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Clinical Cancer Research

Review

Oxford and the Savannah: Can the Hippo Provide an Explanation for Peto's Paradox?

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Abstract

Peto's paradox is the counterintuitive finding that increasing body mass and thereby cell number does not correlate with an increase in cancer incidence across different species. The Hippo signaling pathway is an evolutionarily conserved system that determines organ size by regulating apoptosis and cell proliferation. It also affects cell growth by microRNA-29 (miR-29)–mediated cross-talk to the mTOR signaling pathway. Whether these pathways that decide organ size could explain this paradox merits consideration. Inactivation of most genes of the Hippo pathway in *Drosophila melanogaster* genetic screens causes excessive tissue-specific growth of developing tissues. Altered Hippo pathway activity is frequently found in diverse tumor types, but mutations of component pathway genes are rare. Most Hippo pathway components are encoded by tumor suppressor genes (TSG), but an exception is the downstream effector gene called *YAP*. Activity of the Hippo pathway causes deactivating phosphorylation of YES-associated protein (YAP) with nuclear exclusion. YAP can also be phosphorylated at a second site, S127, by AKT. YAP induces the expression of genes responsible for proliferation and suppression of apoptosis. Resolving Peto's paradox may serendipitously provide new insights into the biology and treatment of cancer. This article considers Hippo signaling and Peto's paradox in the context of TSG–oncogene computed models. Interspecies differences in dietary composition, metabolic rates, and anabolic processes are also discussed in the context of Hippo–mTOR signaling. The metabolically important LKB1-AMPK (liver kinase B1-AMP activated protein kinase) signaling axis that suppresses the mTOR pathway is also considered. *Clin Cancer Res; 20(3); 557–64. ©2013 AACR.*

Introduction

The Hippo pathway is a growth-suppressive pathway that controls tissue growth and organ size. For relevance this article restricts discussion to Hippo signaling in mammals, the core components of which are detailed in Fig. 1. The central axis of the pathway is occupied by the serine/threonine kinases mammalian sterile 20-like kinase 1/2 (MST1/MST2) followed by the serine kinases large tumor suppressor homolog 1/2 (LATS1/LATS2). When the pathway is activated, LATS 1/2 phosphorylates YES-associated protein (YAP) and transcription coactivator with PDZ-binding motif (TAZ). Phosphorylation of YAP and TAZ causes them to be excluded from the nucleus, retained in the cytoplasm, and subsequently degraded. Dephosphorylation of YAP and TAZ permits entry to the nucleus, binding to the Sd homolog TEA domain family member 1/4 (TEAD1/4), and transcription of genes associated with cellular proliferation and inhibition of apoptosis (BIRC5-2, FGF, AREG, CTGF, and GlLI-2; refs. 1–4). It also is established that when the SRC/ABL kinases are phosphorylated, YAP and TAZ acquire the ability to bind p73 and active proapoptotic gene transcription (5).

Peto's paradox and computed modeling

The eponymously named Peto's paradox was first described in 1975 by the University of Oxford epidemiologist Sir Richard Peto. There is interspecies variation in the body mass of mammals with the average weight of a mouse at 20 g, humans, 70 kg, and the blue whale (*Balaenoptera musculus*), 20 tons. Previous literature reviews have substantiated this concept by failing to find an interspecies correlation between body mass and cancer incidence (6, 7). Peto's paradox requires interrogation not only because it may provide clues to cancer causality, but because insights may be found as to why promising preclinical findings in small mammals such as mice often are not fulfilled in early-phase clinical trials in humans.

In 2013, a theoretical mathematical model of the evolutionary dynamics of wild populations was devised by Roche and colleagues (8). In that study, the most prevalent of 100 potential genetic-mutation combinations that emerged was sought from more than 4,000 computed generations. It predicted that the rate of activation of protooncogenes

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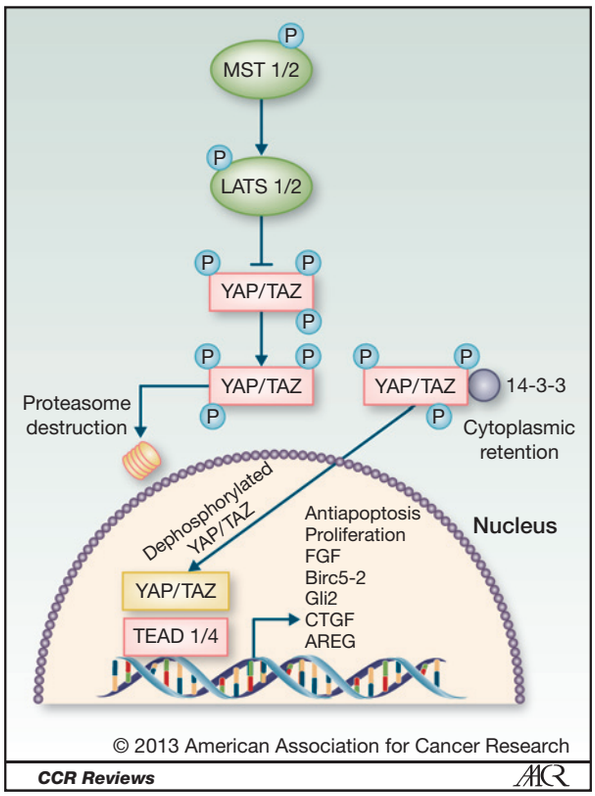

Figure 1. The core axis components of the Hippo signaling pathway. Hippo pathway activity leads to phosphorylation and subsequent nuclear exclusion of YAP and TAZ. This has a proapoptotic and antiproliferative effect.

gradually declined with increasing body mass. The rate of tumor-suppressor gene (TSG) inactivation similarly declined, but at a given threshold increased suddenly for a short period, followed by decreasing again later. At this threshold where the TSG inactivation rate inflexion point occurs, there was an inferred large decrease in birth rate conferred by an assumed defined trade-off function. Put simply, for intermediate-sized animals, the evolutionary cost of reduced fertility caused by possession of numerous wild-type TSGs exceeded the evolutionary benefit of having a reduced prevalence of cancer within a particular species. This model was predicated on a number of assumptions, including a trade-off specified by oncogene activation rate. Massive mammals were inferred to have evolved many mechanisms to slow the rate of inactivation of TSGs and activation rate of protooncogenes (9).

One molecular correlate that may account for the brief period of increasing TSG inactivation rate with increasing body mass is the phenomenon of embryonic dispause. This is of potential evolutionary rather than interspecies relevance to fertility and the computed model. Embryonic dispause is the temporal uncoupling of conception and parturition until maternal and environmental conditions are favorable for maternal and neonatal survival. The expression of Msh homeobox 1 (MSX1) and Msh homeobox 2 (MSX2) in blastocysts is an important determinant of blastocyst implantation and embryonic dispause (10). Blastocyst implantation and malignant invasion are conceptually analogous.

Evolution of pathway configuration: Core axis clues

The configuration of the signaling pathways of Hippo and mTOR require examination in the context of cancer susceptibility and species size. The Hippo pathway also has tissue specificity with signaling activity affected by cell density. In the Hippo pathway there are several TSGs that affect the phosphorylation status and nuclear–cytoplasmic localization of the potentially oncogenic transcription coactivator YAP. Phosphorylation of YAP and TAZ causes cytoplasmic retention and repression of their activity. The signaling cascades of MST1/2 and LAT1/2 upstream of YAP are conserved in mammals (11–13). Consider the highly simplified model but one that represents the core of the Hippo pathway, of the two successive TSGs MST and LATS followed by YAP. Applying the model of Roche and colleagues, it predicts a slow decline in the mutation rate of the TSGs MST1/2 and LATS1/2 with increasing body mass in different species with the exception of the afore-described short period of increase. The implication is that because of Knudson's two-hit hypothesis, the likelihood of homozygous loss of the two succeeding TSGs MST and LATS, such that there would be implications on the phosphorylation status and oncogenic effector function of YAP, would be extremely low. The rate of malignancy arising from aberration in this core axis of the Hippo pathway should have a denominator partly determined by the (MST gene mutation rate)^2 and (LATS gene mutation rate)^2 with unknown coefficients and multiplicative interdependency. Phenotypic consequences of bialleic mutation of MST were only first described in 2012 in three members of a consanguineous Iranian kindred (14). These features were of an immunodeficiency syndrome and atrial septal defects, but malignancies were not described. The apparent initial redundancy of the two succeeding TSGs MST and LATS in the Hippo pathway therefore may partly be a safety measure that has emerged through molecular evolution to obviate the impact of mutations of component pathway genes on pathway activity. Deletion of the downstream potentially oncogenic transcriptional coactivator Yap in mice confers embryonic lethality by impeding cardiomyocyte proliferation, thereby causing cardiac hypoplasia (15). It may be that *YAP* mutations cause similar functional deficits with embryonic lethality and this is an area for future research.

Larger animals have a greater number of cells with a greater chance of accumulating replicative errors. The molecular configuration of the Hippo pathway however ensures that its governance of cell proliferation and apoptosis in determining organ size is not easily corrupted. Cellular growth mediated by the mTOR pathway is also subject to microRNA-29 (miR-29)–mediated cross-talk from the Hippo pathway at the level of YAP so the same upstream safety contingencies partly apply. Some evidence that supports this theory is that *Merlin* (*Neurofibromin 2*) is

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the only gene in the Hippo pathway, in which mutational inactivation occurs in human malignancy. The inference is that the frequent alteration in Hippo signaling observed in human cancer arises by means other than somatic mutations of constituent pathway genes (16). These "other means" may partly hold the key to Peto's paradox. The risk of replicative error in DNA with cell division remains but the organ size governance structures of Hippo and Hippo-mediated cross-talk to mTOR are configured to ensure fidelity of organ size determination pathways. In a contrasting clinical and molecular scenario there are some conditions such as Beckwith Widemann syndrome in which a juxtaposition of increased organ size and an increased rate of malignancy does occur (17). One of the "other means" in which the Hippo pathway is controlled is by epigenetic regulation. Set7 (*Setd7*) is a lysine methyltransferase that methylates histone H3 lysine 4 as well as other substrates. Mice with absent Set7 have increased expression of Yap target genes (18). Monomethylation of lysine 494 has been found to be critical for cytoplasmic retention of Yap.

Hippo, mTOR, and metabolism

Small animals have higher metabolic rates per unit mass than larger mammals (19). In 1932, Max Kleiber devised an allometric law that bears his name in which the basal metabolic rate (B) of an organism was considered to be proportional to body mass (M) to a $^3/_4$ power, i.e., $B = B_0M^{(3/4)}$ (20). The value of this "power" has been subject to controversy. In 2010, the relationship between metabolic rate and mass was found to have a convex curvature on a logarithmic scale (21).

It has previously been postulated that there are fewer reactive oxygen species in larger animals. This would affect the redox state of different pathway intermediates. In humans, circumstances in which different redox states have been described in malignancy include isocitrate dehydrogenase-1 (IDH-1)–mutated diffuse gliomas. Wild-type IDH-1 converts isocitrate to α-ketoglutarate, whereas mutated IDH-1 converts α-ketoglutarate to 2-hyroxyglutarate. Commensurate with this, there is a transition from $NADPH + H^+$ production in normal tissue to $NADPH + H^+$ consumption in *IDH1*-mutated gliomas (22). In general, interspecies differences in the consumption of carbohydrates (polysaccharides vs. mono-/disaccharides), proteins (glutamine affects proliferation; leucine and arginine activate and are required for mTORC1 signaling), and fats may also be relevant to cancer prevalence (23).

Altered cellular metabolism is a recognized hallmark of cancer (24). The principle method of ATP production in cancerous cells is aerobic glycolysis. This is eponymously termed the Warburg effect. The net effect of aerobic glycolysis is:

$$\text{Glucose} + 2\text{ADP} + 2\text{NAD}^+ \rightarrow 2\text{Pyruvate} + 2\text{ATP} + 2\text{NADH}$$

This process is approximately 18 times less efficient than oxidative phosphorylation, which is the principle means of energy production in normal cells with sufficient oxygen (24). An illustrative example of the Warburg effect in carcinogenesis is the hereditary cancer syndrome leiomyomatosis and renal cell carcinoma (25). It arises from a germline mutation of the tricarboxylic acid cycle enzyme fumarate hydratase. This decreases oxidative phosphorylation and increases aerobic glycolysis. One of the phenotypic manifestations of the syndrome is type II renal cell carcinoma. This tumor has decreased levels of AMPK, stabilization of hypoxia-inducible factor-1α, and increased expression of genes including *VEGF* and *GLUT1*.

In general, the increased uptake and consumption of glucose in cancerous cells is observed in ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET; ref. 26). Exceptions do apply, however, such as with prostate cancer, in which ^{18}F-FDG uptake is unpredictable and variable, or the circumstance in which the standard uptake value (SUV_{max}) on ^{18}F-FDG PET of low-grade sarcomas fails to distinguish them from benign tumors (27). Reasons for increased SUV_{max} on PET scan for diverse cancer types include AKT-mediated transcription and plasma membrane localization of the glucose transporter GLUT1. Increased hexokinase and decreased glucose-6-phosphatase in cancerous cell also leads to retention of ^{18}F-FGD. It is postulated that interspecies differences in metabolic rates alter the redox state of pathway intermediates including that of the Hippo pathway and thereby tips the balance away from aerobic glycolysis in nascent malignant cells in a proapoptotic fashion. This is a subject for future research. In the imaginal epithelium of *Drosophila*, mitochondrial dysfunction and activation of Ras stimulates production of reactive oxygen species that activate c-Jun amino (N)-terminal kinase (JNK) signaling (28). JNK and oncogenic RAS then cooperate to inactivate the Hippo pathway with upregulation of its target genes. Therefore, there is some nascent evidence for redox states being important for Hippo signaling.

The PI3K–AKT–mTOR pathway

Hippo and the mTOR pathways are two of the principal molecular determinants of organ size. Hippo controls cell number by inhibiting proliferation and promoting apoptosis, whereas the mTOR pathway regulates cell growth in response to growth factors and nutrients (29). mTOR also participates in cell proliferation, apoptosis, and autophagy as well as controlling protein synthesis and cellular glucose import.

The mTOR pathway is inappropriately activated in many types of cancer (30, 31). This signaling pathway integrates cellular information and has an effector function mediated by phosphorylation of p70S6 kinase and 4E-BP1. At the cell surface, growth factors bind to receptor tyrosine kinases to activate PI3K–AKT signaling. PI3K and Akt phosphorylate the tuberous sclerosis complex (TSC1–TSC2) at different sites. Functionally, this inhibits the complex, thereby permitting Rheb to activate mTORC1. Specifically, TSC2 is a GTPase-activating protein that prevents Rheb from stimulating mTORC1 by hydrolysis of GTP-Rheb. Usually when GTP is bound to Rheb, it strongly stimulates its kinase

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activity. AKT can also activate mTORC1 by phosphorylating proline-rich Akt substrate 40 kDa (PRAS40) as well as alternatively phosphorylating TSC2 (31).

mTOR is an atypical serine/threonine protein kinase that associates with the alternative partners Raptor or Rictor. When mTOR-Raptor combines with GβL they create the TORC1 complex. This then phosphorylates S6K, 4E-BP1, and 4E-BP2 to activated translation of proteins. The alternative combination of mTOR-Rictor and GβL creates TORC2 that phosphorylates and activates Akt. In total, mTORC1 and mTORC2 have six and seven protein components, respectively. mTOR signaling promotes glycolytic metabolism by Akt-mediated membrane localization of glucose transporters, as well as Akt-dependent activation of hexokinase and phosphofructokinase (32–35). Clinically, this has been witnessed in phase I trials of AKT inhibitors in which hyperglycemia was a common side effect. Inhibition of the PI3K–AKT–mTOR pathway can also cause hyperlipidemia (36).

mTOR signaling is part of the molecular adaptive function of mammals that permits transition from anabolic to catabolic states depending on variable environmental conditions such as nutrient availability. Activation of mTORC1 is affected by factors such as energy status, cellular stress, growth factors, oxygen levels, and amino acids (37). mTORC1 anabolic activity is subject to downregulation by AMPK-mediated phosphorylation events including inactivation of Raptor and activation of the TSC1/2 complex (38, 39). mTORC1 is affected by intracellular energy levels through AMP-activated protein kinase–independent and –dependent pathways (39). Therefore, interspecies differences in nutritional states through differences in food consumption, exercise requirements, anabolic, and catabolic demands may all be relevant to Peto's paradox. The TSG Liver Kidney B1 (LKB1) activates (AMPK) under conditions of cellular stress (40). Interestingly, phosphatase and tensin homolog (PTEN), which downregulates the PI3K–AKT–mTOR pathway, can have loss-of-function mutations, which cause insulin sensitivity and obesity (41). Patients with Cowden syndrome attributable to germline PTEN mutations have augmented obesity and increased insulin sensitivity caused by increased PI3K pathway activity. This is evidenced by enhanced phosphorylation of AKT.

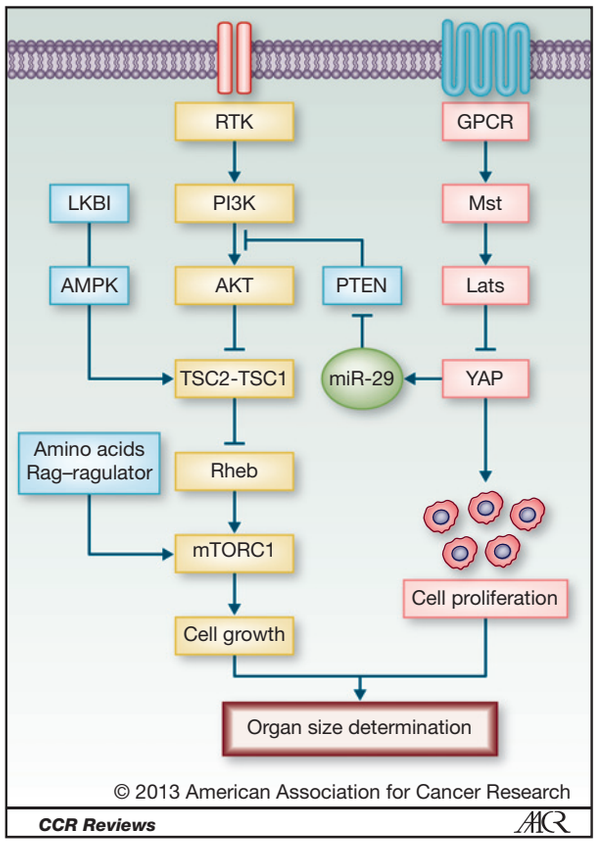

Figure 2. The overlapping mTOR, AMP, and Hippo signaling pathways. The Hippo cotranscriptional activator YAP downregulates PTEN via miR-29 cross-talk. This has the effect of upregulating PI3K–AKT–mTOR signaling. AMPK has a suppressive effect on mTOR signaling.

Cross-talk

In vitro experiments demonstrated that YAP induces miR-29 causing cross-talk between Hippo signaling and the mTOR pathway (miR-29), as detailed in Fig. 2. This inhibits PTEN translation and PTEN is itself an established inhibitor of PI3K and Akt (42). miR-29 regulates myogenic differentiation via TGF-β-Smad3 signaling (43). The inference is that miR-29 has an important role in differentiation of skeletal muscle precursors of importance to muscle development. It is of interest that cardiac rhabdomyomas are a feature of tuberous sclerosis complex, which arise from mutations in the genes that encode the tumor suppressor proteins TSC1 or TSC2. Could Hippo pathway signaling have a tonic tumor suppressor effect in larger animals once they attain their adult size? Further experiments providing *in vivo* detail of the cytoplasmic–nuclear localization/phosphorylated-dephosphorylated status of YAP and its relationship to miR-29 are required. It is interesting that though therapeutics that directly target the Hippo pathway are lacking, the Hippo pathway is downstream of G-protein–coupled receptors, which are putative therapeutic targets (44). If found, interspecies differences in the extent of miR-29 Hippo-mTOR cross-talk and Hippo signaling itself may partly inform how Peto's paradox serendipitously suggests a new anticancer strategy involving Hippo signaling.

Anabolism and growth

These pathways, in addition to having roles in organ size determination, seem to have a more generic anabolic metabolic effect. Within the pleotropic metabolic effects is the finding that Akt stimulates synthesis of fatty acids, mTORC1 increases protein synthesis, and Hippo, via miR-29, regulates myogenic differentiation. In one experiment in mice, soluble activin receptor IIb was used to block myostatin and activins (45). This led to greater muscle-protein synthesis and muscle size that correlated with increased mTORC1 signaling. Phosphorylation of YAP was enhanced. There

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Table 1. Interspecies differences in domestic animals and humans

	Average weight (kg)	Cancer incidence/100,000[a]	Most frequent tumor site in descending order	Hippo/mTOR/AMPK comments
Cat	3	257	Lymph nodes (lymphosarcoma-most common tumor, lymphoma) 32%	Comparison of age-adjusted incidence rates/100,000 in selected cancers cat, dog, and human
		72	Hematopoietic (leukemia) 16%	Breast
			Basal cell carcinoma 7%	7.2, 18.2, 81.1
			Nose paranasal sinuses SCC 4%	Leukemia and lymphoma
			Soft tissue (fibrosarcoma) 4%	50.3, 5.1, 21.3
				Lymphosarcoma in cats is transmissible caused by oncorna virus
Dog	10	828	Mammary (adenocarcinoma) most frequent non-skin cancer 12%	Excess cancer risk in particular breeds
		165	Osteosarcoma incidence 7.9/100,000 in dogs vs. 0.2/100,00 in humans. Peak incidence coincides with adolescent growth. May be IGF mediated.	Osteosarcoma incidence now considered unrelated to breed size
			Osteosarcoma infrequent in cats and rare in horses	Pancreatic islet cell tumor: Standard Poodle (analogous to pancreatic neuroendocrine tumors in humans sensitive to mTOR inhibitor everolimus)
				Hemangiosarcoma: Boxer, Boston Terrier (analogous to PEComa in humans, an mTOR-activated mesenchymal tumor). Dog is only animal in which hemangiopericytoma occurs
Human	70	287	Incidence/100,000	TSC-1/6,000 births. Associated malignancies include subependymal giant cell astrocytoma. Sensitive to mTOR inhibitor everolimus[b]
		287	Prostate 137	Sporadic perivascular epithelioid cell tumors (PEComas) including angiomyolipomas also have mTOR pathway activation.
		(Excluding nonmelanoma skin cancer. Add 150 if included to make interspecies comparison accurate)	Lung 78	Obesity/sedentary lifestyle can suppress LKB1–AMPK signaling and increase cancer risk in obese or diabetic patients
			Colon/rectum 49	Neurofibromin 2 (*NF2*) only Hippo signaling pathway gene classed as a cancer gene in COSMIC database. *NF2* implicated in acoustic neuromas and spinal ependymal tumors
			Bladder 36	
			Cutaneous melanoma 25	

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Table 1. Interspecies differences in domestic animals and humans (Cont'd)

	Average weight (kg)	Cancer incidence/100,000[a]	Most frequent tumor site in descending order	Hippo/mTOR/AMPK comments
Horse	450	256	Skin (papilloma) 28%	Animals of different sizes have different body density and different proportion of fat to lean body mass. Implications for LKB1–AMPK signaling
		117	Soft tissue fibroma 16% Eyelid, conjunctiva, lacrimal gland SCC 10% Eye, orbit SCC 8% Ovary (granulosa cell tumor) 4%	
Cattle	700	177	Eye, orbit SCC 36%	Pancreatic islet cell tumors rarely reported (mTOR)
		53	Lymphomas 20%	Frequency of schwannomas in cattle far exceeds other domestic animals, however includes all peripheral nerves. VIII nerve schwannomas usually solitary (*NF2*)
			Penis papilloma 5% Skin papillomas 5% Fibroma 3%	

Abbreviations: SCC, squamous cell carcinoma; IGF, insulin-like growth factor.

[a]Crude estimated annual rates of all tumors. Lifespan-adjusted equivalents italicized. Lifespan correction factor is: Human 1, cat 0.28, dog 0.20, horse 0.46, and cattle 0.30.

[b]Subependymal giant cell astrocytoma is a major diagnostic criterion for TSC. Tuberous sclerosis complex is an autosomal dominant disorder arising from mutation of *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin). This causes constitutive activation of mTORC1.

Source: Veterinary Cancer Medicine. Philadelphia (PA): Lea and Febiger; 1987. Chapter 3, Epidemiology, p27–52. Human tumor incidence rates from Centers for Disease Control, U.S. 2009.

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also was elevated phosphorylation of AMPK (which negatively affects mTORC1 activity) and 4E-BP1. Protein synthesis increased and mTORC1 signaling was enhanced. The inference was that Hippo signaling might have a role in skeletal muscle in different contexts. Finally, amino acids stimulate mTORC1 signaling via the Rag-Ragulator complex. This is mediated by them modulating the nucleotide-loading states of Rag GTPases (31).

Carbohydrate metabolism is intimately determined by AKT. As mentioned previously, different species have different dietary patterns of carbohydrates, fats, and proteins. They also have different metabolic rates. The interrelationship between Hippo–mTOR signaling and metabolism is undoubtedly complex. It would seem likely, however, that pathways that determine organ size and that have a role in anabolic processes in metabolism are themselves partly influenced by nutritional intake and prevailing metabolic rates per unit mass.

LKB1–AMPK

The LKB1–AMPK pathway has a dual effect on growth control and tumor suppression. It is also an important effector of the cellular response to metabolic stress (46). AMPK potently inhibits mTOR and is activated by an increase in the AMP:ATP ratio. LKB1 is a serine threonine TSG that phosphorylates a family comprising 14 members of AMP-activated protein kinases. LKB1 is inactivated in Peutz–Jeghers syndrome (hereditary intestinal polyposis syndrome). It is mutated in 15% to 35% of sporadic cases of non–small cell lung cancer and 15% of cervical cancers (47, 48). LKB1–AMPK signaling controls cellular growth in response to nutrient changes within the environment. It arrests cell growth when there is depleted intracellular ATP such as in conditions of low nutrition. The LKB1–AMPK axis also suppresses the mTORC1 pathway by AMPK-mediated phosphorylation of mTSC2 and Raptor. Hyperglycemia and overnutrition suppress signaling by the LKB1–AMPK pathway, perhaps providing a molecular explanation for the association of increased rate of cancer with diabetes or sedentary lifestyles. AMPK agonists, including the diabetic medications phenformin and metformin, are also of potential therapeutic promise. In one study of 3,837 patients diagnosed with prostate cancer, the adjusted hazard ratio for prostate cancer–specific mortality was 0.76 for each additional 6 months of metformin use [95% confidence interval, 0.64–0.89; $P < .001$; ref. 49). In general, increased AMPK pathway activity occurs with exercise and decreased caloric consumption. That different metabolic rates, exercise demand, and food consumption of larger compared with smaller animals may increase activity of the LKB1–AMPK axis in larger animals deserves investigation. Also in 2008, a short isoform LKB1(s) was identified as the sole splice isoform expressed in testes with a peak in expression when spermatids mature (50, 51). Male mice lacking LKB1(s) are infertile due to defective spermatozoa, providing tantalizing molecular support for the computed model of Roche and colleagues. This fascinating molecular finding may be of evolutionary relevance to the previously described trade-off between TSG mutation rate and fertility in intermediate-sized animals. The incidence rates, different common cancers, and perspectives on the different overlapping signaling pathways within different species are detailed in Table 1. Interpretative caution is required in light of the innumerable confounders including infectious causes of cancer.

In another consideration, AMPK regulates NADPH homeostasis to promote survival of cancer cells during energy stress such as ATP depletion (52). In cellular stress, impaired NADPH production by the pentose phosphate pathway can be circumvented by AMPK-inducing alternative routes to maintain NADPH and obviate cellular death. This arises by AMPK inhibition of the acetyl-CoA carboxylases ACC1 and ACC2. This may be a partial molecular example of the previously mentioned postulate of less-reactive oxygen states in larger animals affecting the redox state. Could increased LKB1–AMPK pathway activity in larger animals provide the answer?

Conclusions

In conclusion, the 38-year-old paradox remains unsolved. The different overlapping axes of Hippo, mTor, PI3K, and LKB1–AMPK would seem to hold all or part of the answer. The plasticity of cancer risk, metabolism, fertility, nutrition, and the evolution of molecular pathway configuration may all be causally interrelated. Much remains to be discovered but future research in this area may reveal a solution as elegant as the species that pose the problem.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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