Cancer and Altered Metabolism: Potential Importance of Hypoxia-Inducible Factor and 2-Oxoglutarate-Dependent Dioxygenases

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Hypoxia-inducible factor (HIF) deregulation contributes to the Warburg effect. HIF consists of an unstable α subunit and a stable β subunit. In the presence of oxygen, HIF α becomes prolyl hydroxylated by members of the EglN (also called PHD) family, leading to its proteasomal degradation. Under hypoxic conditions, EglN activity is diminished and HIF levels rise. EglN1 is the primary HIF prolyl hydroxylase with EglN2 and EglN3 playing compensatory roles under certain conditions. EglN2 and EglN3 also appear to play HIF-independent roles in regulating cell proliferation and apoptosis, respectively. The EglNs belong to a large family of 2-oxoglutarate-dependent dioxygenases that includes the TET DNA hydroxymethylases and JmjC-containing histone demethylases. Members of this superfamily can be inhibited by endogenous metabolites, including fumarate and succinate, which accumulate in tumors that have fumarate hydratase (FH) or succinate dehydrogenase (SDH) mutations, respectively, as well as by the 2-hydroxyglutarate detected in isocitrate dehydrogenase (IDH) mutant tumors. 2-Oxoglutarate-dependent dioxygenases therefore provide a link between altered metabolism and cancer.

Otto Warburg noted decades ago that cancer cells maintain very high rates of glycolysis, converting glucose to lactate, despite sufficient oxygen to perform oxidative phosphorylation, which is the more efficient means of generating energy (ATP) from glucose. This conundrum has generated considerable speculation as to whether altered metabolism, including altered glucose metabolism, is a cause or consequence of malignancy and, if the former, what benefits altered metabolism might confer on cancer cells. Several lines of evidence, including the recent identification of mutations affecting fumarate hydratase (FH), succinate dehydrogenase (SDH), and isocitrate dehydrogenase (IDH), have strengthened the notion that altered metabolism can cause cancer, and a number of nonmutually exclusive models have been put forth to rationalize why cancer cells might benefit from a high rate of glycolysis and decreased oxidative phosphorylation. This chapter focuses on the role of hypoxia-inducible factor (HIF), 2-oxoglutarate, and 2-oxoglutarate-dependent enzymes in cancer and cancer metabolism.

THE HIF TRANSCRIPTION FACTOR

When cells are placed in a low-oxygen environment, they normally undergo a series of metabolic adaptations, including an increase in glucose uptake and glycolysis and a decrease in oxidative phosphorylation. Conversely, the presence of oxygen is associated with a decrease in glycolysis and an increase in oxidative phosphorylation. The coupling of oxidative phosphorylation to oxygen availability is known as the Pasteur effect and is mediated by the HIF transcription factor (Seagroves et al. 2001).

HIF is a heterodimer consisting of an unstable α subunit and a stable β subunit (also frequently called ARNT; Kaelin and Ratcliffe 2008). Under low-oxygen conditions, the HIF α subunit is stabilized, dimerizes with a HIF β subunit, translocates to the nucleus, and transcriptionally activates a suite of genes that increase glucose uptake, increase glycolysis, and decrease oxidative phosphorylation. The latter is mediated by an increase in PDK (pyruvate dehydrogenase kinase), which phosphorylates, and thereby inactivates, pyruvate dehydrogenase (Kim et al. 2006a; Papandreou et al. 2006). This limits the entry of pyruvate into the Krebs cycle. Instead, pyruvate is converted to lactate and extruded from the cell by the HIF-responsive gene products lactate dehydrogenase A and monocarboxylate transporter 4, respectively (Ebert and Bunn 1998; Ullah et al. 2006; Perez de Heredia et al. 2010).

The stability of HIF α is linked to oxygen availability because it is a substrate for the EglN (also called PHD) family of prolyl hydroxylases (Kaelin and Ratcliffe 2008). In the presence of oxygen, EglN hydroxylates HIF α on one (or both) of two conserved prolyl residues. Hydroxylation of either site creates a binding site for a ubiquitin ligase that contains the pVHL tumor suppressor protein. This complex then polyubiquitinates HIF α , thereby targeting it for destruction by the proteasome. There are three EglN family members. EglN1 appears to be the primary HIF prolyl hydroxylase, with EglN2 and EglN3 playing compensatory roles under certain conditions (Berra et al. 2003; Appelhoff et al. 2004; Marxsen et al. 2004; Stiehl et al. 2006; Minamishima et al. 2009). The oxygen K_m values for the hydroxylation of HIF α by

Egln family members are slightly above the oxygen concentrations likely to be encountered in tissues under normal conditions (Hirsila et al. 2003). Accordingly, the Egln family members are sensitive to further decrements in oxygen availability (hypoxia), leading to reduced hydroxylation of HIF α and therefore higher steady-state levels of HIF α . In addition to oxygen, Egln family members also require reduced iron and 2-oxoglutarate (also called α -ketoglutarate) and their activity can be influenced by reactive oxygen species (ROS) and changes in specific Krebs cycle intermediates (Fig. 1; see also below; Kaelin 2005; Kaelin and Ratcliffe 2008).

THE WARBURG EFFECT

The Warburg effect is due, at least in part, to the failure of cancer cells to appropriately down-regulate HIF under well-oxygenated conditions because of mutations that either increase HIF production or decrease HIF destruction (Fig. 2). With respect to increased HIF α production, mutations that directly or indirectly inactivate the tuberous sclerosis complex (TSC), such as activating mutations of PI3K or AKT, lead to increased TORC1 activity (Brugarolas and Kaelin 2004). Increased TORC1, in turn, promotes HIF α transcription and translation (Hudson et al. 2002; Arsham et al. 2003; Brugarolas et al. 2003; Fig. 2). With respect to decreased HIF α destruction, inactivating mutations of the *VHL* tumor suppressor gene lead to impaired HIF α proteasomal degradation for the reasons outlined above (Fig. 2). Similarly, inactivating SDH and FH mutations lead to the accumulation of succinate and fumarate, respectively, which inhibit Egln activity by competing with 2-oxoglutarate, thereby allowing HIF α to escape recognition by pVHL (Fig. 1; Dahia et al. 2005; Pollard et al. 2005; Selak et al. 2005, 2006; Koivunen et al. 2007; Pollard et al. 2007; Kaelin 2009; Sudarshan et al. 2009). A recent study suggested that IDH mutations reduce 2-oxoglutarate production and hence Egln activity, leading to HIF α stabilization, although this finding has been disputed (Zhao et al. 2009). More recent studies indicate that cancer-relevant

IDH mutants acquire the neomorphic ability to produce R-2-hydroxyglutarate (R-2HG) but R-2HG does not appear to inhibit Egln activity in cells (Dang et al. 2009b; Chowdhury et al. 2011; P Koivunen, S Lee, and WG Kadin, unpubl.).

Although HIF contributes to the Warburg effect, it does not act alone. For example, many of the effects of HIF on cell metabolism are reinforced by other molecular perturbations in cancer cells, including those leading to activation of c-Myc or loss of p53 (Matoba et al. 2006; Yeung et al. 2008; Feng and Levine 2010; Kaelin and Thompson 2010). Indeed, HIF and c-Myc share a number of common targets that promote glycolysis (Dang 2007; Dang et al. 2009a). Cancer cells also frequently express the M2 isoform of PFK (phosphofructokinase) rather than the M1 isoform found in most somatic tissues (Christofk et al. 2008). Expression of the M2 isoform appears to facilitate the diversion of glucose-derived carbons for anabolism (Christofk et al. 2008). c-Myc promotes glutaminolysis, which provides an alternative source of carbon precursors for anabolism as well as for NADPH production in the Krebs cycle (anaplerosis; Dang et al. 2009a; Dang 2010).

The metabolic changes characteristic of the Warburg effect are believed to allow cancer cells to outcompete their neighbors for nutrients and to use those nutrients for anabolic reactions necessary for growth in addition to energy production. Lactate produced by tumors might also alter the microenvironment in a manner that facilitates both growth and invasion. In addition, changes in mitochondrial ROS production and mitochondrial metabolites (including 2-oxoglutarate) might indirectly affect the behavior of multiple enzymes within the cell, including phosphatases and 2-oxoglutarate-dependent enzymes, that control cell growth and survival.

HIF AND CANCER: BYSTANDER OR CULPRIT?

Intratumoral hypoxia and hence increased HIF levels are very consistently associated with poor patient outcomes (Semenza 2003). At one extreme, this would reflect the ability of HIF itself to promote tumor growth. On the other hand, it is possible that the correlation simply reflects the fact that the most aggressive tumors are the ones most likely to outgrow their blood supplies and hence to develop intratumoral hypoxia. In favor of the former model, HIF activates a number of genes that might, in theory, promote tumor cell growth, invasion, and metastasis. For example, HIF induces autocrine and paracrine cancer cell growth factors such as TGF α and PDGF B, and promotes invasion by transcriptionally up-regulating genes such as *MMP* and *LOX* and angiogenesis by up-regulating genes such as *VEGF* (Semenza 2003). It is therefore understandable that HIF is usually viewed as an oncoprotein. Moreover, deletion of HIF α (or ARNT) has been shown to decrease tumor growth in nude mouse subcutaneous xenograft assays (Maxwell et al. 1997; Ryan et al. 1998). On the other hand, there is evidence that HIF α can act as a tumor suppressor, at

Figure 1. 2-Oxoglutarate-dependent dioxygenase reaction. 2-Oxoglutarate-dependent enzymes require 2-oxoglutarate (also called α ketoglutarate), oxygen, and reduced iron to hydroxylate their substrates. 2-Oxoglutarate is decarboxylated to succinate during the reaction. In the case of histone demethylases, a methyl group is hydroxylated and the resulting hydroxymethyl group is spontaneously given off as formaldehyde. These enzymes are variably susceptible to inhibition by Krebs cycle intermediates such as succinate and fumarate, to 2-hydroxyglutarate, and to reactive oxygen species (ROS).

Figure 2. Central role of HIF in Warburg metabolism. Many oncogenic mutations lead to increased HIF accumulation, which promotes the Warburg effect. Increased Myc expression and loss of p53 function can also contribute to such metabolic changes.

least in some preclinical models. For example, deletion of HIF1 α promotes the growth of teratocarcinomas formed by embryonic stem cells and orthotopic tumors formed by transformed astrocytes (Carmeliet et al. 1998; Blouw et al. 2003; Covello et al. 2005). Deletion of HIF2 α has been shown to promote the growth of K-Ras-driven lung adenocarcinomas in genetically engineered mice and the growth of astrocytomas (Acker et al. 2005; Mazumdar et al. 2010).

A causal role for HIF α (particularly HIF2 α) has been perhaps most convincingly demonstrated in pVHL-defective kidney cancers. These tumors produce high levels of both HIF1 α and HIF2 α or, importantly, HIF2 α only (Maxwell et al. 1999; Gordan et al. 2008; Shen et al. 2011). In preclinical models, including orthotopic models, elimination of HIF2 α is sufficient to inhibit pVHL-defective tumor growth (Kondo et al. 2003; Zimmer et al. 2004), whereas restoring HIF2 α (but not HIF1 α) production is sufficient to override tumor suppression by pVHL (Kondo et al. 2002; Maranchie et al. 2002; Raval et al. 2005). In genetically engineered mice, HIF2 α appears to be necessary and sufficient for much of the pathology observed in tissues that lack pVHL (Kim et al. 2006b; Rankin et al. 2007, 2008, 2009). In patients with germline VHL mutations, the degree to which their *VHL* alleles are compromised with respect to HIF regulation tracks closely with their risk of kidney cancer (Li et al. 2007) and single-nucleotide HIF2 polymorphisms in the general population have been linked to the risk of kidney cancer (Purdue et al. 2011). Collectively, these results suggest that HIF2 α is a kidney cancer oncoprotein. In stark contrast, HIF1 α appears to behave as a kidney cancer tumor suppressor.

Three signature chromosomal abnormalities in kidney cancer are loss of chromosome 3p, spanning the *VHL* gene, loss of chromosome 14q, and gain of chromosome 5q. Chromosome 14q loss is most common in kidney cancer relative to other tumor types and almost invariably leads to loss of *HIF1 α* located at 14q22 (Shen et al.

2011). Many pVHL-defective renal carcinoma lines harbor focal, homozygous, *HIF1 α* deletions that lead to the production of either no HIF1 α protein or the production of HIF1 α variants that reflect alternative splicing events that circumvent the missing exons (Shen et al. 2011). Restoration of wild-type HIF1 α in such cells suppresses their ability to proliferate in vitro and in vivo (Raval et al. 2005; Shen et al. 2011). Conversely, elimination of wild-type HIF1 α in HIF1 α -proficient cells enhances their proliferation in vitro and in vivo (Gordan et al. 2008; Shen et al. 2011). Intragenic HIF1 α mutations have been identified in kidney cancer genome sequencing projects and, when tested, have proven to be loss of function (Morris et al. 2009; Dalglish et al. 2010; Shen et al. 2011). Such mutations are, however, rare when compared with the frequency of 14q loss in kidney cancer. Specifically, many 14q deleted kidney cancers retain a wild-type *HIF1 α* allele (Shen et al. 2011). This suggests that HIF1 α haploinsufficiency contributes to kidney cancer growth. In keeping with this idea, 14q deleted tumors have a transcriptional signature indicative of HIF1 α loss (Shen et al. 2011).

Egln PROLYL HYDROXYLASES AS TARGETS OF SDH, FH, AND IDH MUTATIONS

Deregulation of HIF is also suspected of playing a pathogenic role in papillary renal carcinomas linked to FH deficiency and to paragangliomas linked to SDH deficiency (Gimenez-Roqueplo et al. 2001; Isaacs et al. 2005; Pollard et al. 2005; Selak et al. 2005, 2006; MacKenzie et al. 2007; Pollard et al. 2007; Sudarshan et al. 2009, 2011), although the paucity of relevant cell culture and mouse models has so far prevented the types of preclinical validation experiments described above for pVHL-defective clear cell renal carcinomas to determine whether HIF truly plays a causal, as opposed to correlative, role in these settings. It has also been suggested that SDH mutations lead to paraganglioma in an Egln-dependent, but HIF-independent, manner based on the

following observations. A number of different genes, including *VHL*, *NF1*, *c-Ret*, and *SDH* subunit genes, lead to an increased risk of extraadrenal and intradrenal paragangliomas (the latter are called pheochromocytomas), but only when mutated in the germline (Nakamura and Kaelin 2006; Kaelin 2007). This suggests that these genes control a paraganglioma-relevant biologic process that takes place during embryological development. Notably, some germline *VHL* mutations lead to a high risk of paraganglioma but not kidney cancer or the blood vessel tumors (hemangioblastomas) observed in classical VHL disease (Kaelin 2002). When tested, the products of such mutant *VHL* alleles are essentially normal with respect to HIF regulation (Clifford et al. 2001; Hoffman et al. 2001). Conversely, *VHL* mutations that confer a high risk of kidney cancer and low risk of paraganglioma lead to significant deregulation of HIF (Maxwell et al. 1999; Clifford et al. 2001; Hoffman et al. 2001; Li et al. 2007). The simplest interpretation of these findings is that the development of paraganglioma in cells lacking wild-type pVHL reflects the loss of an HIF-independent pVHL function.

Paragangliomas are tumors of the sympathetic nervous system. During embryological development, primitive neuronal cells with the potential to become sympathetic neurons compete for growth factors such as NGF (nerve growth factor), with the losers undergoing apoptosis (Deckwerth and Johnson 1993; Deppmann et al. 2008). NGF withdrawal leads to the induction of EglN3, which appears to be necessary and sufficient for apoptosis in this setting (Lipscomb et al. 1999; Straub et al. 2003; Lee et al. 2005). Loss of the *NF1* gene product neurofibromin, which is a Ras-GAP for the NGF receptor, or gain of *c-Ret*, which can activate the NGF receptor in *cis*, leads to decreased apoptosis after NGF withdrawal (Vogel et al. 1995; Dechant 2002; Lee et al. 2005). Paraganglioma-associated *VHL* mutations lead to activation of aPKC and Jun B, which represses EglN3 levels (Lee et al. 2005). Finally, *SDH* mutations lead to the accumulation of succinate, which inhibits EglN3-induced apoptosis (Lee et al. 2005). Hence, all of the genes linked to familial paraganglioma can potentially regulate apoptosis of sympathetic neuronal precursors during embryological development, suggesting that paragangliomas arise in this setting owing to impaired culling of this cell population. The sympathetic nervous system abnormalities observed in *EglN3*^{-/-} mice are consistent with this view (Bishop et al. 2008).

EglN3-induced apoptosis appears to be HIF independent (Schlisio et al. 2008). Interestingly, induction of apoptosis appears, instead, to be linked to its ability to increase expression of *KIF1Bβ*, which encodes a kinesin family member (Munirajan et al. 2008; Schlisio et al. 2008). *KIF1Bβ* maps to the minimal region of 1p36 that is deleted in a number of neural-crest-derived tumors, including the sympathetic nervous system tumor neuroblastoma. Loss-of-function *KIF1Bβ* mutations have been identified in a family with neural crest tumors and in a small subset of pheochromocytomas, medulloblastomas, and neuroblastomas (Schlisio et al. 2008; Yeh et al.

2008). The frequency of such mutations is low, however, relative to the frequency of 1p36 deletions in such tumors. Among several possibilities, this might indicate that haploinsufficiency for *KIF1Bβ*, perhaps together with loss of contiguous genes, is sufficient to promote neural crest tumor development and that complete loss of *KIF1Bβ* would not.

NON-EglN TARGETS OF SDH, FH, AND IDH MUTATIONS

It is also possible that the accumulation of succinate and fumarate observed in *SDH* and *FH* mutant tumors, as well as the accumulation of R-2HG in *IDH* mutant tumors, transforms cells by affecting the behavior of other 2-oxoglutarate-dependent enzymes in addition to (or in some cases, perhaps instead of) the EglN family members (Fig. 1). For example, the jumonji-C domain-containing histone demethylases are 2-oxoglutarate-dependent enzymes (Klose et al. 2006). It is possible that inhibition of one or more of these enzymes, through changes in chromatin structure and gene expression, leads to transformation. In biochemical assays, R-2HG can, with variable potencies, inhibit various histone demethylases (Chowdhury et al. 2011; Xu et al. 2011). The histone demethylase Jhd1, an H3K36 demethylase, is inhibited in a yeast model of *SDH* deficiency (Smith et al. 2007), as is the H3K27 demethylase KDM6B (JMJD3) in mammalian cells after knockout of *SDH* with siRNA (small interfering RNA) (Cervera et al. 2009). KDM6B and its paralog KDM6A (UTX) are attractive candidates as targets of succinate, fumarate, and R-2HG because they behave as tumor suppressors in cell culture models by virtue of their ability to increase the expression of the *Ink4A/ARF* locus in response to oncogenic stress and to cooperate with the pRB tumor suppressor (Agger et al. 2009; Barradas et al. 2009; Herz et al. 2010; Wang et al. 2010). Moreover, UTX is mutationally inactivated in a variety of tumors (van Haaften et al. 2009; Dalglish et al. 2010).

More recently, TET2 has been implicated as a target of R-2HG (Figueroa et al. 2010; Xu et al. 2011). TET2 belongs to a family of 2-oxoglutarate-dependent enzymes that hydroxylate methylcytosine, which is suspected of playing a role in the turnover of methylated DNA (Noushmehr et al. 2010; Ficiz et al. 2011). Inactivating TET2 mutations, like *IDH* mutations, have been observed in acute leukemia, and TET2 and *IDH* mutations are mutually exclusive, consistent with the notion that *IDH* mutations lead to TET2 inactivation (and thereby eliminate the selection pressure to mutate TET2; Figueroa et al. 2010). Overexpression of mutant *IDH* decreases the enzymatic activity of coexpressed TET2 and impairs hematopoietic differentiation (Figueroa et al. 2010; Xu et al. 2011). DNA hypermethylation is also a feature of *IDH* mutant brain tumors and leukemia, consistent with the idea that *IDH* mutations impair TET2 activity and thereby impair DNA demethylation (Figueroa et al. 2010; Noushmehr et al. 2010).

2-OXOGLUTARATE-DEPENDENT DIOXYGENASES AS CANCER THERAPEUTIC TARGETS

As described above, inactivation of specific 2-oxoglutarate-dependent dioxygenases is suspected of contributing to transformation, especially in the context of SDH, FH, and IDH mutations. It is also possible that HIF, by limiting the entry of pyruvate into the Krebs cycle, indirectly inhibits such enzymes through changes in Krebs cycle intermediates, although this remains to be proven. At the same time, it is also clear that certain 2-oxoglutarate-dependent enzymes can stimulate, rather than inhibit, cancer cells, at least in certain contexts. In addition, HIF increases the transcription of certain 2-oxoglutarate-dependent enzymes (see below), perhaps to compensate for their reduced activity under hypoxia.

It is important to note that different 2-oxoglutarate-dependent enzymes can differ substantially with respect to their requirements for oxygen and 2-oxoglutarate (K_m values) and sensitivity to inhibition by metabolites such as succinate and R-2HG (IC₅₀ values). As a result, genetic or pharmacological perturbations that affect intracellular oxygen and metabolite levels might affect (indirectly) some enzymes in this family more than others. It has also become clear that members of this family can be directly inhibited with drug-like small molecules that bind to their catalytic sites and interfere with 2-oxoglutarate binding, iron binding, or both (Ivan et al. 2002; Mole et al. 2003; Schlemminger et al. 2003; Safran et al. 2006). Moreover, a number of preclinical studies, described below, support inhibition of specific 2-oxoglutarate-dependent dioxygenases having an antitumor effect.

EglN1

EglN1 suppresses HIF and would therefore be predicted to be a cell-autonomous tumor suppressor in most (but not all) cellular contexts for the reasons outlined above. Interestingly, however, tumor cell invasion, intravasation, and metastasis are impaired in *EglN1*^{+/-} mice, possibly owing to vessel pseudonormalization and improved intratumoral oxygenation (Mazzone et al. 2009).

EglN2

EglN2, a member of the EglN family, is induced by estrogen in estrogen-receptor-positive breast cancers (Seth et al. 2002; Appelhoff et al. 2004; Zhang et al. 2009). Estrogen is an important mitogen for breast cancer cells, simulating progression through the cell cycle. Cyclin D1 promotes cell-cycle progression by directing (together with cdk4 or cdk6) the phosphorylation of the pRB tumor suppressor protein (Sellers and Kaelin 1997). Overexpression and, at times, amplification of cyclin D1 is common in breast cancer (Steeg and Zhou 1998; Roy and Thompson 2006). Notably, certain cyclin D1-dependent phenotypes are lost in flies that lack *Egl9*, the sole EglN family member in this organism (Frei and Edgar 2004). Collectively, these observations point to a possible connection between EglN2 and cyclin D1.

Indeed, loss of EglN2, but not loss of EglN1 or EglN3, decreases the cyclin D1 level in vitro and in vivo. *EglN2*^{-/-} mice are viable but do not breastfeed appropriately, owing to mammary gland hypoproliferation reminiscent of mammary glands that lack cyclin D1 (Zhang et al. 2009). Inactivation of EglN2 suppresses breast cancer proliferation in vitro and in vivo, owing specifically to loss of cyclin D1 and impaired pRB phosphorylation (Zhang et al. 2009). Loss of EglN2 also impairs the fitness of a variety of other cancers in addition to breast cancer (Zhang et al. 2009). Control of cyclin D1 by EglN2 requires EglN2 catalytic activity but appears to be HIF independent (Zhang et al. 2009). EglN2 does not hydroxylate cyclin D1 directly (at least under the conditions tested so far) and appears to influence cyclin D1 transcriptionally and postranscriptionally (Zhang et al. 2009).

LOX

HIF induces the expression of LOX, which encodes a lysyl oxidase. LOX expression by primary tumors appears to play a role in mobilization of bone-marrow-derived cells that promote the formation of metastatic niches and hence metastasis (Erler et al. 2006, 2009). LOX has also been implicated in the ability of cancer cells to undergo an epithelial–mesenchymal transition, which is often associated with increased invasiveness and drug resistance (Schietke et al. 2010). It remains to be determined, however, whether inhibition of LOX would cause the regression of established tumors or otherwise favorably alter their natural history.

KDM2A and KDM2B

KDM2A (JHDM1A or FBX11) and KDM2B (JHDM1B or FBXL10) demethylate H3K36. Loss of KDM2B impairs proliferation and induces senescence, at least partly through an increase in p15/Ink4b or p16/Ink4a expression (He et al. 2008; Tzatsos et al. 2009). Similarly, depletion of KDM2B in hematopoietic progenitors significantly impairs HOXA9/MEIS1-induced leukemic transformation, at least partly through impaired self-renewal (He et al. 2011). Conversely, KDM2B is the target of a recurrent integration event in a MoMuLV rat lymphoma model and is overexpressed in a subset of leukemia (Pfau et al. 2008; He et al. 2011). Overexpression of KDM2A and/or KDM2B can immortalize mouse embryo fibroblasts and transform hematopoietic progenitors (Pfau et al. 2008; He et al. 2011). Collectively, these observations credit KDM2A and KDM2B as potential oncogenes.

KDM3A

KDM3A (JMJD1A, JHDM2A) is an H3K9 demethylase that has been implicated in stem cell maintenance (Ko et al. 2006; Loh et al. 2007). KDM3A is overexpressed in renal carcinoma, presumably because it is the product of an HIF-responsive gene (Beyer et al. 2008; Pollard et al. 2008; Wellmann et al. 2008; Sar et al.

2009; Xia et al. 2009; Krieg et al. 2010). Down-regulation of KDM3A impairs cancer cell proliferation and invasiveness (Krieg et al. 2010; Yamada et al. 2011).

KDM4B and KDM4C

KDM4C (JMJD2C, JHDM3, or GASC1) maps to chromosome 9p23-24, which is amplified in esophageal and breast cancers, and demethylates H3K9 (Yang et al. 2000, 2001; Cloos et al. 2006). In keeping with its suspected role as an oncogene, shRNA-mediated knockout of KDM4C inhibits cancer cell proliferation in vitro. Conversely, KDM4C induces transformed phenotypes, including growth-factor-independent proliferation, anchorage-independent growth, and mammosphere forming ability when overexpressed in immortalized, nontransformed mammary epithelial cells (Liu et al. 2009). KDM4C was also recently shown to be coamplified with JAK2 in a subset of lymphomas (Rui et al. 2010). KDM4C cooperates with JAK2 in this setting to regulate chromatin structure and promote lymphomagenesis (Rui et al. 2010). KDM4C might also play a role in androgen receptor signaling in prostate cancer (Wissmann et al. 2007), whereas its paralog KDM4B (JMJD2B) has been implicated in estrogen receptor signaling and the control of breast cancer proliferation (Yang et al. 2010; Kawazu et al. 2011; Shi et al. 2011). Both KDM4B and KDM4C can be induced by hypoxia (Beyer et al. 2008; Xia et al. 2009; Yang et al. 2010).

KDM5A and KDM5B

KDM5A (also called RBP2 or JARID1A) and KDM5B (also called PLU-1 or JARID1B) are JmjC-containing histone demethylases that recognize methylated H3K4, a mark that is usually associated with transcriptionally active chromatin (Christensen et al. 2007; Hayakawa et al. 2007; Iwase et al. 2007; Klose et al. 2007; Secombe et al. 2007; Yamane et al. 2007). Methylated H3K4 is also found in association with the repressive-mark-methylated H3K27 in so-called bivalent chromatin domains, which are believed to play an important role in stem cell fate determination (Bernstein et al. 2006; Gan et al. 2007; Ohm et al. 2007). Increased expression of PLU-1 and RBP2 has been linked to an increase in stem-like properties in cancer cells and to drug resistance (Dey et al. 2008; Roesch et al. 2010).

RBP2 was originally identified as a pRB-binding protein and has been linked to control of senescence and differentiation by pRB (Defeo-Jones et al. 1991; Fattaey et al. 1993; Benevolenskaya et al. 2005). Inactivation of RBP2 impairs the growth of pRB-defective human cancer lines in vitro and in vivo and the development of tumors in *Rb1*^{+/-} mice (Benevolenskaya et al. 2005; Lin et al. 2011). Similarly, loss of RBP2 impairs the development of tumors driven by loss of the MEN1 tumor suppressor, which is a component of an H3K4 methylase complex (Lin et al. 2011). This latter observation suggests that tumors driven by loss of a particular histone

methylase might be treated by inhibiting one or more demethylases that normally serve to antagonize its function (or vice versa). This is noteworthy given the frequency with which mutations affecting histone methylases and demethylases are being identified in cancer (Northcott et al. 2009; Dalglish et al. 2010; Chapman et al. 2011; Yoshimi and Kurokawa 2011).

PLU-1 is frequently overexpressed in breast cancer, and down-regulation of PLU-1 impairs breast cancer growth in vivo (Barrett et al. 2002; Catchpole et al. 2011). Similarly, PLU-1 is overexpressed in bladder and lung cancer, where its inhibition leads to apoptosis (Hayami et al. 2010). The overexpression of PLU-1 in tumors might be due, at least partly, to its induction by hypoxia (Xia et al. 2009).

SUMMARY

There are now multiple examples of mutations affecting metabolic enzymes that play a causal role in cancer. Derangements in cellular metabolism can affect oncogenic signaling pathways and vice versa. The HIF transcription factor plays an important role in reprogramming cancer cell metabolism as well as being responsive to changes in cellular metabolism. Recent genetic and biochemical studies related to cancer metabolism point to a potentially important role for 2-oxoglutarate and hence, 2-oxoglutarate-dependent enzymes, in transformation. Pharmacological manipulation of these enzymes might be useful for the treatment of cancer.

ACKNOWLEDGMENTS

I thank Christine McMahon for careful reading of the manuscript and for fellow laboratory members and colleagues for useful discussions. The research is supported by the National Institutes of Health, Howard Hughes Medical Institute, and Doris Duke Charitable Foundation. I apologize to colleagues whose work was not cited owing to space limitations or my ignorance. Please bring errors and egregious omissions to my attention.

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Cold Spring Harb Symp Quant Biol 2011 76: 335-345 originally published online November 16, 2011

Access the most recent version at doi:[10.1101/sqb.2011.76.010975](https://doi.org/10.1101/sqb.2011.76.010975)

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