantley, M.G.V. Heiden, D. Vitkup, Heterogeneity of tumor-induced gene expression changes in the human metabolic network. Nat. Biotechnol. **31**, 522–529 (2013)
31. C. Frezza, P.J. Pollard, E. Gottlieb, Inborn and acquired metabolic defects in cancer. J. Mol. Med. **89**, 213–220 (2011)
32. D. Krell, P. Mulholland, A.E. Frampton, J. Krell, J. Stebbing, C. Bardella, IDH mutations in tumorigenesis and their potential role as novel therapeutic targets. Future Oncol. **9**, 1923–1935 (2013)
33. J.R. Prensner, A.M. Chinnaiyan, Metabolism unhinged: IDH mutations in cancer . Nat. Med. **17**, 291–293 (2011)
34. H. Yan, D.W. Parsons, G. Jin, R. McLendon, B.A. Rasheed, W. Yuan, I. Kos, I. Batinic-Haberle, S. Jones, G.J. Riggins, H. Friedman, A. Friedman, D. Reardon, J. Herndon, K.W. Kinzler, V.E. Velculescu, B. Vogelstein, Bigner, IDH1 and IDH2 mutations in gliomas . N. Engl. J. Med. **360**, 765–773 (2009)
35. B.C. Medeiros, A.T. Fathi, C.D. DiNardo, D.A. Pollyea, S.M. Chan, R. Swords, Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia **31**, 272–281 (2017)
36. S. Wu, H. Lu, Y. Bai, Nrf2 in cancers: A double-edged sword. Cancer Med. **8**, 2252–2267 (2019)
37. T. Iizuka, Y. Ishii, K. Itoh, T. Kiwamoto, T. Kimura, Y. Matsuno, Y. Morishima, A.E. Hegab, S. Homma, A. Nomura, T. Sakamoto, M. Shimura, A. Yoshida, M. Yamamoto, K. Sekizawa, Nrf2-deficient mice are highly susceptible to cigarette smoke-induced emphysema. Genes Cells **10**, 1113–1125 (2005)
38. Y. Aoki, H. Sato, N. Nishimura, S. Takahashi, K. Itoh, M. Yamamoto, Accelerated DNA adduct formation in the lung of the Nrf2 knockout mouse exposed to diesel exhaust. Toxicol. Appl. Pharmacol. **173**, 154–160 (2001)
39. K. Iida, K. Itoh, Y. Kumagai, R. Oyasu, K. Hattori, K. Kawai, T. Shimazui, H. Akaza, M. Yamamoto, Nrf2 is essential for the chemopreventive efficacy of oltipraz against urinary bladder carcinogenesis. Cancer Res. **64**, 6424–6431 (2004)
40. P. Zhang, A. Singh, S. Yegnasubramanian, D. Esopi, P. Kombairaju, M. Bodas, H. Wu, S.G. Bova, S. Biswal, Loss of kelch-like ECH-associated protein 1 function in prostate cancer cells causes chemoresistance and radioresistance and promotes tumor growth. Mol. Cancer Ther. **9**, 336–346 (2010)
41. X.J. Wang, Z. Sun, N.F. Villeneuve, S. Zhang, F. Zhao, Y. Li, W. Chen, X. Yi, W. Zheng, G.T. Wondrak, P.K. Wong, D.D. Zhang, Nrf2 enhances resistance of cancer cells to chemotherapeutic drugs, the dark side of Nrf2. Carcinogenesis **29**, 1235–1243 (2008)
42. A. Singh, V. Misra, R.K. Thimmulappa, H. Lee, S. Ames, M.O. Hoque, J.G. Herman, S.B. Baylin, D. Sidransky, E. Gabrielson, M.V. Brock, S. Biswal, Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. PLoS Med. **3**, e420 (2006)
43. T. Shibata, A. Kokubu, M. Gotoh, H. Ojima, T. Ohta, M. Yamamoto, S. Hirohashi, Genetic alteration of Keap1 confers constitutive Nrf2 activation and resistance to chemotherapy in gallbladder cancer. Gastroenterology **135**, 1358–1368 (2008)
44. Y.R. Kim, J.E. Oh, M.S. Kim, M.R. Kang, S.W. Park, J.Y. Han, H.S. Eom, N.J. Yoo, S.H. Lee, Oncogenic NRF2 mutations in squamous cell carcinomas of oesophagus and skin. J. Pathol. **220**, 446–451 (2010)
45. M.B. Sporn, K.T. Liby, NRF2 and cancer: The Good, the bad and the importance of context. Nat. Rev. Cancer **12**, 564–571 (2012)
46. P. Basak, P. Sadhukhan, P. Sarkar, P.C. Sil, Perspectives of the Nrf-2 signaling pathway in cancer progression and therapy. Toxicol. Reports **4**, 306–318 (2017)
47. B. Padmanabhan, K.I. Tong, T. Ohta, Y. Nakamura, M. Scharlock, M. Ohtsuji, M. Il Kang, A. Kobayashi, S. Yokoyama, M. Yamamoto, Structural basis for defects of Keap1 activity provoked by its point mutations in lung cancer. Mol. Cell **21**, 689–700 (2006)
48. G.M. Denicola, F.A. Karreth, T.J. Humpton, A. Gopinathan, C. Wei, K. Frese, D. Mangal, K.H. Yu, C.J. Yeo, E.S. Calhoun, F. Scrimieri, J.M. Winter, R.H. Hruban, C. Iacobuzio-Donahue, S.E. Kern, I.A. Blair, D.A. Tuveson, Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature **475**, 106–109 (2011)
49. N. Chen, X. Yi, N. Abushahin, S. Pang, D. Zhang, B. Kong, W. Zheng, Nrf2 expression in endometrial serous carcinomas and its precancers. Int. J. Clin. Exp. Pathol. **4**, 85 (2011)
50. S. Zhou, W. Ye, Q. Shao, M. Zhang, J. Liang, Nrf2 is a potential therapeutic target in radioresistance in human cancer. Crit. Rev. Oncol. Hematol. **88**, 706–715 (2013)
51. L. Milkovic, N. Zarkovic, and L. Saso, Controversy about pharmacological modulation of Nrf2 for cancer therapy. Redox Biol. **12**, 727–732 (2017)
52. E. Kansanen, S.M. Kuosmanen, H. Leinonen, A.L. Levonenn, The Keap1-Nrf2 pathway: Mechanisms of activation and dysregulation in cancer. Redox Biol. **1**, 45–49 (2013)
53. H.C. Huang, T. Nguyen, C.B. Pickett, Phosphorylation of Nrf2 at Ser-40 by protein kinase C regulates antioxidant response element-mediated transcription. J. Biol. Chem. **277**, 42769–42774 (2002)
54. A.N.T. Kong, E. Owuor, R. Yu, V. Hebbar, C. Chen, R. Hu, S. Mandlekar, Induction of xenobiotic enzymes by the map kinase pathway and the antioxidant or electrophile response element (ARE/EpRE). Drug Metab. Rev. **33**, 255–271 (2001)
55. J.M. Lee, J.M. Hanson, W.A. Chu, J.A. Johnson, Phosphatidylinositol 3-Kinase, not extracellular signal-regulated Kinase, Regulates activation of the antioxidant-responsive element in IMR-32 human neuroblastoma cells. J. Biol. Chem. **276**, 20011–20016 (2001)
56. T. Nguyen, P.J. Sherratt, C.B. Pickett, Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. Annu. Rev. Pharmacol. Toxicol. **43**, 233–260 (2003)
57. R. Yu, C. Chen, Y.Y. Mo, V. Hebbar, E.D. Owuor, T.H. Tan, A.N.T. Kong, Activation of mitogen-activated protein kinase pathways induces antioxidant response element-mediated gene expression via a Nrf2-dependent mechanism. J. Biol. Chem. **275**, 39907–39913 (2000)
58. L.E. Tebay, H. Robertson, S.T. Durant, S.R. Vitale, T.M. Penning, A.T. Dinkova-Kostova, J.D. Hayes, Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease. Free Radic. Biol. Med. **88**, 108–146 (2015)
59. A. Ooi and K. A. Furge, Fumarate hydratase inactivation in renal tumors: HIF1α, NRF2 and "cryptic targets" of transcription factors. Chin. J. Cancer. **31**, 413–420 (2012)
60. J. Adam, E. Hatipoglu, L. O'Flaherty, N. Ternette, N. Sahgel, H. Lockstone, D. Baban, G.W. NyeE, K. Stamp, M. Wolhuter, R. Stevens, P. Fischer, P.H. Carmeliet, C.W. Maxwell, N. Pugh, T. Frizzell, B.M. Soga, M. Kessler, P.J. El-Bahrawy, Ratcliffe, P. Pollard, Renal Cyst formation in FH1-deficient mice is

independent of the hif/phd pathways: roles for fumarate in keap1 succination and nrf2 signalling. Cancer Cell **20**, 524–537 (2011)
61. S.K. Niture, A.K. Jaiswal, Nrf2 protein up-regulates antiapoptotic protein Bcl-2 and prevents cellular apoptosis. J. Biol. Chem. **287**, 9873–9886 (2012)
62. M. Zhang, C. Zhang, L. Zhang, Q. Yang, S. Zhou, Q. Wen, J. Wang, Nrf2 is a potential prognostic marker and promotes proliferation and invasion in human hepatocellular carcinoma. BMC Cancer **15**, 1–12 (2015)
63. J. Chen, Z. Zhang, L. Cai, Diabetic cardiomyopathy and its prevention by Nrf2: Current status. Diabetes Metab. J. **38**, 337 (2014)
64. X. Sun, S. Wang, J. Gai, J. Guan, J. Li, Y. Li, J. Zhao, C. Zhao, L. Fu, Q. Li, SIRT5 promotes cisplatin resistance in ovarian cancer by suppressing dna damage in a ROS-dependent manner via regulation of the Nrf2/HO-1 pathway. Front. Oncol. **9**, 754 (2019)
65. M. Xia, H. Yu, S. Gu, Y. Xu, J. Su, H. Li, J. Kang, M. Cui, P62/SQSTM1 is involved in cisplatin resistance in human ovarian cancer cells via the Keap1-Nrf2-ARE system. Int. J. Oncol. **45**, 2341–2348 (2014)
66. W. Ge, K. Zhao, X. Wang, H. Li, M. Yu, M. He, X. Xue, Y. Zhu, C. Zhang, Y. Cheng, S. Jiang, Y. Hu, iASPP is an antioxidative factor and drives cancer growth and drug resistance by competing with Nrf2 for Keap1 binding. Cancer Cell **32**, 561–573 (2017)
67. X. Tang, H. Wang, L. Fan, X. Wu, A. Xin, H. Ren, X.J. Wang, Luteolin inhibits Nrf2 leading to negative regulation of the Nrf2/ARE pathway and sensitization of human lung carcinoma A549 cells to therapeutic drugs. Free Radic. Biol. Med. **50**, 1599–1609 (2011)
68. T. Wu, B.G. Harder, P.K. Wong, J.E. Lang, D.D. Zhang, Oxidative stress, mammospheres and Nrf2-new implication for breast cancer therapy? Mol. Carcinog. **54**, 1494–1502 (2015)
69. S. Falone, S. Santini, V. Cordone, P. Cesare, A. Bonfigli, M. Grannonico, G. Di Emidio, C. Tatone, M. Cacchio, F. Amicarelli, Power frequency magnetic field promotes a more malignant phenotype in neuroblastoma cells via redox-related mechanisms. Sci. Rep. **7**, 1–14 (2017)
70. Y. Xiang, W. Ye, C. Huang, D. Yu, H. Chen, T. Deng, F. Zhang, B. Lou, J. Zhang, K. Shi, B. Chen, and M. Zhou, Brusatol enhances the chemotherapy efficacy of gemcitabine in pancreatic cancer via the Nrf2 signalling pathway. Oxid. Med. Cell. Longev (2018). https://doi.org/10.1155/2018/2360427
71. B. Halliwell, Free radicals and antioxidants - Quo vadis? Trends Pharmacol. Sci. **32**, 125–130 (2011)
72. B. Shen, P.J. He, C.L. Shao, Norcantharidin induced DU145 cell apoptosis through ROS-mediated mitochondrial dysfunction and energy depletion. PLoS One **8**, e84610 (2013)
73. P. Brenneisen, A.S. Reichert, Nanotherapy and reactive oxygen species (ROS) in cancer: A novel perspective. Antioxidants **7**, 31 (2018)
74. M.L. Circu, T.Y. Aw, Reactive oxygen species, cellular redox systems, and apoptosis. Free Radic. Biol. Med. **48**, 749–762 (2010)
75. S. Orrenius, V. Gogvadze, B. Zhivotovsky, Calcium and mitochondria in the regulation of cell death. Biochem. Biophys. Res. Commun. **460**, 72–81 (2015)
76. P. Pallepati, D.A. Averill-Bates, Mild thermotolerance induced at 40 °c protects HeLa cells against activation of death receptor-mediated apoptosis by hydrogen peroxide. Free Radic. Biol. Med. **50**, 667–679 (2011)
77. G. Mellier, S. Pervaiz, The three Rs along the TRAIL: Resistance, re-sensitization and reactive oxygen species (ROS). Free Radic. Res. **46**, 996–1003 (2012)
78. M. Redza-Dutordoir, D.A. Averill-Bates, Activation of apoptosis signalling pathways by reactive oxygen species. Biochim. Biophys. Acta - Mol. Cell Res. **1863**, 2977–2992 (2016)
79. X. Bai, Y. Chen, X. Hou, M. Huang, and J. Jin, Emerging role of NRF2 in chemoresistance by regulating drug-metabolizing enzymes and efflux transporters. Drug Metab. Rev. **84**, 541–567 (2016)
80. B. Choi, M.K. Kwak, Shadows of NRF2 in cancer: Resistance to chemotherapy. Curr. Opin. Toxicol. **1**, 20–28 (2016)
81. M. Cojoc, K. Mäbert, M.H. Muders, A. Dubrovska, A role for cancer stem cells in therapy resistance: Cellular and molecular mechanisms. Semin. Cancer Biol. **31**, 16–27 (2015)
82. Y. Yang, V. Valera, C. Sourbier, C.D. Vocke, M. Wei, L. Pike, Y. Huang, M.A. Merino, G. Bratslavsky, M. Wu, C.J. Ricketts, W.M. Linehan, A novel fumarate hydratase-deficient HLRCC kidney cancer cell line, UOK268: A model of the Warburg effect in cancer. Cancer Genet. **205**, 377–390 (2012)
83. K.M. Holmström, L. Baird, Y. Zhang, I. Hargreaves, A. Chalasani, J.M. Land, L. Stanyer, M. Yamamoto, A.T. Dinkova-Kostova, A.Y. Abramov, Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration. Biol. Open **2**, 761–770 (2013)
84. T.H. Kim, E.G. Hur, S.J. Kang, J.A. Kim, D. Thapa, Y. Mie Lee, S.K. Ku, Y. Jung, M.K. Kwak, NRF2 blockade suppresses colon tumor angiogenesis by inhibiting hypoxia-induced activation of HIF-1α. Cancer Res. **71**, 2260–2275 (2011)
85. P. Vaupel, H. Schmidberger, A. Mayer, The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. Int. J. Radiat. Biol. **95**, 912–919 (2019)
86. J.C. Ghosh, M.D. Siegelin, V. Vaira, A. Faversani, M. Tavecchio, Y.C. Chae, S. Lisanti, P. Rampini, M. Giroda, M.C. Caino, J.H. Seo, A.V. Kossenkov, R.D. Michalek, D.C. Schultz, S. Bosari, L.R. Languino, D.C. Altieri, Adaptive mitochondrial reprogramming and resistance to PI3K therapy. J. Natl. Cancer Inst. **107**, dju502 (2015)
87. A. Viale, P. Pettazzoni, C.A. Lyssiotis, H. Ying, N. Sánchez, M. Marchesini, A. Carugo, T. Green, S. Seth, V. Giuliani, M. Kost-Alimova, F. Muller, S. Colla, L. Nezi, G. Genovese, A.K. Deem, A. Kapoor, W. Yao, E. Brunetto, Y. Kang, M. Yuan, J.M. Asara, Y.A. Wang, T.P. Heffernan, A.C. Kimmelman, H. Wang, J.B. Fleming, L.C. Cantley, R.A. DePinho, G.F. Draetta, Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. Nature **514**, 628–632 (2014)
88. K.M. Havas, V. Milchevskaya, K. Radic, A. Alladin, E. Kafkia, M. Garcia, J. Stolte, B. Klaus, N. Rotmensz, T.J. Gibson, B. Burwinkel, A. Schneeweiss, G. Pruneri, K.R. Patil, R. Sotillo, M. Jechlinger, Metabolic shifts in residual breast cancer drive tumor recurrence. J. Clin. Invest. **127**, 2091–2105 (2017)
89. R. Su, L. Dong, C. Li, S. Nachtergaele, M. Wunderlich, Y. Qing, X. Deng, Y. Wang, X. Weng, C. Hu, M. Yu, J. Skibbe, Q. Dai, D. Zou, T. Wu, K. Yu, H. Weng, H. Huang, K. Ferchen, X. Qin, B. Zhang, J. Qi, A.T. Sasaki, D.R. Plas, J.E. Bradner, M. Wei, G. Marcucci, X. Jiang, J.C. Mulloy, J. Jin, C. He, J. Chen, R-2HG exhibits anti-tumor activity by targeting FTO/m6A/MYC/CEBPA. Cell **172**, 90–105 (2018)
90. L. Bunse, S. Pusch, T. Bunse, F. Sahm, K. Sanghvi, M. Friedrich, D. Alansary, J.K. Sonner, E. Green, K. Deumelandt, M. Kilian, C. Neftel, S. Uhlig, T. Kessler, A. von Landenberg, A.S. Berghoff, K. Marsh, M. Steadman, D. Zhu, B. Nicolay, B. Wiestler, M.O. Breckwoldt, R. Al-Ali, S. Karcher-Bausch, M. Bozza, I. Oezen, M. Kramer, J. Meyer, A. Habel, J. Eisel, G. Poschet, M. Weller, M. Preusser, M. Nadji-Ohl, N. Thon, M.C. Burger, P.N. Harter, M. Ratliff, R. Harbottle, A. Benner, D. Schrimpf, J. Okun, C. Herold-Mende, S. Turcan, S. Kaulfuss, H. Hess-Stumpp, K. Bieback, D.P. Cahill, K.H. Plate, D. Hänggi, M. Dorsch, M.L. Suvà, B.A. Niemeyer, A. von Deimling, W. Wick, M. Platten, Suppression of antitumor T cell immunity by the oncometabolite (R)-2-hydroxyglutarate. Nat. Med. **24**, 1192–1203 (2018)
91. P.S. Ward, J. Patel, D.R. Wise, O. Abdel-Wahab, B.D. Bennett, H.A. Coller, J.R. Cross, V.R. Fantin, C.V. Hedvat, A.E. Perl, J.D.

Rabinowitz, M. Carroll, S.M. Su, K.A. Sharp, R.L. Levine, C.B. Thompson, The common feature of leukemia-associated IDH1 and IDH2 mutations is a Neomorphic enzyme activity converting α-Ketoglutarate to 2-Hydroxyglutarate. Cancer Cell **17**, 225–234 (2010)
92. A.T. Fathi, B.V. Nahed, S.A. Wander, A.J. Iafrate, D.R. Borger, R. Hu, A. Thabet, D.P. Cahill, A.M. Perry, C.P. Joseph, A. Muzikansky, A.S. Chi, Elevation of urinary 2-Hydroxyglutarate in IDH -mutant glioma. Oncologist **21**, 214–219 (2016)
93. Y.W. Chen, Y.F. Chen, Y.T. Chen, W.T. Chiu, M.R. Shen, The STIM1-Orai1 pathway of store-operated Ca2 + entry controls the checkpoint in cell cycle G1/S transition. Sci. Rep. **6**, 1–13 (2016)
94. G.S. Bird, S.Y. Hwang, J.T. Smyth, M. Fukushima, R.R. Boyles, J.W. Putney, STIM1 is a calcium sensor specialized for digital signaling . Curr. Biol. **19**, 1724–1729 (2009)
95. C.Y. Park, P.J. Hoover, F.M. Mullins, P. Bachhawat, E.D. Covington, S. Raunser, T. Walz, K.C. Garcia, R.E. Dolmetsch, R.S. Lewis, STIM1 clusters and activates CRAC channels via direct binding of a cytosolic domain to Orai1. Cell **136**, 876–890 (2009)
96. A. Gudlur, Y. Zhou, and P. G. Hogan, STIM-ORAI Interactions That Control the CRAC Channel. Curr. Top. Membr. **71**, 33–58 (2013)
97. Y. Zhou, P. Srinivasan, S. Razavi, S. Seymour, P. Meraner, A. Gudlur, P.B. Stathopulos, M. Ikura, A. Rao, P.G. Hogan, Initial activation of STIM1, the regulator of store-operated calcium entry. Nat. Struct. Mol. Biol. **20**, 973–981 (2013)
98. M.D. Cahalan, STIMulating store-operated Ca2 + entry. Nat. Cell Biol. **31**, 597–601 (2009)
99. M. Sieber, R. Baumgrass, Novel inhibitors of the calcineurin/NFATc hub - Alternatives to CsA and FK506? Cell Commun. Signal (2009). https://doi.org/10.1186/1478-811X-7-25
100. R. Wang, C.P. Dillon, L.Z. Shi, S. Milasta, R. Carter, D. Finkelstein, L.L. McCormick, P. Fitzgerald, H. Chi, J. Munger, D.R. Green, The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity **35**, 871–882 (2011)
101. N. Nishida, H. Yano, T. Nishida, T. Kamura, M. Kojiro, Angiogenesis in cancer. Vasc. Health Risk Manag. **2**, 213–219 (2006)
102. P. Carmeliet, VEGF as a key mediator of angiogenesis in cancer. Oncology **69**, 4–10 (2005)
103. R.T.P. Poon, S.T. Fan, J. Wong, Clinical implications of circulating angiogenic factors in cancer patients. J. Clin. Oncol. **19**, 1207–1225 (2001)
104. N. Ferrara, H.P. Gerber, The role of vascular endothelial growth factor in angiogenesis. Acta Haematol. **106**, 148–156 (2001)
105. M.A. McDonough, C. Loenarz, R. Chowdhury, I.J. Clifton, C.J. Schofield, Structural studies on human 2-oxoglutarate dependent oxygenases Curr. Opin. Struct. Biol. **20**, 659–672 (2010)
106. A. King, M.A. Selak, E. Gottlieb, Succinate dehydrogenase and fumarate hydratase: Linking mitochondrial dysfunction and cancer. Oncogene **25**, 4675–4682 (2006)
107. C. Lin, R. McGough, B. Aswad, J.A. Block, R. Terek, Hypoxia induces HIF-1α and VEGF expression in chondrosarcoma cells and chondrocytes. J. Orthop. Res. **22**, 1175–1181 (2004)
108. M. Safran, W.G. Kaelin, HIF hydroxylation and the mammalian oxygen-sensing pathway J. Clin. Invest. **111**, 779–783 (2003)
109. L.E. Huang, Z. Arany, D.M. Livingston, H. Franklin, Bunn, Activation of hypoxia-inducible transcription factor depends primarily upon redox-sensitive stabilization of its α subunit. J. Biol. Chem. **271**, 32253–32259 (1996)
110. T. Zhao, X. Mu, Q. You, Succinate: An initiator in tumorigenesis and progression. Oncotarget **8**, 53819–53828 (2017). https://doi.org/10.18632/oncotarget.17734
111. J.S. Isaacs, J.J. Yun, D.R. Mole, S. Lee, C. Torres-Cabala, Y.L. Chung, M. Merino, J. Trepel, B. Zbar, J. Toro, P.J. Ratcliffe, W.M. Linehan, L. Neckers, HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: Novel role of fumarate in regulation of HIF stability. Cancer Cell. **8**, 143–153 (2005). https://doi.org/10.1016/j.ccr.2005.06.017
112. R. Vatrinet, G. Leone, M. De Luise, G. Girolimetti, M. Vidone, G. Gasparre, A.M. Porcelli, The α-ketoglutarate dehydrogenase complex in cancer metabolic plasticity. Cancer Metab. Cancer Metab. **5**, 1–14 (2017)
113. D.A. Tennant, C. Frezza, E.D. MacKenzie, Q.D. Nguyen, L. Zheng, M.A. Selak, D.L. Roberts, C. Dive, D.G. Watson, E.O. Aboagye, E. Gottlieb, Reactivating HIF prolyl hydroxylases under hypoxia results in metabolic catastrophe and cell death. Oncogene **28**, 4009–4021 (2009)
114. P. Koivunen, M. Hirsilä, A.M. Remes, I.E. Hassinen, K.I. Kivirikko, J. Myllyharju, Inhibition of hypoxia-inducible factor (HIF) hydroxylases by citric acid cycle intermediates: Possible links between cell metabolism and stabilization of HIF. J. Biol. Chem. **282**, 4524–4532 (2007)
115. W. Xu, H. Yang, Y. Liu, Y. Yang, P. Wang, S.H. Kim, S. Ito, C. Yang, P. Wang, M.T. Xiao, L.X. Liu, W.Q. Jiang, J. Liu, J.Y. Zhang, B. Wang, S. Frye, Y. Zhang, Y.H. Xu, Q.Y. Lei, K.L. Guan, S.M. Zhao, Y. Xiong, Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. Cancer Cell **19**, 17–30 (2011)
116. V. Cocetta, E. Ragazzi, and M. Montopoli, Mitochondrial involvement in cisplatin resistance. Int. J. Mol. Sci. (2019). https://doi.org/10.3390/ijms20143384
117. J.L. Spees, S.D. Olson, M.J. Whitney, D.J. Prockop, Mitochondrial transfer between cells can rescue aerobic respiration. Proc. Natl. Acad. Sci. U. S. A. **103**, 1283–1288 (2006)
118. M.V. Jackson, T.J. Morrison, D.F. Doherty, D.F. McAuley, M.A. Matthay, A. Kissenpfennig, C.M. O'Kane, A.D. Krasnodembskaya, Mitochondrial transfer via tunneling nanotubes is an important mechanism by which mesenchymal stem cells enhance macrophage phagocytosis in the in vitro and in vivo models of ARDS. Stem Cells **34**, 2210–2223 (2016)
119. X. Li, Y. Zhang, S.C. Yeung, Y. Liang, X. Liang, Y. Ding, M.S.M. Ip, H.F. Tse, J.C.W. Mak, Q. Lian, Mitochondrial transfer of induced pluripotent stem cell-derived mesenchymal stem cells to airway epithelial cells attenuates cigarette smoke-induced damage. Am. J. Respir. Cell Mol. Biol. **51**, 455–465 (2014)
120. K. Liu, K. Ji, L. Guo, W. Wu, H. Lu, P. Shan, C. Yan, Mesenchymal stem cells rescue injured endothelial cells in an in vitro ischemia-reperfusion model via tunneling nanotube like structure-mediated mitochondrial transfer. Microvasc. Res. **92**, 10–18 (2014)
121. J. Varga, F.R. Greten, Cell plasticity in epithelial homeostasis and tumorigenesis. Nat. Cell Biol. **19**, 1133–1141 (2017)
122. N. Boukelmoune, G.S. Chiu, A. Kavelaars, C.J. Heijnen, Mitochondrial transfer from mesenchymal stem cells to neural stem cells protects against the neurotoxic effects of cisplatin . Acta Neuropathol. Commun. **6**, 1–13 (2018)
123. J. Pasquier, B.S. Guerrouahen, H. Al Thawadi, P. Ghiabi, M. Maleki, N. Abu-Kaoud, A. Jacob, M. Mirshahi, L. Galas, S. Rafii, F. Le Foll, A. Rafii, Preferential transfer of mitochondria from endothelial to cancer cells through tunneling nanotubes modulates chemoresistance. J. Transl. Med. **11**, 1–14 (2013)
124. R. Burt, A. Dey, S. Aref, M. Aguiar, A. Akarca, K. Bailey, W. Day, S. Hooper, A. Kirkwood, K. Kirschner, S.W. Lee, C. Lo Celso, J. Manji, M.R. Mansour, T. Marafioti, R.J. Mitchell, R.C. Muirhead, K.C.Y. Ng, C. Pospori, I. Puccio, K. Zuborne-Alapi, E. Sahai, A.K. Fielding, Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. Blood **134**, 1415–1429 (2019)

125. C.R. Marlein, L. Zaitseva, R.E. Piddock, S.D. Robinson, D.R. Edwards, M.S. Shafat, Z. Zhou, M. Lawes, K.M. Bowles, S.A. Rushworth, NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. Blood **130**, 1649–1660 (2017)
126. J.M. Yang, Z. Xu, H. Wu, H. Zhu, X. Wu, W.N. Hait, Overexpression of extracellular matrix metalloproteinase inducer in multidrug resistant cancer cells. Mol. Cancer Res. **1**, 420–427 (2003)
127. K. Sone, K. Maeno, A. Masaki, E. Kunii, O. Takakuwa, Y. Kagawa, A. Takeuchi, S. Fukuda, T. Uemura, K. Fukumitsu, Y. Kanemitsu, H. Ohkubo, M. Takemura, Y. Ito, T. Oguri, H. Inagaki, A. Niimi, Nestin expression affects resistance to chemotherapy and clinical outcome in small cell lung cancer. Front. Oncol. **10**, 1367 (2020)
128. V.S. Jones, R.Y. Huang, L.P. Chen, Z.S. Chen, L. Fu, R.P. Huang, Cytokines in cancer drug resistance: Cues to new therapeutic strategies. Biochim. Biophys. Acta - Rev. Cancer **1865**, 255–265 (2016)
129. B. Perillo, M. Di Donato, A. Pezone, E. Di Zazzo, P. Giovannelli, G. Galasso, G. Castoria, A. Migliaccio, ROS in cancer therapy: the bright side of the moon. Exp. Mol. Med. **52**, 192–203 (2020)
130. R. Moschoi, V. Imbert, M. Nebout, J. Chiche, D. Mary, T. Prebet, E. Saland, R. Castellano, L. Pouyet, Y. Collette, N. Vey, C. Chabannon, C. Recher, J.E. Sarry, D. Alcor, J.F. Peyron, E. Griessinger, Protective mitochondrial transfer from bone marrow stromal cells to acute myeloid leukemic cells during chemotherapy. Blood **128**, 253–264 (2016)
131. A. Caicedo, V. Fritz, J.M. Brondello, M. Ayala, I. Dennemont, N. Abdellaoui, F. De Fraipont, A. Moisan, C.A. Prouteau, H. Boukhaddaoui, C. Jorgensen, M.L. Vignais, MitoCeption as a new tool to assess the effects of mesenchymal stem/stromal cell mitochondria on cancer cell metabolism and function. Sci. Rep. **5**, 1–10 (2015)
132. X. Wang and H. H. Gerdes, Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. Death Differ. **22**, 1181–1191 (2015)
133. F. Guerra, A.A. Arbini, L. Moro, Mitochondria and cancer chemoresistance Biochim. Biophys. Acta - Bioenerg. **1858**, 686–699 (2017)
134. E.A. Zaal, C.R. Berkers, The influence of metabolism on drug response in cancer Front. Oncol. **8**, 500 (2018)
135. E.J. Choi, B.J. Jung, S.H. Lee, H.S. Yoo, E.A. Shin, H.J. Ko, S. Chang, S.Y. Kim, S.M. Jeon, A clinical drug library screen identifies clobetasol propionate as an NRF2 inhibitor with potential therapeutic efficacy in KEAP1 mutant lung cancer. Oncogene **36**, 5285–5295 (2017)
136. Y. Zhou, Y. Zhou, M. Yang, K. Wang, Y. Liu, M. Zhang, Y. Yang, C. Jin, R. Wang, R. Hu, Digoxin sensitizes gemcitabine-resistant pancreatic cancer cells to gemcitabine via inhibiting Nrf2 signaling pathway. Redox Biol. **22**, 101131 (2019)
137. H. Lin, Y. Qiao, H. Yang, Q. Nan, W. Qu, F. Feng, W. Liu, Y. Chen, H. Sun, Small molecular Nrf2 inhibitors as chemosensitizers for cancer therapy. Future Med. Chem. **12**, 243–267 (2020)
138. F. Chen, H. Wang, J. Zhu, R. Zhao, P. Xue, Q. Zhang, M. Bud Nelson, W. Qu, B. Feng, J. Pi, Camptothecin suppresses NRF2-ARE activity and sensitises hepatocellular carcinoma cells to anticancer drugs. Br. J. Cancer. **117**, 1495–1506 (2017)
139. S.R. Kim, Y.M. Ha, Y.M. Kim, E.J. Park, J.W. Kim, S.W. Park, H.J. Kim, H.T. Chung, K.C. Chang, Ascorbic acid reduces HMGB1 secretion in lipopolysaccharide-activated RAW 264.7 cells and improves survival rate in septic mice by activation of Nrf2/HO-1 signals. Biochem. Pharmacol. **95**, 279–289 (2015)
140. A. Arlt, S. Sebens, S. Krebs, C. Geismann, M. Grossmann, M.L. Kruse, S. Schreiber, H. Schäfer, Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. Oncogene **32**, 4825–4835 (2013)
141. A. Olayanju, I.M. Copple, H.K. Bryan, G.T. Edge, R.L. Sison, M.W. Wong, Z.Q. Lai, Z.X. Lin, K. Dunn, C.M. Sanderson, A.F. Alghanem, M.J. Cross, E.C. Ellis, M. Ingelman-Sundberg, H.Z. Malik, N.R. Kitteringham, C.E. Goldring, B.K. Park, Brusatol provokes a rapid and transient inhibition of Nrf2 signaling and sensitizes mammalian cells to chemical toxicity - Implications for therapeutic targeting of Nrf2 Free Radic. Biol. Med. **78**, 202–212 (2015)
142. G. Montalban-Bravo, C.D. DiNardo, The role of ID Hmutations in acute myeloid leukemia. Futur. Oncol. **14**, 979–993 (2018)
143. K. Lee, Y.S. Song, Y. Shin, X. Wen, Y. Kim, N.Y. Cho, J.M. Bae, G.H. Kang, Intrahepatic cholangiocarcinomas with IDH1/2 mutation-associated hypermethylation at selective genes and their clinicopathological features. Sci. Rep. **10**, 1–10 (2020)
144. M.F. Amary, K. Bacsi, F. Maggiani, S. Damato, D. Halai, F. Berisha, R. Pollock, P. O'Donnell, A. Grigoriadis, T. Diss, M. Eskandarpour, N. Presneau, P.C.W. Hogendoorn, A. Futreal, R. Tirabosco, A.M. Flanagan, IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. J. Pathol. **224**, 334–343 (2011)
145. S. Han, Y. Liu, S.J. Cai, M. Qian, J. Ding, M. Larion, M.R. Gilbert, C. Yang, IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br. J. Cancer. **122**, 1580–1589 (2020)
146. A. Chaturvedi, L. Herbst, S. Pusch, L. Klett, R. Goparaju, D. Stichel, S. Kaulfuss, O. Panknin, K. Zimmermann, L. Toschi, R. Neuhaus, A. Haegebarth, H. Rehwinkel, H. Hess-Stumpp, M. Bauser, T. Bochtler, E.A. Struys, A. Sharma, A. Bakkali, R. Geffers, M.M. Araujo-Cruz, F. Thol, R. Gabdoulline, A. Ganser, A.D. Ho, A. Von Deimling, K. Rippe, M. Heuser, A. Krämer, Pan-mutant-IDH1 inhibitor BAY1436032 is highly effective against human IDH1 mutant acute myeloid leukemia in vivo. Leukemia **31**, 2020–2028 (2017)
147. S. Pusch, S. Krausert, V. Fischer, J. Balss, M. Ott, D. Schrimpf, D. Capper, F. Sahm, J. Eisel, A.C. Beck, M. Jugold, V. Eichwald, S. Kaulfuss, O. Panknin, H. Rehwinkel, K. Zimmermann, R.C. Hillig, J. Guenther, L. Toschi, R. Neuhaus, A. Haegebart, H. Hess-Stumpp, M. Bauser, W. Wick, A. Unterberg, C. Herold-Mende, M. Platten, A. von Deimling, Pan-mutant IDH1 inhibitor BAY 1436032 for effective treatment of IDH1 mutant astrocytoma in vivo. Acta Neuropathol. **133**, 629–644 (2017)
148. D. Golub, N. Iyengar, S. Dogra, T. Wong, D. Bready, K. Tang, A.S. Modrek, D.G. Placantonakis, Mutant isocitrate dehydrogenase inhibitors as targeted cancer therapeutics. Front. Oncol. **9**, 417 (2019)
149. E. Lou, S. Fujisawa, A. Barlas, Y. Romin, K. Manova-Todorova, M.A.S. Moore, S. Subramanian, Subramanian, Tunneling nanotubes: A new paradigm for studying intercellular communication and therapeutics in cancer. Commun. Integr. Biol. **5**, 399–403 (2012)
150. E. Lou, S. Fujisawa, A. Morozov, A. Barlas, Y. Romin, Y. Dogan, S. Gholami, A.L. Moreira, K. Manova-Todorova, M.A.S. Moore, Tunneling nanotubes provide a unique conduit for intercellular transfer of cellular contents in human malignant pleural mesothelioma. PLoS One **7**, e33093 (2012)

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