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Leveraging insights into cancer metabolism—a symposium report

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Abstract

Tumor cells have devised unique metabolic strategies to garner enough nutrients to sustain continuous growth and cell division. Oncogenic mutations may alter metabolic pathways to unlock new sources of energy, and cells take the advantage of various scavenging pathways to ingest material from their environment. These changes in metabolism result in a metabolic profile that, in addition to providing the building blocks for macromolecules, can also influence cell signaling pathways to promote tumor initiation and progression. Understanding what pathways tumor cells use to synthesize the materials necessary to support metabolic growth can pave the way for new cancer therapeutics. Potential strategies include depriving tumors of the materials needed to grow or targeting pathways involved in dependencies that arise by virtue of their altered metabolis.

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Competing interests

The authors declare no competing interests. B.R.S. is an inventor on patents and patent applications related to ferroptosis, and holds equity in and serves as a consultant to Inzen Therapeutics.

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Keywords

cancer; cell signaling; ferroptosis; micropinocytosis; metabolism

Introduction

Tumor cells face unique metabolic challenges to support their growth and survival. They require a continuous source of nutrients and macromolecules to sustain the synthesis of new proteins, nucleic acids, and lipids needed to support cell division. To meet these demands, many oncogenes induce metabolic shifts that change the way tumor cells use metabolites and produce macromolecules to unlock new energy sources.[1,2]

Tumor cells must also deal with a microenvironment that is not conducive to efficient nutrient delivery. Inadequate tumor perfusion combined with a disordered, permeable vasculature and high interstitial pressure limits the flow of nutrients into the tumor.[3] Tumor cells therefore turn to mechanisms like autophagy—degrading and recycling cellular components—and macropinocytosis—nonspecifically engulfing extracellular material—to provide them with extra nutrients.[4]

These changes in metabolic processes result in a metabolic profile that can look quite different from that of normal cells. These metabolites are not passive players in tumor growth. Aberrant accumulation of metabolites can disrupt cell signaling pathways and affect gene expression, stress response, and chromatin modifications within tumor cells. For example, mutations in isocitrate dehydrogenase (IDH) are a common occur-rence in glioma, leukemia, and several other types of cancer. Mutation causes a gain of function in the enzyme where, instead of catalyzing the conversion of isocitrate to α-ketoglutarate, it converts α-ketoglutarate to 2-hydroxyglutarate. Accumulation of 2-hydroxyglutarate can inhibit enzymes that use α-ketoglutarate as a substrate, such as branched-chain amino acid aminotransferase 1, which synthesizes glutamate.[5]

Given the unique features of cancer cell metabolism and nutrient uptake, targeting tumor metabolism may provide a strategy to selectively limit tumor growth. On May 9, 2019, experts in cancer metabolism and signaling met at the New York Academy of Sciences to discuss their latest findings in understanding some of the unique metabolic mechanisms and leveraging those insights to find new targets for cancer therapies. This report describes the speakers' presentations at the one-day symposium.

A role for metabolites in p53-mediated tumor suppression

Lydia Finley from Memorial Sloan Kettering Cancer Center opened the meeting. Her laboratory is interested in understanding whether and how metabolites can affect cell fate decisions in both normal and cancer cells. While it is fairly well established that metabolites can contribute to various aspects of tumor progression, it is less well understood whether metabolites can play a role in tumor suppressive responses. Finley presented unpublished data on the effect of p53 activation on metabolism in a mouse model of pancreatic ductal adenocarcinoma (PDAC), a particularly deadly cancer in humans. In PDAC, loss of p53

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generally occurs during the transition from a benign panIN tumor to a malignant tumor. Finley investigated the effect of p53 activity on metabolism in a p53-inducible PDAC model in which p53 can be activated in established malignant cells and tumors both in culture and mice.[6] She showed that p53 activity caused changes in metabolism and a shift in metabolite concentration that were essential to its tumor suppressive activities. These changes corresponded with morphological and genetic features consistent with reverting back to a panIN-like state. Finley hopes that understanding how various metabolites exert these tumor suppressive activities will uncover latent tumor suppressive pathways that can be leveraged in p53-deficient tumors to inhibit tumor growth.

ACSS2 in responding to fuel availability

Benjamin Tu of the University of Texas Southwestern Medical Center discussed his work on acetyl-CoA synthetase 2 (ACSS2). ACSS2 converts acetate to acetyl-CoA, a precursor to fatty acids and a source of acetyl groups for histone acetylation. Acetyl-CoA is normally produced via the tricarboxylic acid (TCA) cycle. However, because cancer cells often live under hypoxic conditions, they are forced to bypass the TCA cycle and therefore require alternative means to generate acetyl-CoA. Previous evidence has shown that some tumors have increased acetate uptake and utilization;[7] Tu suggested that this may reflect ACSS2 activity in using acetate to provide cancer cells with acetyl-CoA.

Tu's work has shed some light on the physiologic role of ACSS2. Normally, ACSS2 expression is most abundant in liver and kidney.[8] However, ACSS2 expression has been observed in several human tumor samples, including breast cancer, ovarian cancer, and pancreatic cancer. While *Acss2* knockout mice do not display an obvious phenotype, Tu showed that they do have lower tumor burdens in several models of liver and pancreatic cancer.[9] Tu examined the effect of *Acss2* knockout in mice under different feeding conditions. *Acss2* knockout protected mice against obesity when fed a high-fat diet (HFD) and resulted in more weight loss under fasted conditions. Knockout mice exhibited the downregulation of many genes involved in energy metabolism and fatty acid oxidation, suggesting that ACSS2 activity normally upregulates those genes. Tu proposed that ACSS2 is responsible for the proper storage or utilization of fat depending on fed or fasted state.[10]

In cancer, Tu suggested that the production of acetyl-CoA by ACSS2 provides a source of acetyl groups for histone acetylation of genes involved in oxidation and metabolism. This model is supported by data in yeast, which show that yeast acetyl-CoA synthetase (ACS) facilitates the acetylation of histones depending on the fed conditions. In a high-fed state, bulk acetylation is high; acetylation marks locate to genes associated with cell growth. Under starvation conditions, bulk acetylation decreases, and histone acetylation marks are redistributed to stress-response genes.[11] Tu proposed that ACS facilitates the redistribution of acetylation marks between growth and fasted states and thus regulates the yeast cell's ability to adapt to varying fuel supply. He suggested that ACSS2 may play a similar role in tumor cells. Future work will investigate whether small molecule inhibitors of ACSS2 can prevent tumor growth in preclinical cancer models.

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Lactate metabolism in cancer cells

Gary J. Patti from Washington University in St Louis presented work from his laboratory on using untargeted metabolomics to understand lactate metabolism in cancer cells.

First, Patti discussed performing untargeted metabolomics with mass spectrometry. Such experiments often reveal tens of thousands of signals, but less than 5% are typically identified with chemical structures. Patti explained that while he used to believe that many of these unidentified signals represented unknown metabolites, his laboratory has generated evidence that most of them are actually artifacts, contaminants, and signal redundancies in their experiments. Using a $^{13}C/^{12}C$ labeling technique called *credentialing*, Patti showed that less than 10% of the ~25,000 signals his laboratory detected from *Escherichia coli* cells are bona fide metabolites. Similar ratios of metabolites to noise were seen in other cell types. Although some signals likely do correspond to unknown metabolites, Patti believes that the current metabolic pathway charts account for the majority of metabolites being detected by existing metabolomic technologies.[12]

Patti then discussed using untargeted metabolomics in combination with isotope tracers to map the comprehensive fates of nutrients in cancer cells. The example he presented focused on lactate. Patti showed that in various cancer cell lines, most lipids are synthesized from lactate, which supports a role for lactate beyond a simple metabolic waste product. Patti's work provides an example in which lactate can be a major carbon source for tumor cells, even when other carbon sources are plentiful.[13]

The first step in synthesizing lipids from lactate involves oxidation of lactate to pyruvate. Pyruvate can then enter the TCA cycle in the mitochondria to produce citrate and eventually lipids. Patti was interested in determining whether lactate is oxidized in the cytosol or mitochondria. By following the fate of deuterated lactate, he showed that lactate can be imported into the mitochondria and oxidized into pyruvate via lactate dehydrogenase B.[14] Lactate can be a major source of energy for mitochondria—isolated mitochondria from cancer cells can respire using only lactate as a carbon source.[13] In addition, importing lactate into mitochondria can be a major source of carbon for lipids—inhibiting lactate dehydrogenase (LDH) activity in the cytosol and mitochondria suppressed ^{13}C labeling of lactate-derived metabolites while inhibiting LDH activity only in the cytosol did not.[14]

Patti believes that oxidizing lactate in mitochondria (compared to the cytoplasm) is advantageous for tumor cells because it provides an additional source of electrons for the respiratory chain. Mitochondrial lactate transport could therefore supplement the malate-aspartate shuttle and glycerol phosphate shuttle.

Arginine dependence of MYC-driven lung cancer

Trudy Oliver from the University of Utah presented work from her laboratory on understanding metabolic dependencies in different forms of small-cell lung cancer (SCLC). SCLC is a highly aggressive and metastatic form of lung cancer that has largely proven intractable to various targeted and immunotherapies. While most patients will respond initially to chemotherapy, resistance inevitably develops.

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Large-scale genomics studies have revealed genetic trademarks of SCLC, including loss of the tumor suppressors RB1 and TP53 and overexpression of the MYC family members, C-MYC and L-MYC. Most mouse models of SCLC are based on loss of RB1 and TP53, generating a form of SCLC known as classic. Oliver's laboratory has created the first C-MYC–driven mouse model of SCLC, dubbed variant. Oliver showed that the variant and classical forms of SCLC have different histologic and morphologic phenotypes as well as different gene expression profiles and sensitivities to targeted therapies.[15]

Steady-state metabolomic profiling in collaboration with Ralph DeBerardinis's laboratory has shown that C-MYC–driven tumors are metabolically distinct from L-MYC–driven tumors.[16,17] C-MYC–driven tumors show an enrichment in nucleotide biosynthesis and arginine metabolism.[16] Oliver's work has focused on understanding the effect of arginine metabolism, while DeBerardinis presented their work on understanding the effect of increased nucleotide biosynthesis later in the symposium.

Arginine has several functions in cells, including a role in nitric oxide signaling, polyamine biosynthesis, and mechanistic target of rapamycin (mTOR) activation.[18] By using drugs that inhibit each of these processes, Oliver showed that in C-MYC–driven tumor cells, arginine promotes growth primarily via polyamine biosynthesis and mTOR activation. In addition, chemotherapy-resistant cells are more likely to have high levels of C-MYC and are more sensitive to arginine depletion. In mouse models of SCLC, depleting arginine had no effect on survival in mice with L-MYC–driven tumors, but was significantly better than chemotherapy in improving the survival in mice with C-MYC–driven tumors.[16]

Oliver's data show that C-MYC–driven SCLC has unique metabolic vulnerabilities and is highly dependent on arginine for survival. Drugs that deplete arginine may be effective for a disease that has eluded both targeted and immunotherapies to date.

Data blitz presentations

T cell metabolic function and immunotherapy sensitivity

Immunotherapies have ushered in a new paradigm in oncology. Checkpoint inhibitors, like anti–programmed cell death protein-1 and anti–cytotoxic T lymphocyte-associated protein-4 antibodies, have demonstrated efficacy and are approved for a variety of cancers, including lung cancer, renal cell carcinoma, melanoma, and colorectal cancer (CRC). However, many patients do not respond to treatment. Checkpoint inhibitors rely on inhibiting immune suppressive pathways to activate T cells, most of which are exhausted and unable to exert their cytotoxic effects.[19]

Santosha Vardhana from Memorial Sloan Kettering Cancer Center presented data on understanding how metabolic changes may play a role in T cell exhaustion. Vardhana investigated the metabolism of exhausted T cells using a novel *in vitro* coculture system that generates exhausted, nonfunctional T cells that recapitulate many of the phenotypes of exhausted T cells observed in patients that do not respond to immunotherapy. Vardhana presented unpublished data that showed that exhausted T cells exhibit metabolic changes.

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Reversing this metabolic dysfunction can restore T cell activity and restore sensitivity to checkpoint inhibition.

Targeting stem cell metabolism to prevent obesity-related cancer

Miyeko Mana from the Massachusetts Institute of Technology presented her work on understanding how diet influences stem cell function in the intestine and its role in carcinogenesis. She showed that mice fed an HFD develop more low-grade tumors and carcinomas than those fed a control diet. The HFD increased stem cell activity and number in the intestinal epithelium, which correlated with an increase in peroxisome proliferator-activated receptor-δ (PPAR-δ) activity. PPAR-δ is a nuclear receptor that senses fatty acids and promotes the expression of genes involved in fatty acid metabolism.[20] Mana showed that intestinal stem cell progenitors in mice in the HFD group showed changes in metabolites consistent with an increase in fatty acid oxidation and a decrease in glycolysis. She proposed that intestinal stem cells develop a reliance on fatty acid oxidation as an energy source and that therapeutic strategies could target that vulnerability to selectively inhibit stem cell activity. Inhibiting fatty acid oxidation had little effect on intestinal stem cells or tumor development in a mouse model of intestinal cancer fed a control diet but decreased stem cell activity and reduced tumor number and size in the HFD group.

Accumulation of branch-chain amino acids promotes tumor growth

Russell Ericksen of A*STAR Singapore showed how branch-chain amino acid (BCAA) catabolism differs between cancer and normal cells and how this might lead to new therapeutic strategies. Transcriptomic and metabolomic characterization of hepatocellular carcinomas revealed that tumor cells exhibit a loss in genes involved in BCAA degradation, resulting in the accumulation of the BCAAs valine, leucine, and isoleucine. Loss of BCAA catabolism was also observed in several cancer types, including gastric cancer, CRC, and kidney cancers. This catabolic difference correlated with tumor stage and grade as well as patient survival—low expression of genes involved in BCAA catabolism was observed in the most advanced tumors and was independently associated with worse survival.[21]

Ericksen showed that BCAA accumulation may contribute to cancer cell growth and survival by activating mTORC1. mTORC1 requires two signals for activation—a growth factor signal via Rheb activity and a nutrient sufficiency signal, which regulates mTOR localization. Enhancing BCAA catabolism with BT2, an activator of branch-chain α-ketoacid dehydrogenase downregulated mTORC1 activity and suppressed cell growth in several cancer cell lines.[21]

Urea cycle dysfunction in RCC

Sanika Khare of the University of Pennsylvania presented her data on understanding the role of the urea cycle in clear-cell renal cell carcinoma (ccRCC). Previous data have shown that the urea cycle is downregulated in ccRCC.[22,23]

The urea cycle is responsible for converting ammonia, which is toxic, to urea, which is excreted in the urine. Khare showed that in ccRCC, all the enzymes and metabolites associated with the urea cycle are downregulated. She focused on two enzymes:

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argininosuccinate synthase 1, which catalyzes the production of arginosuccinate from citrate and aspartate, and arginosuccinate lyase. Khare's data suggest that downregulating the urea cycle can enhance cell growth and proliferation while activating it can suppress cell growth.[22]

Upregulating purine synthesis in SCLC

Ralph DeBerardinis presented his work on understanding the role of C-MYC in nucleotide biosynthesis in C-MYC–driven SCLC. DeBerardinis' presentation complemented Trudy Oliver's talk earlier in the day. Work between the two laboratories has shown that C-MYC–driven SCLC cells have upregulated nucleotide biosynthesis and arginine metabolism. DeBerardinis described the role of nucleotide biosynthesis, while Oliver focused on the role of arginine metabolism.

DeBerardinis showed that levels of achaete-scute homolog-1 (ASCL1) and C-MYC are often inversely related in SCLC tumors. Their expression levels can be used to define SCLC molecular subsets that have distinct metabolic profiles. In SCLC cell lines as well as tissue samples from treatment-naive patients, $ASCL1^{low}/C\text{-}MYC^{high}$ tumors had abundant purine nucleotides.[17]

DeBerardinis showed that C-MYC can directly drive the expression of inosine monophosphate dehydrogenase (IMPDH), which is involved in guanosine triphosphate (GTP) synthesis. High levels of C-MYC are both necessary and sufficient to induce dependence on IMPDH. At least two approved drugs that inhibit IMPDH are available—mizoribine and mycophenolate. Inhibition of IMPDH suppressed tumor growth in $ASCL1^{low}/C\text{-}MYC^{high}$ mouse xenografts, but not $ASCL1^{high}/C\text{-}MYC^{low}$ xenografts. In a genetic mouse model of $C\text{-}MYC^{high}$ SCLC, IMPDH inhibition alone modestly improved survival, while the combination of IMPDH inhibition and chemotherapy showed synergistic effects.[17]

While most SCLC tumors are initially sensitive to chemotherapy, patients inevitably develop resistance and are left with few second-line options. DeBerardinis provided new evidence that cell lines derived from relapsed patients were more likely to have enhanced expression of both C-MYC and IMPDH, and increased GTP synthesis. Furthermore, selecting for chemotherapy resistance in culture caused cells to acquire the sensitivity to IMDPH inhibition *in vivo*.[17]

DeBerardinis proposed a model in which C-MYC overexpression promotes tumor cell growth via two complementary mechanisms—providing cancer cells with a steady supply of nucleotides to synthesize nucleic acids, and enabling protein synthesis via GTP-dependent activation of ribosome biogenesis.

Inducing cancer cell death via ferroptosis

Brent R. Stockwell of Columbia University described how leveraging cancer cells' susceptibility to ferroptosis may provide a therapeutic strategy in some cancers. Ferroptosis is a form of cell death originally described by Stockwell that has distinct genetic,

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morphological, and biochemical characteristics from other forms of cell death, such as apoptosis, necroptosis, and necrosis.[24] While cancer cells are generally resistant to apoptotic cell death, Stockwell showed that some types of cancer are susceptible to ferroptotic death.

Ferroptosis occurs when lipid peroxides build up in cellular membranes. In the laboratory, ferroptosis can be induced by inhibiting the cell's ability to repair lipid peroxides, for example, by inhibiting glutathione peroxidase 4, which uses glutathione to repair lipid peroxides, or by depleting glutathione via inhibition of system x_c^-.[24–26] Stockwell is currently investigating whether any cells may initiate ferroptosis under natural conditions.

Stockwell described recent results of imidazole ketone erastin (IKE), a small molecule inhibitor of system x_c^- that induces ferroptosis, in preclinical studies of diffuse large B cell lymphoma (DLBCL). Many DLBCL cell lines are sensitive to ferroptosis because they lack the machinery to synthesize cysteine, a precursor for glutathione. In a mouse xenograft model of DLBCL, IKE slowed tumor growth and induced pharmacodynamic markers of ferroptosis: reduced levels of glutathione, increases in lipid peroxidation, and a genetic profile consistent with ferroptosis.[27]

Stockwell proposed that ferroptosis inducers can synergize with some other standard therapeutic regimens; work in this area is ongoing in the Stockwell Laboratory and may be published by the year's end. In addition, the laboratory is identifying biomarkers to predict which tumors will respond most sensitively to ferroptosis inducers. Together, these ongoing studies may indicate the most promising avenues for developing ferroptosis inducers, such as IKE as anticancer agents.

Nutrient scavenging via macropinocytosis

Aimee Edinger from the University of California, Irvine presented her work on understanding how macropinocytosis can contribute to tumor survival and therapeutic resistance. Macropinocytosis is a nonspecific scavenging pathway in which the plasma membrane internalizes material from the extracellular environment. While macropinocytosis is a recognized feature of pancreatic cancer—oncogenic KRAS can promote macropinocytosis via the phosphoinositide-3 kinase (PI3K) pathway—Edinger showed that other cancer types with activating mutations in the PI3K pathway, including prostate cancer and breast cancer, also use macropinocytosis.[28] She argued that we should think of macropinocytosis more broadly and that it may be a common mechanism by which solid tumors scavenge nutrients.

A common way to monitor macropinocytosis is to provide cells with bovine serum albumin (BSA) and monitor its uptake. Edinger showed that this approach may not provide an accurate picture of the effects of macropinocytosis. Tumor cells can ingest BSA via nonmacropinocytic processes, and BSA does not provide many of the macromolecules that tumor cells need to survive and proliferate. Instead, Edinger assesses the anabolic value of macropinocytosis by growing tumor cells in nutrient-poor media supplemented with necrotic cell debris. She showed that tumor cells can extract amino acids, sugars, and lipids from necrotic cells and incorporate these building blocks into their own macromolecules.[29] She

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argued that the ability of tumor cells to scavenge macromolecules from their environment may make them less susceptible to cancer therapies that target metabolic pathways. This may also explain some of the different metabolic dependencies observed in cell culture and *in vivo* since macropinocytic materials are not generally provided in cell culture media. She suggested that macropinocytosis inhibitors may be an important strategy to prevent tumor growth and survival and that it is worthwhile investigating the effects of combining macropinocytosis inhibitors with a variety of standard of care and new drugs that target metabolic pathways.

Metabolic dysfunction in tumor and immune cells

Marcia Haigis from Harvard Medical School discussed how interactions between tumor and immune cells can affect immune cell function. Haigis is interested in how the unique properties of the tumor microenvironment, including the accumulation of metabolites, affect tumor cell metabolism. For example, in breast cancer, ammonia accumulates in the tumor environment. Ammonia is a byproduct of amino acid and nucleotide catabolism that is usually regarded as a waste product. However, Haigis's laboratory has shown that in breast cancer, ammonia can be recycled via the activity of glutamate dehydrogenase and used to generate amino acids.[30]

Tumor cells are not only affected by their environment, but they also affect their environment. In particular, tumor cells often reside within an immunosuppressive environment and can even display cellular markers that enable them to down-regulate the activity of inhibitory T cells. Haigis is interested in understanding whether tumor cells and T cells have unique metabolic vulnerabilities that can enable one to target tumor cells without negatively affecting T cells within the same environment. In addition, there may be therapeutic metabolic strategies that could enhance T cell function. Previous work from Haigis's laboratory has shown that T cells, while not typically thought of as a metabolic cell type, become metabolically active upon activation. Both mitochondrial biogenesis and one-carbon metabolism pathways are turned on response to T cell activation. These metabolic activities directly affect immune cell function as perturbing them can alter the fate of the T cell.[31]

Finally, Haigis is investigating how metabolites within the tumor environment contribute to crosstalk between tumor and immune cells and the role of systemic metabolism on the tumor environment. She presented unpublished data from her laboratory on the effects of an HFD in a mouse model of colon cancer, characterizing both immune cell function and metabolite profiles in tumors from obese and normal mice.

From metabolic dysfunction to therapeutics

William Kaelin from Dana-Farber Cancer Institute and Harvard Medical School ended the meeting with the keynote address. Kaelin discussed several examples of how his work has used insights from metabolic changes in cancer cells to develop therapeutics. The first half of Kaelin's talk focused on members of the α-ketoglutarate–dependent dioxygenase family, specifically prolyl hydroxylase domain-containing protein 2 (PHD2) and KDM6A. These

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enzymes use O_2 and α-ketoglutarate to hydroxylate their substrate. PHD2 acts as an oxygen sensor and controls the activity of hypoxia inducible factor (HIF), which is responsible for turning on multiple hypoxia-related genes. Under normoxic conditions, PHD2 uses O_2 and α-ketoglutarate to hydroxylate the HIF-α subunit, which is then recognized by the von Hippel–Lindau tumor suppressor protein (pVHL) and subjected to proteasomal degradation. Under hypoxic conditions, PHD2 is inactive, and HIF transcriptionally activates hypoxia-related genes, including vascular endothelial growth factor and erythropoietin.[32,33]

Activating HIF function can be advantageous in diseases like anemia—PHD2 inhibitors are being investigated in phase 3 clinical trials for the treatment of chronic kidney disease—associated anemia,[34] and the first inhibitor, roxadustat, was approved for this indication in China in 2018.[35] However, increased HIF activity due to mutations that inactivate pVHL is a common feature of RCC.[36] Kaelin has done preclinical work in *VHL*-mutant models of RCC on an allosteric inhibitor that prevents HIF assembly. One agent, PT2977, is being developed by Peloton Therapeutics and is in phase 2 clinical trials in patients with RCC.[37] While some patients appear to benefit from treatment, others do not. Kaelin is interested in understanding the basis for this heterogeneity in clinical response.

Kaelin also showed that another α-ketoglutarate–dependent dioxygenase, the histone demethylase KDM6A, can also act as an O_2 sensor. In cells, hypoxic conditions caused the accumulation of hypermethylated histones even in the absence of a functioning HIF response. Kaelin's data suggest that hypoxia directly downregulates KDM6A, which has a low affinity for O_2. These results may have implications for understanding gene expression in hypoxic environments, including tumors.[38]

The second half of Kaelin's talk focused on IDH1-mutant glioma. Mutations in IDH1 or IDH2 can cause aberrant activity that results in the accumulation of 2-hydroxyglutarate, which can inhibit the activity of many enzymes that use α-ketoglutarate, including α-ketoglutarate–dependent dioxygenases described above. Preclinical work in Kaelin's laboratory laid the groundwork for the use of IDH inhibitors in hematopoietic cancers.[39] An IDH1 inhibitor, Tibsovo®, and an IDH2 inhibitor, Idhifa®, are now approved for acute myeloid leukemia (AML) caused by mutant IDH1 or mutant IDH2, respectively.[40]

Despite their success in AML, IDH1 inhibitors have shown the limited efficacy in models of solid tumors. Kaelin is pursuing another strategy in IDH1-mutant glioma. He showed that the accumulation of 2-hydroxyglutarate in IDH1-mutant glioma cells inhibits BCAT-1 and −2, which use α-ketoglutarate to generate glutamate. Given that one major pathway of glutamate production is shut down, IDH1-mutant glioma cells are more dependent on glutamine and glutaminase activity to generate glutamate.[41] Kaelin proposed that treating cells with a glutaminase inhibitor should deprive them of glutamate and its derivative glutathione, making them more sensitive to radiation treatment. A clinical trial investigating the glutaminase inhibitor CB-839 in combination with radiation and temozolomide in patients with IDH mutant glioma is underway.[42]

Kaelin ended his talk with a call to action for his fellow researchers. A significant portion of basic and preclinical research never finds applications in the clinic—findings are either not

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reproducible or the studies are not robust enough to warrant clinical development. He cautioned researchers to be more rigorous and to not be too quick to jump to conclusions regarding the translational nature of their results. In 2017, Kaelin published an article entitled “Common pitfalls in preclinical cancer target validation” that he hopes will help researchers identify and investigate therapeutic targets.[43]

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