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Geroncogenesis: Metabolic Changes during Aging as a Driver of Tumorigenesis

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Abstract

Why does cancer risk increase as we age? Frequently attributed to the multi-hit hypothesis and the time required to accumulate genomic mutations, this question is a matter of ongoing debate. Here, we propose that the normal decline in oxidative metabolism during aging constitutes an early and important "hit" that drives tumorigenesis. Central to these metabolic changes are the sirtuins, a family of NAD^+-dependent deacylases that have evolved as coordinators of physiological responses to nutrient intake and energetic demand. Thus, the modulation of sirtuins might be a fruitful approach to reversing the age-related metabolic changes that could underlie tumorigenesis.

Of all the factors that contribute to cancer, aging is the most potent (Frank, 2007). More than 60% of all cancers occur in those aged 65 and above. Why is this so? The most common explanation is the "multi-hit," or Knudson, hypothesis, which states that cancer occurs more frequently as we age because time is necessary for cells to accumulate sufficient genetic mutations to push them over a certain mutagenic threshold and into full-blown carcinogenesis (Knudson, 1971). What this hypothesis fails to adequately explain is why cancer risk is greatly reduced by calorie restriction (CR) and physical exercise, and why calorie overload and a sedentary lifestyle has the opposite effect (Ligibel, 2012). Restriction of calories to a level 70% of ad libitum intake, for example, can completely block tumor growth even in situations where chemical carcinogens would normally evoke a 100% penetrance of cancer (Lagopoulos and Stalder, 1987; Wallace, 2005). The accumulation of genomic mutations from external causes such as sunlight and mutagenic compounds might be expected to occur regardless of diet or physical activity. Here, we propose that it is not simply the time taken to accumulate genomic hits that accounts for the increased rate of cancer with age, but the decline in metabolic homeostasis and gene regulation that occurs normally as we age. This hypothesis is consistent with the strong association between cancer prevalence and type 2 diabetes (Giovannucci et al., 2010), obesity (Renehan et al., 2008), exercise (Ligibel, 2012), and small molecules that modulate energy utilization, such as resveratrol (Baur et al., 2006; Oberdoerffer et al., 2008) and metformin (Lee et al., 2011).

Mitochondrial Homeostasis: A Unifying Link between Tumorigenesis and the Aging Process?

Recently, it has been established that dysregulated cellular energetic pathways are not just coincident with tumorigenesis but are a hallmark of it (Vander Heiden et al., 2009). Known

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as the Warburg effect, cancer cells can reprogram carbon metabolism by reducing energy production from oxidative phosphorylation and upregulating glycolysis. This change in mitochondrial metabolism appears to be advantageous to cancer cells: reduced oxidative phosphorylation diverts glycolytic and tricarboxylic acid (TCA) cycle intermediates into biosynthetic pathways including nucleotide biosynthesis and de novo lipogenesis, which allows the biosynthesis of macromolecules and organelles required for the rapid cell growth and division characteristic of cancer (Vander Heiden et al., 2009). Moreover, disruption of mitochondrial homeostasis is usually correlated with increased reactive oxygen species (ROS), which are not only powerful damaging agents that can induce mutagenesis but can also function as signaling molecules that contribute to cancer progression (Hamanaka and Chandel, 2010).

Though it is clear that metabolic reprogramming is necessary to support tumor growth, it is less clear what drives the cell to rewire its metabolism in the first place. Some clues come from rare genetic diseases caused by mutations in metabolic regulators. Peutz-Jegher's syndrome, for example, is characterized by an increased risk of cancer in the gastrointestinal tract, pancreas, cervix, ovary, and breast. The disease is caused by mutations in *Lkb1*, a kinase that regulates modulators of the Warburg effect such as the energy sensor AMP-dependent kinase (AMPK) and the regulator of growth and proliferation mammalian target of rapamycin (mTOR; Faubert et al., 2013; Sedelnikova et al., 2004). Pharmacological agents have also provided clues to the importance of metabolic reprogramming in cancer. For example, metformin, a drug that activates AMPK, lowers cancer risk (Lee et al., 2011) and mTOR inactivation is viewed as an effective therapy against cancer, with several mTOR inhibitors in clinical trials (Guertin and Sabatini, 2007).

Another illustrative example is von Hippel Lindau disease, characterized by tumors predominately in the central nervous system, retina, kidney, and pancreas. This disease is caused by a mutation in *Vhl*, which encodes an E3 ubiquitin ligase that targets the oxygen-sensitive hypoxia-inducible factor α (HIF-α) transcriptional regulatory complex for degradation (Maxwell et al., 1999). Without functional VHL, the tissues of von Hippel Lindau patients accumulate HIF-1α, which suppresses oxidative metabolism and promotes aerobic glycolysis, a metabolic shift commonly observed in cancer cells (Semenza, 2011). How HIF-1α promotes these changes is largely understood. By binding to specific promoters and sequestering other transcriptional activators such as c-Myc away from promoters, HIF-1α alters metabolism to favor cell growth (Simon, 2006). HIF-1α was originally thought to be a survival adaptation by cells within the hypoxic core of solid tumors, however it is emerging that HIF-1α is frequently activated in cancers independently of oxygen availability (Zhong et al., 1999).

Other pathways have been implicated in mediating the metabolic shift during cancer, including the tumor suppressor p53, which maintains transcription of cytochrome c oxidase subunits and subsequent functional respiration through synthesis of cytochrome c oxidase 2 (Matoba et al., 2006), and the proto-oncogene B-Raf, which regulates mitochondrial biogenesis through its regulation of peroxisome proliferator-activated receptor γ co-activator 1-α (PGC-1α) and AMPK (Faubert et al., 2013; Haq et al., 2013). The M2 isoform of pyruvate kinase has also been implicated as a regulator of the metabolic shift in cancer (Christofk et al., 2008), although conflicting results have been reported (Bluemlein et al., 2011).

The mechanisms underlying metabolic reprogramming in common cancers are still unclear. The prevailing view is that Warburg-like metabolic changes are genetic in origin, caused by mutations that accumulate in cells with high levels of genome instability (Vander Heiden et al., 2009). An alternative possibility is that the metabolic shift occurs early in a cancer cell

lineage due to epigenetic changes during aging itself (Figure 1). In favor of this idea, aging in mammals is associated with a reduction in oxidative phosphorylation and a concomitant increase in aerobic glycolysis in many tissues including brain, liver, and muscle (Bowling et al., 1993; Hagen et al., 1997; Trounce et al., 1989). Old animals also have increased lactate levels both in tissues and in serum, a hallmark of increased glycolysis and reduced oxidative phosphorylation (Ross et al., 2010). Similarly, type 2 diabetes, a disease known to accelerate the rate of metabolic aging, is associated with a gene expression signature of glycolytic metabolism similar to that of hypoxia and HIF-1α accumulation (Ptitsyn et al., 2006) and a decline in oxidative phosphorylation (Petersen et al., 2004), paralleling the Warburg effect. Thus, in addition to oncogenic mutations, a shift toward Warburg metabolism during aging may be one of the "hits" required to push cells into carcinogenesis. This putative mechanism, which we refer to as "geroncogenesis," may help explain why the greatest risk of carcinogenesis is age and why interventions that maintain metabolic health such as metformin and dietary restriction also prevent cancer.

If the natural decline in oxidative metabolism is a contributor to tumorigenesis, it is critical we understand why this decline occurs in the first place. As descendants of symbiotic α-proteobacteria, mitochondria maintain a separate genome that encodes tRNA and 13 subunits of the electron transport chain (Wallace, 2005). The mitochondrial genome is subjected to constant onslaught from ROS and is highly prone to mutation (Wallace, 2005). Accumulation of mitochondrial mutations is considered to be a major contributor to mitochondrial decline during aging (Trifunovic et al., 2004). Indeed, mice expressing error-prone mitochondrial DNA polymerase (*Polg*$^{mut/mut}$) exhibit severe electron transport chain deficiencies along with a premature aging phenotype (Trifunovic et al., 2004). There is also some evidence that mitochondrial mutations can promote tumorigenesis: mitochondrial mutations are found in human cancers, and cybrid cell lines containing mitochondria with a point mutation in cytochrome oxidase I proliferate into tumors seven times the size of those in wild-type controls (Wallace, 2005).

Though mitochondrial mutations provide a satisfying explanation for aging, there are some confounding observations. Mice heterozygous for only one copy of the error-prone mitochondrial DNA polymerase (*Polg*$^{+/mut}$) display a mitochondrial genome mutation rate over 500 times higher than that of normal aged mice but, unlike *Polg*$^{mut/mut}$ homozygous mice, display no change in lifespan (Vermulst et al., 2007). Also, the redundancy of having hundreds to thousands of mitochondria present in each cell, subject to continual fusion, fission, and mitophagy, allows for dysfunctional mitochondria to be quickly eliminated (Ono et al., 2001). A high mutation load therefore must be reached before major metabolic changes become apparent. Together, these findings suggest that mitochondrial mutations are but one part of a process that drives the metabolic shift during aging.

Over the past few years, a role for "epigenetic" alterations in age-related metabolic decline has become increasingly appreciated. There is evidence, for example, that metabolism becomes Warburg-like during old age because of a shift in balance between members of the lactate dehydrogenase complex to favor the production of lactate, resulting in diversion of pyruvate away from the TCA cycle and subsequent oxidative phosphorylation (Ross et al., 2010). The mechanism underlying these changes remains to be determined, and the importance of these changes to normal physiology has been the subject of debate (Quistorff and Grunnet, 2011). Another emerging idea is that the decline in metabolism during aging is due to a loss in activity of longevity regulators that are critical for the maintenance of cellular homeostasis. Central to this longevity regulation are the "sirtuins," a seven-member family of nicotinamide adenine dinucleotide $(NAD)^+$-dependent lysine deacylases.

Sirtuins: Relevance for Age-Induced Tumorigenesis and the Warburg Effect

The founding member of the sirtuin family was Sir2, a yeast transcriptional silencing protein that delays aging in response to low calorie intake (Lin et al., 2000). In mammals, the seven sirtuins (SIRT1–SIRT7) play key roles in the regulation of metabolism, inflammation, DNA repair, circadian rhythms, and aging. Sirtuins impart their effects largely via their catalytic activity, removing acyl-lysine moieties from proteins via a multi-step reaction that consumes NAD^+ (Feldman et al., 2012). The number of lysine modifications that are known to be removed by sirtuins has grown in recent years to include acetyl-, succinyl-, malonyl-, and long-chain fatty acyl groups. Decreased activity of sirtuin family members during aging, especially SIRT1, SIRT3, and SIRT6, has been strongly implicated in the susceptibility of organs to aging and age-related diseases (Baur et al., 2006; Brown et al., 2013; Kanfi et al., 2012). A major cause of the decline in sirtuin activity is a decrease in NAD^+ levels with age, a decline that is accelerated by obesity and counteracted by CR and physical activity (Koltai et al., 2010; Yang et al., 2007).

Over the past few years, it has become increasingly clear that the maintenance of sirtuin activity is likely to be critical for preventing tumorigenesis and slowing tumor growth in many tissues, but there are also studies indicating the opposite (Table 1). Mechanisms of tumor suppression by sirtuins initially focused on their ability to halt the cell cycle, inactivate oncogenic transcription factors, and promote DNA repair, but more recent studies have shown that their effects on energy metabolism may be equal, if not more important, for tumor suppression (Figure 2; Csibi et al., 2013; Finley et al., 2011; Firestein et al., 2008; Herranz et al., 2010; Jeong et al., 2013; Kim et al., 2010; Narayan et al., 2012; Oberdoerffer et al., 2008; Sebastián et al., 2012; Serrano et al., 2013). The sirtuin with the strongest known influence on tumorigenesis is SIRT3, a mitochondrial enzyme that regulates ROS production and enzymes that facilitate the TCA cycle, oxidative phosphorylation, and fatty acid metabolism (Finley et al., 2011; Hirschey et al., 2010). Deletion of *Sirt3* results in chromosomal instability in vitro and causes spontaneous mammary tumorigenesis in mice, with metabolic changes that include increased glucose uptake, decreased ATP generation, and a metabolic reprogramming that parallels the Warburg effect (Kim et al., 2010). This metabolic switch is mediated by increased ROS that stabilize HIF-1α, thereby upregulating glycolysis and decreasing mitochondrial respiration (Bell et al., 2011; Finley et al., 2011). In one study, *Sirt3* was deleted in 30% of breast cancer samples (Finley et al., 2011). Though these data are compelling, the tumor-suppressive role of SIRT3 is not clear cut: other studies indicate that *Sirt3* is overexpressed in breast cancer compared to healthy mammary tissue (Alhazzazi et al., 2011b; Ashraf et al., 2006) and knockdown of this protein reduces tumor burden in an oral cancer model (Alhazzazi et al., 2011a).

Another sirtuin implicated in tumorigenesis is SIRT6, a chromatin-associated enzyme with deacetylase and long-chain deacylase activities. *Sirt6* deletion increases HIF-1α and c-Myc transcriptional activity, with a corresponding upregulation of glycolysis (Sebastián et al., 2012; Zhong et al., 2010). Remarkably, knockdown of *Sirt6* in otherwise normal mouse embryonic fibroblasts (MEFs) transforms them, independently of activation of known oncogenes (Sebastián et al., 2012). Although SIRT6 is required for genomic stability (Mostoslavsky et al., 2006), re-introduction of *Sirt6* into knockout MEF cells in which genomic instability might already have been expected to take place represses tumor formation, effectively ruling out mutations as a cause (Sebastián et al., 2012). These findings further underscore the idea that metabolic alterations are required, if not sufficient, to induce tumor growth.

SIRT1, a nuclear sirtuin, was the first family member shown to act as a tumor suppressor. Pharmacological activation or genetic overexpression of *Sirt1* increases genomic stability in

cells treated with DNA-damaging agents, delays lymphoma, and improves the survival of irradiated $p53^{+/-}$ mice (Oberdoerffer et al., 2008), while *Sirt1* deletion has the opposite effect (Wang et al., 2008). By localizing to sites of DNA damage and facilitating the recruitment of DNA repair factors such as histone deacetylase 1, Rad51, and Nbs1, SIRT1 plays a key role in promoting genome stability, a function that declines with age (Dobbin et al., 2013; Oberdoerffer et al., 2008). One of the strongest effects of SIRT1 in vivo is its ability to protect mice in the heterogeneous diethylnitrosamine-induced model of hepatocellular carcinoma (Herranz et al., 2010), potentially by suppressing inflammatory responses in this organ. SIRT1 can also suppress tumorigenesis by negatively regulating oncogenic transcription factors, including β-catenin (Firestein et al., 2008) and c-Myc (Yuan et al., 2009), though opposing findings for Myc have been reported (Menssen et al., 2012).

Similar to SIRT3 and SIRT6, SIRT1 might influence tumorigenesis, not only through its ability to regulate genomic stability, but also by regulating cellular metabolism. SIRT1 regulates the transcriptional activity of HIF-1α (Lim et al., 2010), which is also an important regulator of the Warburg effect as well as angiogenesis and metastasis. SIRT1 also deacetylates and activates liver kinase B1 (LKB1; Lan et al., 2008), a known tumor suppressor that regulates mTOR and AMPK (Sedelnikova et al., 2004). Interestingly, the effects of SIRT1 on tumorigenesis are context dependent. For example, inhibition of SIRT1 improves the efficacy of a chemotherapeutic agent (Imatinib) against chronic myeloid leukemia (Li et al., 2012) and blocks the proliferation of hepatocellular carcinoma cell lines in vitro and in a xenograft model (Portmann et al., 2013). Conversely, *Sirt1* overexpression can accelerate thyroid cancers in vivo (Herranz et al., 2013). These latter findings likely reflect the ability of SIRT1 to inhibit the tumor suppressor p53, which promotes survival under situations of cell stress (Luo et al., 2001).

There is evidence that SIRT2, the cytosolic sirtuin, is also a tumor suppressor. Deletion of *Sirt2* results in spontaneous tumorigenesis in the liver and accelerates the 7,12-dimethyl-benz(a)anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate model of skin cancer (Narayan et al., 2012; Serrano et al., 2013). One mechanism is likely to be cell cycle control, as SIRT2 deacetylates and regulates CDH1 and CDC20, members of the anaphase-promoting complex (Narayan et al., 2012). Moreover, SIRT2 transiently migrates to the nucleus during mitosis (North and Verdin, 2007), where it modulates the activity of the methyltransferase PR-Set7, resulting in H4K20 methylation (Serrano et al., 2013), a chromatin mark involved in genomic stability (Oda et al., 2009). Although primarily studied in the context of its cytosolic regulation of cell cycle, one interesting possibility is that SIRT2 influences mitochondrial function and the Warburg effect by deacetylating CDH1, a protein that limits glycolysis and proliferation of cancer cell lines through ubiquitination and degradation of the glycolysis-promoting enzyme 6-phosphofructo-2-kinase (Almeida et al., 2010). Again, the data are not clear cut; an in vitro study found that SIRT2 knockdown or small molecule inhibition reduced neuroblastoma cell growth through stabilization of Myc oncoproteins (Liu et al., 2013).

Recently, two other sirtuins, SIRT4 and SIRT7, have also been implicated in the regulation of tumorigenesis. The mitochondrial sirtuin SIRT4 promotes metabolic reprogramming by facilitating the cataplerotic diversion of carbons from the TCA cycle to aerobic glycolysis and lactate generation, forcing cancer cells to rely on glutamine for replenishment of the TCA cycle (Csibi et al., 2013; Jeong et al., 2013). Upon DNA damage, *Sirt4* expression is upregulated, leading to a repression of glutamine metabolism through its inhibition of glutamate dehydrogenase, which converts glutamate into α-ketoglutarate (Csibi et al., 2013; Jeong et al., 2013). This shift prevents the cell from upregulating nonessential biosynthetic pathways and undergoing premature cellular division prior to genomic repair (Csibi et al., 2013; Jeong et al., 2013). The nucleolar sirtuin, SIRT7, may also regulate cellular

metabolism by negatively regulating HIF-1α and HIF-2α (Hubbi et al., 2013), potentially underlying the Warburg effect. The role of SIRT7 in tumorigenesis, however, also seems context dependent: SIRT7 may help maintain a pro-oncogenic phenotype by interacting with the transcription factor ELK4 and deacetylating H3-K18, a modification that promotes tumor growth (Barber et al., 2012).

Therapeutic Strategies to Combat Age-Induced Tumorigenesis

Mutations that give rise to cancer are essentially irreversible. However, if age-related metabolic changes are an early driver of tumorigenesis, molecules that prevent and reverse metabolic aging may be useful as cancer therapies. Indeed, molecules such as metformin and HIF-1α inhibitors in development show promise as anticancer agents (Onnis et al., 2009). Given the key role of sirtuins in tumorigenesis, it is feasible that lifestyle interventions and/or small molecules that activate sirtuins could induce a youthful metabolic state and serve to prevent and treat cancer. Direct SIRT1 activators that work by allosteric mechanisms (Hubbard et al., 2013) have been developed. These molecules are in human clinical trials to treat metabolic and inflammatory diseases, but they are not yet under investigation as chemotherapy adjuncts.

An alternative approach to activating sirtuins, one that raises the activity of the entire family of enzymes, is to exploit their common requirement for NAD^+. Increasing NAD^+ levels has been shown to protect mice from metabolic decline in mouse models of obesity and aging (Cantó et al., 2012; Escande et al., 2013; Yoshino et al., 2011), but it is not yet considered a viable strategy for cancer, in part because raising overall NAD^+ levels is not without risks. As described above, there is evidence that SIRT1 and SIRT7 may promote the growth of cancers. It is also important to consider the role of NAD^+ as a redox carrier that is essential to glycolysis, which cancer cells heavily rely upon. Another consideration is the fact that raising NAD^+ may not be as simple as it sounds. NAD^+ is compartmentalized into cytosolic, nuclear, and mitochondrial pools (Nikiforov et al., 2011), and it is unclear what degree of flux exists between these pools and whether a particular pool of NAD^+ influences the Warburg effect and tumorigenesis.

Some researchers have taken the opposite approach, seizing upon the fact that NAD^+ is an essential redox carrier for glycolysis and cancer cell viability. FK866, a small molecule inhibitor of the NAD^+ recycling enzyme Nampt, has strong antiproliferative effects in cancer cells and has entered clinical trials (Hasmann and Schemainda, 2003). Of course, NAD^+ depletion can also be toxic to normal cells. If the approach does prove effective as a chemotherapeutic strategy, it will be important to optimize dosing to avoid toxicity to noncancerous cell types. Clearly, more work is required to determine whether raising or decreasing NAD^+ levels will be beneficial for the treatment of cancer in humans and which specific pools of NAD^+ influence tumorigenesis.

Conclusions and Future Perspectives

While the “multi-hit” concept of oncogenic DNA mutations has dominated cancer biology for the past few decades, aberrant tumor metabolism and disruption of mitochondrial homeostasis are emerging as key drivers of both initiation and progression of cancer. Metabolic reprogramming is currently viewed as a late stage of tumorigenesis, the result of mutations that accumulate over time. Here, we propose that one of the early drivers of tumorigenesis is aging-induced dysregulation of mitochondrial metabolism. This may be driven, in part, by an age-related decline in NAD^+ and sirtuin activity. These metabolic changes likely occur independently of, and may even precede, genomic lesions, acting as an early “hit” that pushes cells toward complete cellular transformation. If seen though this lens, aging induces a gradual reprogramming of metabolism toward a “cancer-like” state, a

transformation that is accelerated by increased calorie intake and a sedentary lifestyle and that is counteracted by low-calorie diets and exercise. This may explain why diet, exercise, and CR mimetics, which alter the pace of metabolic aging, strongly influence cancer susceptibility (Baur et al., 2006; Lee et al., 2011; Ligibel, 2012; Oberdoerffer et al., 2008; Renehan et al., 2008). If this hypothesis holds true, there may come a day when lifestyle interventions along with CR mimetics are used to reverse the metabolic reprogramming of tumors and even to prevent aging tissues from undergoing the metabolic switch in the first place.

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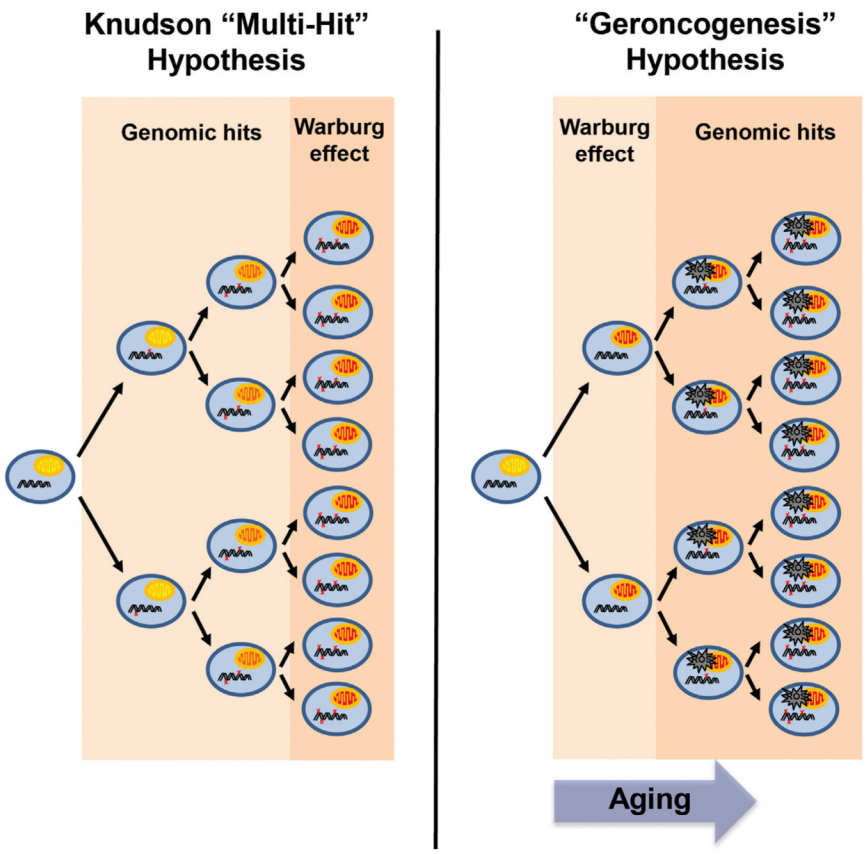

Figure 1. The Geroncogenesis Hypothesis: Aging-Induced Metabolic Decline as a Driver of Tumorigenesis

According to the Knudson, or "multi-hit," hypothesis, cancer occurs more frequently as we age because time is necessary for cells to acquire genetic mutations that drive carcinogenesis (indicated by red "x"). According to this model, the shift to oxidative glycolysis, known as the Warburg effect, occurs subsequent to these early hits. An alternative possibility is that the natural decline in oxidative metabolism as we age induces a Warburg-like metabolic state in normal tissues (indicated by red mitochondria). This increases the ROS production and sets the metabolic stage for later mutations to drive tumorigenesis. Low-calorie diets, exercise, and CR mimetic compounds delay this metabolic shift, thereby reducing the chance that oncogenic mutations will occur in a cell with optimal metabolism for tumorigenesis. The model predicts that CR mimetics could be used to reverse the metabolic reprogramming of tumors and even to prevent aging tissues from undergoing this switch in the first place.

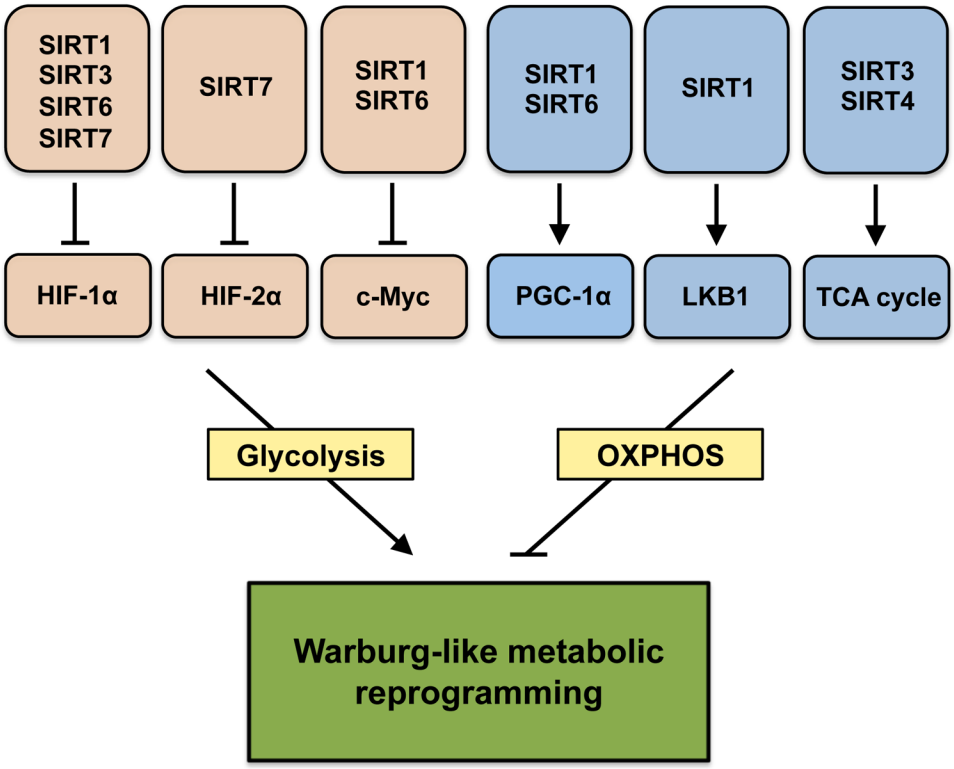

Figure 2. Sirtuins Are Central to Metabolic Reprogramming during Aging and Cancer

Sirtuins control key nodes in the regulation of glycolysis (HIF-1α, HIF-2α, and c-Myc) and oxidative phosphorylation (PGC-1α, LKB1, and TCA enzymes). A decline in the activity of the sirtuin family of enzymes in old age is hypothesized to lead to a shift toward a predominantly glycolytic, Warburg-like metabolism that could contribute to the exponential increase in cancer susceptibility during aging.

Table 1

Evidence for Sirtuins as Tumor Suppressors or Promoters

Sirtuin	Examples of Tumor Suppression	Examples of Tumor Promotion
SIRT1	*Sirt1* overexpression suppresses hepatocellular carcinoma in diethylnitrosamine-treated mice (Herranz et al., 2010)	small molecule inhibition of SIRT1 reduces growth of transplanted Bcr-Abl chronic myeloid leukemia cells (Li et al., 2012)
	Sirt1 overexpression suppresses colon cancer in $Apc^{Min/+}$ mice (Firestein et al., 2008)	
	Sirt1 overexpression and resveratrol suppress lymphoma in irradiated $p53^{+/-}$ mice (Oberdoerffer et al., 2008)	SIRT1 inhibits the tumor suppressor p53 (Luo et al., 2001)
	tumorigenesis in *Sirt1* knockout mice (Wang et al., 2008)	Sirt1 overexpression promotes thyroid tumorigenesis in $Pten^{+/-}$ mice (Herranz et al., 2013)
	SIRT1 promotes degradation of c-Myc; overexpression represses colony formation in HO15 and Myc3 Rat1 cells (Yuan et al., 2009)	SIRT1 promotes stabilization of c-Myc; partial reduction in proliferation of Myc transformed U937 monoblasts in vitro (Menssen et al., 2012)
	SIRT1 allosteric activator resveratrol suppresses DMBA-induced skin cancer (Jang et al., 1997)	*Sirt1* overexpression increases tumor growth in orthotopic xenografted hereditary colon cancer cell lines (Portmann et al., 2013)
SIRT2	*Sirt2* deletion causes spontaneous tumorigenesis in mice (Narayan et al., 2012)	SIRT2 inhibition reduces proliferation of BE(2)-C and MiaPaca cell lines in vitro (Liu et al., 2013)
	Sirt2 deletion causes spontaneous tumorigenesis in mice (Serrano et al., 2013)	
SIRT3	*Sirt3* knockdown increases, and overexpression reduces tumor size in orthotopic xenografts (Bell et al., 2011)	*Sirt3* knockdown increases tumor burden in orthotopic xenograft tumor model (Alhazzazi et al., 2011a)
	Increased soft agar colony formation in knockout MEF cells, *Sirt3* deletion in 30% of breast cancers (Finley et al., 2011)	increased *Sirt3* expression in node positive breast cancer (Ashraf et al., 2006)
	tumor formation in Myc, Ras transformed immortalized MEF cells (Kim et al., 2010)	
SIRT4	decreased tumor growth in orthotopic immortalized $Tsc2^{-/-}$ MEF cells overexpressing *Sirt4* (Csibi et al., 2013)	no strong evidence
	increased tumor growth in immortalized $Sirt4^{-/-}$ MEF cells (Jeong et al., 2013)	
SIRT6	increased tumorigenesis in immortalized $Sirt6^{-/-}$ MEF cells (Sebastián et al., 2012)	no strong evidence
	Sirt6 overexpression induces apoptosis in cancer cells but not normal cells in vitro (Van Meter et al., 2011)	
SIRT7	SIRT7 negatively regulates HIF-1α and HIF-2α (Hubbi et al., 2013), potentially underlying aspects of the Warburg effect	decreased growth of U251 xenografts with *Sirt7* knockdown (Barber et al., 2012)