The Critical Connection Between Protein, Cancer, Aging and TOR

Ron Rosedale M.D.

The Answer First...

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Your health and likely your lifespan will be determined by the proportion of fat versus sugar you burn over a lifetime

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...and that will be determined by the communication of nutrient sensors

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...you should eat today to control the sensors that will tell your cells what they will need to eat tomorrow

Evolution of Life in Reverse

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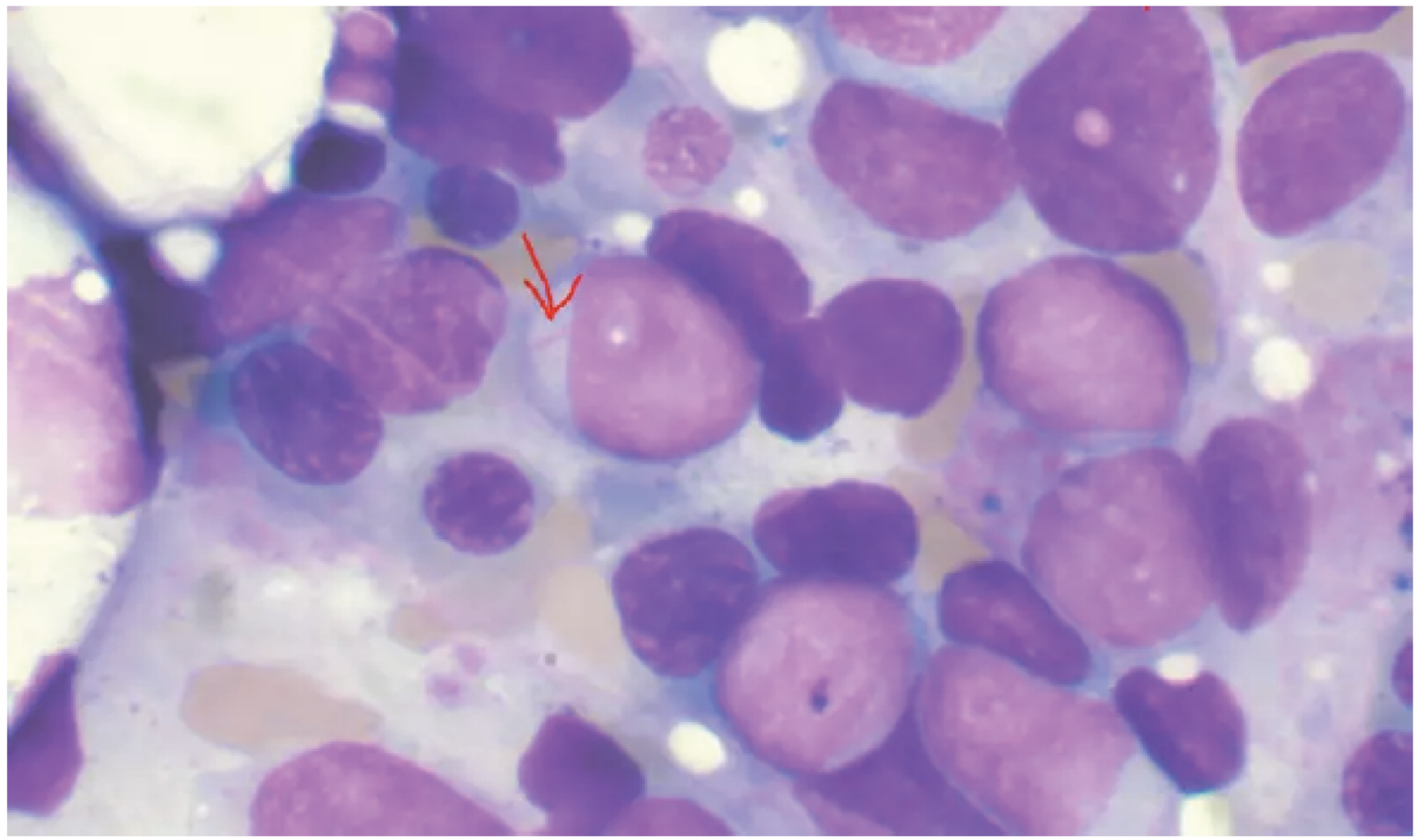
Is Cancer A Genetic Disease,
caused by the accumulation of 2-3 oncogenetic mutations?

Medical Xpress

Landmark study shows Acute Myeloid Leukaemia is at least 11 different diseases

June 8, 2016 in Medicine & Health / Cancer



"…most patients had a unique combination of genetic changes driving their leukaemia."

Study unmasks the genetic complexity of cancer cells within the same tumor

December 28, 2016

"A new study led by Cedars-Sinai investigators dramatically illustrates the complexity of cancer by identifying more than 2,000 genetic mutations in tissue samples of esophageal tumors. The findings reveal that even different areas of individual tumors have various genetic patterns."

Is Cancer A Metabolic Disease?

Otto Warburg
"The Warburg Effect"

Cancer relies on glucose, aerobic glycolysis for fuel
(due to mitochondrial failure)

Not

"The most useful piece of learning for the uses of life is to unlearn what is untrue." Antisthenes

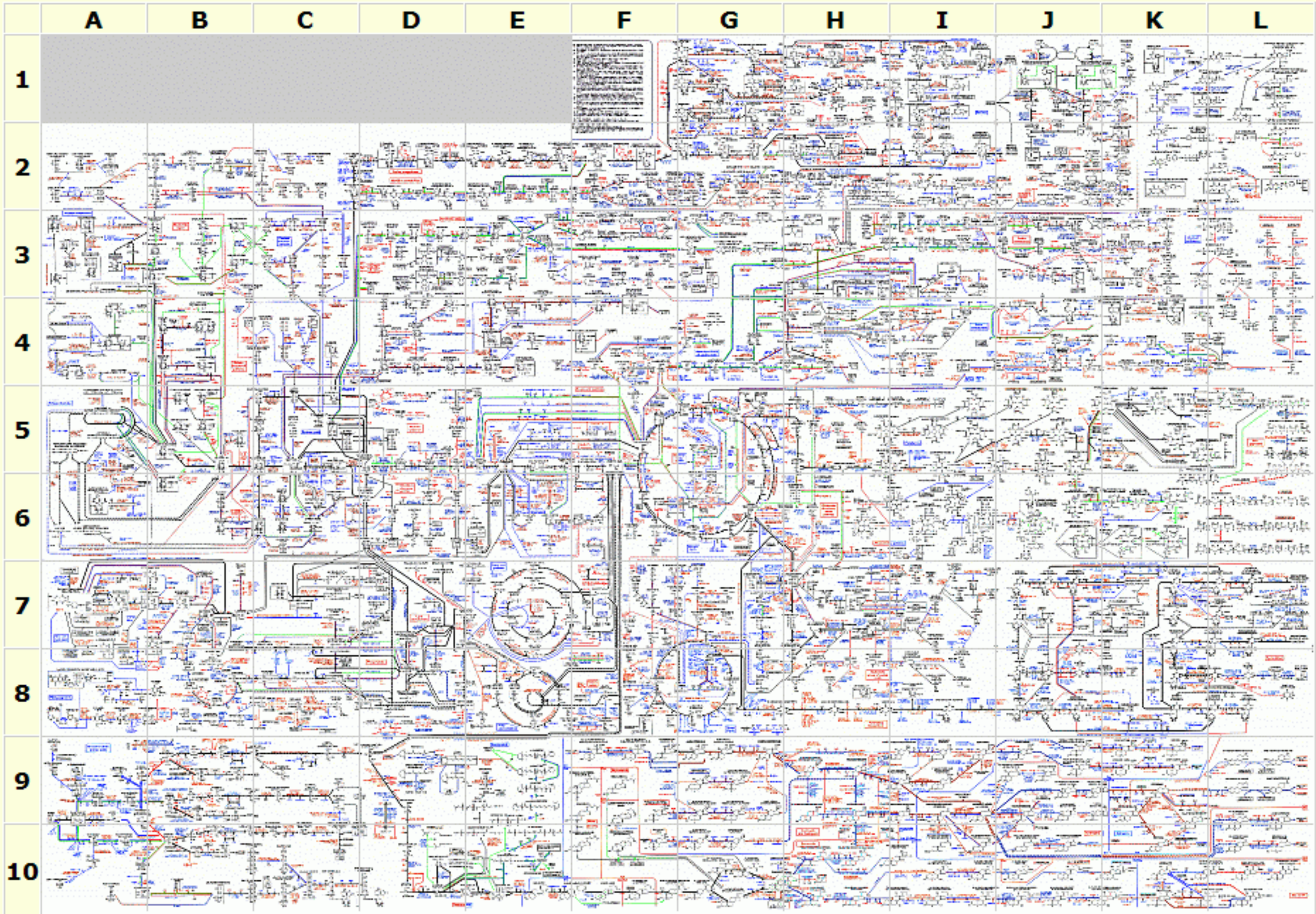
"Our ability to open the future will depend not on how well we learn but on how well we are able to unlearn".

—Alan Kay

Cancer Is Not Just A Glucose Disease

Just Like;
Diabetes is Not A Disease Of Glucose
Coronary Disease Is Not A Disease Of Cholesterol
Osteoporosis Is Not A Disease Of Calcium

That Ignores The Communication In Between



What About Insulin, Jan,1995

Ron Rosedale M.D.

Hyperinsulinemia adversely effects most degenerative diseases:

- CAD
- HTN
- CANCER
- STROKE
- DIABETES
- OBESITY
- AUTOIMMUNE DISORDERS
- MENTAL DISEASE AND DECLINE

"Insulin and its Metabolic Effects"

Boulderfest, 1999 Ron Rosedale M.D.

"Insulin increases cellular proliferation.
What does that do to cancer? It increases it."

Tele-Clinic with Joe Mercola

Ron Rosedale M.D. 2005

"Two of the major factors that will determine whether a person has cancer are the amount of sugar and insulin…Sugar is just listening to orders. It's listening to orders from insulin and leptin. You get insulin and leptin right, your sugar's going to be right. However, the converse is not necessarily true. You can bring down sugar with drugs, but you're not really improving that person's health if it's causing insulin and leptin to increase. All you're going to do is increase your risk of cancer."

Metabolic reprogramming in cancer: Unraveling the role of glutamine in tumorigenesis

Seminars in Cell & Developmental Biology 23 (2012) 362– 369, Dania Daye, Kathryn E. Wellen

a b s t r a c t
Increased glutaminolysis is now recognized as a key feature of the metabolic profile of cancer cells,

"Increased glutaminolysis is now recognized as a key feature of the metabolic profile of cancer cells…and cells coordinate glucose and glutamine as nutrient sources"

Simple Sugar, Lactate, Is Like 'Candy for Cancer Cells': Cancer Cells Accelerate Aging and Inflammation in the Body to Drive Tumor Growth

ScienceDaily (May 28, 2011) — Researchers at the Kimmel Cancer Center at Jefferson have shed new light on the longstanding conundrum about what makes a tumor grow -- and how to make it stop. Interestingly, cancer cells accelerate the aging of nearby connective tissue cells to cause inflammation,

> "The researchers see that lactate is like 'candy' for cancer cells. And cancer cells are addicted to this supply of 'candy.'"

Lisanti, M.D., Ph.D., Professor and Chair of Stem Cell Biology & Regenerative Medicine at Jefferson Medical College of Thomas Jefferson University and a member of the Kimmel Cancer Center. "What we found is that cancer cells are accelerating aging and inflammation, which is making high-energy nutrients to feed cancer cells."

In normal aging, DNA is damaged and the body begins to deteriorate because of oxidative stress. "We are all slowly rusting, like the Tin-man in the Wizard of Oz," Dr. Lisanti said. "And there is a very similar process going on in the tumor's local environment." Interestingly, cancer cells induce "oxidative stress," the rusting process, in normal connective tissue, in order to extract vital nutrients.

Dr. Lisanti and his team previously discovered that cancer cells induce this type of stress response (autophagy) in nearby cells, to feed themselves and grow. However, the mechanism by which the cancer cells induce this stress and, more importantly, the relationship between the connective tissue and how this "energy" is transferred was unclear.

"Nobody fully understands the link between aging and cancer," said Dr. Lisanti, who used pre-clinical models, as well as tumors from breast cancer patients, to study these mechanisms. "What we see now is that as you age, your whole body becomes more sensitive to this parasitic cancer mechanism, and the cancer cells selectively accelerate the aging process via inflammation in the connective tissue."

This helps explain why cancers exist in people of all ages, but susceptibility increases as you age. If aggressive enough, cancer cells can induce accelerated aging in the tumor, regardless of age, to speed up the process.

Lactate metabolism is associated with mammalian mitochondria

Nature Chemical Biology, 12 September 2016

Abstract;
It is well established that lactate secreted by fermenting cells can be oxidized or used as a gl he fe e the p ce ze a large percentage of their lipids. Using high-resolution mass spectrometry, we found that both 13C and 2-2H labels from enriched lactate enter the mitochondria. The lactate dehydrogenase (LDH) inhibitor oxamate decreased respiration of isolated mitochondria incubated in lactate, but not of isolated mitochondria incubated in pyruvate. Additionally, transmission electron microscopy (TEM) showed that LDHB localizes to the mitochondria. Taken together, our results demonstrate a link between lactate metabolism and the mitochondria of fermenting mammalian cells.

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Ketone body utilization drives tumor growth and metastasis

Cell Cycle 11:21, 3964–3971; November 1, 2012

We have previously proposed that catabolic fibroblasts generate mitochondrial fuels (such as ketone bodies) to promote the anabolic growth of human cancer cells and their metastasic dissemination. We have termed this new paradigm "two-compartment tumor metabolism." Here, we further tested this hypothesis by using a genetic approach. For this purpose, we generated hTERT-immortalized fibroblasts overexpressing the rate-limiting enzymes that promote ketone body production, namely BDH1 and HMGCS2. Similarly, we generated MDA-MB-231 human breast cancer cells overexpressing the key enzyme(s) that allow ketone body re-utilization, OXCT1/2 and ACAT1/2. Interestingly, our results directly show that ketogenic fibroblasts are catabolic and undergo autophagy, with a loss of caveolin-1 (Cav-1) protein expression. Moreover, ketogenic fibroblasts increase the mitochondrial mass and growth of adjacent breast cancer cells. However, most importantly, ketogenic fibroblasts also effectively promote tumor growth, without a significant increase in tumor angiogenesis. Finally, MDA-MB-231 cells overexpressing the enzyme(s) required for ketone re-utilization show dramatic increases in tumor growth and metastatic capacity. Our data provide the necessary genetic evidence that ketone body production and re-utilization drive tumor progression and metastasis. As such, ketone inhibitors should be designed as novel therapeutics to effectively treat advanced cancer patients, with tumor recurrence and metastatic disease. In summary, ketone bodies behave as onco-metabolites, and we directly show that the enzymes HMGCS2, ACAT1/2 and OXCT1/2 are bona fide metabolic oncogenes.

Hepatocellular carcinoma redirects to ketolysis for progression under nutrition deprivation stress

Cell Research (2016) :1-19, De Huang

Abstract;
Cancer cells are known for their capacity to rewire metabolic pathways to support survival and proliferation under various stress conditions. Ketone bodies, though

"…nutrition-deprived HCC cells employ ketone bodies for energy supply and cancer progression."

adult liver tissues, is re-induced by serum starvation-triggered mTORC2-AKT-SP1 signaling in HCC cells. Moreover, we observe that enhanced ketolysis in HCC is critical for repression of AMPK activation and protects HCC cells from excessive autophagy, thereby enhancing tumor growth. Importantly, analysis of clinical HCC samples reveals that increased OXCT1 expression predicts higher patient mortality. Taken together, we uncover here a novel metabolic adaptation by which nutrition-deprived HCC cells employ ketone bodies for energy supply and cancer progression.

PHD3 Loss in Cancer Enables Metabolic Reliance on Fatty Acid Oxidation

Harvard Medical School, Molecular Cell 63, 1006–1020, September 15, 2016

SUMMARY

While much research has examined the use of glucose and glutamine by tumor cells, many cancers instead prefer to metabolize fats. Despite the

"While much research has examined the use of glucose and glutamine by tumor cells, many cancers instead prefer to metabolize fats. Despite the pervasiveness of this phenotype, knowledge of pathways that drive fatty acid oxidation in cancer is limited."

of acetyl-coA carboxylase 2 (ACC2). We find that PHD3 expression is strongly decreased in subsets of cancer including acute myeloid leukemia (AML) and is linked to a reliance on fat catabolism regardless of external nutrient cues. Overexpressing PHD3 limits FAO via regulation of ACC2 and consequently impedes leukemia cell proliferation. Thus, loss of PHD3 enables greater utilization of fatty acids but may also serve as a metabolic and therapeutic liability by indicating cancer cell susceptibility to FAO inhibition.

Mitochondrial dysfunction and longevity in animals: Untangling the knot

Ying Wang and Siegfried Hekimi
SCIENCE; 4 DECEMBER 2015 • VO L 350

Mitochondria generate adenosine 5′-triphosphate (ATP) and are a source of potentially toxic reactive oxygen species (ROS). It has been suggested that the gradual mitochondrial dysfunction that is observed to accompany aging could in fact be causal to the aging process. Here **we review findings that suggest that age-dependent mitochondrial dysfunction is not sufficient to limit life span. Furthermore, mitochondrial ROS are not always deleterious and can even stimulate pro-longevity pathways.** Thus, mitochondrial dysfunction plays a complex role in regulating longevity.

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nd

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> the "mutator" mouse. In these mice, the proofreading function of the mtDNA polymerase gamma (Polg) is defective…Heterozygous mutator mice are born with a [mitochondrial] mutation burden 30 times higher than that of aged wild-type mice, yet they lack overt phenotypes and have a normal life span. This calls into question whether the naturally occurring slow accumulation of age-related mtDNA mutations has a leading role in causing aging, rather than representing only one of the types of damage accumulation that accompany aging.

Cancer is not due to type of fuel
Cancer is not due to mitochondrial dysfunction

Then What?

Growth Factors

Peer Reviewed

Caloric Restriction, Slowing Aging, and Extending Life

Science 26 February 2003

Edward J. Masoro

sageke.sciencemag.org/cgi/content/full/sageke;2003/8

"...mice with pituitary glands devoid of growth hormone-producing cells exhibit a markedly extended life-span as do genetically engineered mice with a targeted disruption of the growth hormone receptor, which results in low concentrations of plasma IGF-1 (50, Bartke)."

Introduction

In an article entitled "The History of Gerontology," Jim Birren

duced food intake on aging and longevity in rats (*4*, *5*). They blunted the growth of one group of female rats by decreasing their food intake over the period from 45 days of age to 6

Gerontologists have used an increase in the maximum length of life of a population (or preferably, maximal length of life, defined as the mean age at death of the 10th-percentile survivors) as an indicator of the slowing of aging. Lowering the environmental temperature of several poikilothermic species and restricting the caloric intake of several poikilothermic and homeothermic species have been found to increase the maximal length of life of these species (*2*). There are claims that other environmental manipulations and the administration of a variety of chemical agents increase the maximal length of life, but none of these exhibit a consistently observed robust effect. Indeed, only caloric restriction has resulted in a consistent robust increase in the maximal length of life in mammalian species, specifically rats and mice.

Before 1930

In 1914, Francis Peyton Rous (who was to receive a Nobel Prize in 1966 for his work on cancer) published a paper in the *Journal of Experimental Medicine* that showed that reducing food intake inhibited the occurrence of spontaneous tumors in rodents (*3*). Although this paper did not directly address the effects of caloric restriction on longevity and aging, it was the first in a long line of reports showing that decreasing food intake retards carcinogenesis. Moreover, because the onset of most cancers is age-associated, many of those reports have ad-

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ciates (*7*) showed that feeding a low-protein diet slowed the growth rate of brook trout and increased their longevity. This group of Cornell nutritionists was well aware of the discrepancy in the literature in regard to the relationship between growth rate and longevity in rodents, and they decided to explore the issue further, a decision that resulted in their classic research on caloric restriction.

1930s Studies of McCay and Colleagues

In their first study, begun in 1930, they used three groups of weanling rats (*8*). One group, fed ad libitum, grew to maturity at what the investigators felt to be a normal rate. Food intake was restricted for the other two groups, so that no growth occurred until death seemed imminent, whereupon the allotment of food was increased just enough to keep the rats alive. Thus, the rats on the restricted food intake underwent long periods of no growth interspersed with periods of growth. One of the two groups was kept on the restricted diet for 700 days and the other for 900 days. The rats that grew normally had a mean length of life of about 600 days, but many of the rats in the two restricted groups lived much longer than that.

The first study of McCay and associates had involved the restriction of all components of the diet. In a subsequent study (*9*), the intake of fat and carbohydrate was restricted but not that of protein, minerals, and vitamins. Again, the group of rats on the restricted rations lived much longer.

McCay and colleagues concluded that the longer length of life of rats on the restricted diets was due to the decreased rate of growth. However, it should be noted that such a conclusion

The role of insulin and IGF-1 signaling in longevity

* Cell. Mol. Life Sci. 62 (2005) 320–343

M. Katic and C. R. Kahn

Joslin Diabetes Center and Department of Medicine Harvard Medical School, One Joslin Place, Boston, Massachusetts 02215 (USA), e-mail:

…common and consistent effects of calorie restriction in rodents and nonhuman primates include… lower circulating insulin and IGF-1 concentrations, increased insulin sensitivity, lower body temperature, lower fat-free mass, decreased levels of thyroid hormones

Abstract

especial… …mily in a complex interaction to influence lifespan.

Insulin and IGF-1 initiate their action via highly homologous signaling systems…

Key …tione; thior… …s; *D. melanogaster;* mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.

Introduction

What is aging? Why do we age? Why do some species live longer than the others? Do genes determine lifespan? What is the role of metabolism on longevity? These are some of the questions that have intrigued biologists for ages.

Social scientists have raised other considerations: Do we want to live longer? And if so, how much longer? Is in-creasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolutionary processes? How do we balance quality of life with quantity of life?

These two perspectives of aging and longevity are certainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evolutionary forces that may interact with the biology. In this review, we will focus on the biology of aging, and try to answer some of the first group of questions. We will fo- cus especially on the role of metabolism and insulin and

* Corresponding author.

insulin-like growth factor-1 (IGF-1) signaling in this process.

What is aging?

Aging is a progressive loss of physiological functions that increases the probability of death. This decline in function occurs both within individual cells and within the organism as a whole. Life expectancy (or average lifespan) depends highly on both the biology of aging and the life circumstances of the organism.

Evolutionarily speaking, very few organisms or animals were allowed to age, since mortality from starvation, predators, infection, diseases or environmental stresses often resulted in death before the biology of aging could play a role. Even human aging has become common in only the past few centuries. Two hundred years ago average lifespan was about 24 years due to high infant mortality, poor hygiene and inability to treat infectious disease [1, 2]. Now, with the development of good principles of hygiene, a wide range of effective

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Insulin and IGF-1 initiate their action via highly homologous signaling systems…

In conclusion, strong similarities exist between insulin and IGF-1 signaling systems in yeast, worms, flies, mammals and humans…Such similarities suggest that the insulin/IGF-1 system arose early in evolution and that it is a central component of an anti-aging system, which is conserved from yeast to humans.

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Study: Dwarfism Gene May Offer Protection From Cancer, Diabetes

PBS HEALTH -- **February 16, 2011**

Dr. Jaime Guevara-Aguirre, with members of an Ecuadorian family with Laron syndrome (photo courtesy Dr. Jaime Guevara-Aguirre)

Study: Dwarfism Gene May Offer Protection From Cancer, Diabetes

PBS HEALTH -- **February 16, 2011**

From Science Translational Medicine

…in yeast, worms and mice restricting growth hormone makes those creatures live longer. Guevara-Aguirre had diagnosed the family members with Laron syndrome, a rare syndrome caused by a gene mutation. Over the course of his years with the family members, Guevara-Aguirre noticed that the people with Laron syndrome almost completely avoided cancer and diabetes. It could be because cells must invest energy in either trying to grow and reproduce, or in protection. In nature, dwarf models live longer. Ponies live longer than horses, small dogs live longer than large dogs. It's a very fascinating field in aging.' "

'Un-Growth Hormone' Increases Longevity, Researchers Find

Proceedings of the National Academy of Sciences Dec. 6, 2010
From ScienceDaily (Dec. 23, 2010) — A compound which acts in the opposite way as growth hormone can reverse some of the signs of aging, a research team that includes a Saint Louis University physician has shown. The

"A compound which acts in the opposite way as growth hormone can reverse some of the signs of aging, a research team that includes shown…like many GHRH antagonists, [it] inhibited several human cancers, including prostate, breast, brain and lung cancers."

The findings are significant, says John E. Morley, M.D., study co-investigator and director of the divisions of geriatric medicine and endocrinology at Saint Louis University School of Medicine, because people sometimes take growth hormone, believing it will be the fountain of youth.

"Many older people have been taking growth hormone to rejuvenate themselves," Morley said. "These results strongly suggest that growth hormone, when given to middle aged and older people, may be hazardous."

Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans

Aging Cell. 2008 October ; 7(5): 681–687.

Luigi Fontana John O. Holloszy

Summary
Reduced function mutations in the insulin/IGF-I signaling pathway increase maximal lifespan and that reduced protein intake may become an important component of anticancer and anti-aging dietary interventions.

"our data provide evidence that protein intake is a key determinant of circulating IGF-1 levels in humans, and suggest that reduced protein intake may become an important component of anticancer and anti-aging dietary interventions."

Keywords
aging; calorie restriction; IGF-1; metabolism; protein restriction

Introduction

In the last few decades, large amounts of money and research effort have been, and continue to be, devoted to the study of the anti-aging and anticancer mechanisms underlying calorie restriction (CR) in yeast, worms, insects and rodents. Presumably this expenditure of funds and research effort is motivated by the belief that the data obtained in various short-lived species showing that CR improves health and slows aging has relevance to humans. To date, several studies have consistently shown that long-term CR without malnutrition and reduced function mutations in the insulin/IGF-1 signaling pathway are the most robust interventions known to

Correspondence, Luigi Fontana, Washington University School of Medicine, Campus Box 8113, 4566 Scott Avenue, St. Louis, MO

Insulin analogues and cancer risk: cause for concern or cause ce´le`bre?

Int J Clin Pract, April 2010, 64, 5, 628–636

M. Pollak, D. Russell-Jones

SUMMARY

People with diabetes, particularly those with type 2 diabetes, may be at an increased risk of cancer. Furthermore, their cancer risk may be modified by treatment

findings, suggesting that there could be different relative risks for cancer associated with different insulins, although these studies have attracted some methodological criticism. However, it is biologically plausible that hormonal factors that influence neoplasia could begin to manifest their effects in surprisingly short timescales (within 2 years) and hence these epidemiological studies justify further research. Even if future research were to document an increase in cancer risk among insulin users, this would be unlikely to significantly diminish the favourable benefit-risk ratio for patients requiring insulin therapy. There is a need for further population studies and for the development of new laboratory models that are more sophisticated than previous experimental methods employed to assess potential tumour growth-promoting properties of insulin

"..insulin and insulin analogues can function as growth factors and therefore have theoretical potential to promote tumour proliferation. Some recent epidemiological studies appear to be consistent with these experimental findings."

Leptin

Vol 443|21 September 2006|doi:10.1038/nature05026 nature

Vol 4431:21 September 2006: nature

Central nervous system control of food intake and body weight

G. J. Morton[1], D. E. Cummings[2], D. G. Baskin[2,3], G. S. Barsh[4] & M. W. Schwartz[1]

has provided an insight into the molecular, cellular and behavioural mechanisms that link changes of body fat stores to adaptive adjustments of feeding behaviour. The physiological importance of this homeostatic control system is

"...genetic and pharmacological studies suggest a more critical role for leptin than insulin in mammalian energy homeostasis"

environmental constituents. Using taste information, the food's palatability is then assessed and integrated with both short- and long-term signals regarding nutritional state. One consequence of this integration is that the drive to eat decreases as food is ingested (termed 'satiation'), ensuring that the amount consumed in a single meal does not exceed what the body can safely handle. Changing energy requirements is another factor that can influence food consumption. Through a process known as energy homeostasis, food intake is adjusted over time so as to promote stability in the amount of body fuel stored as fat. In this way, through diverse blood-borne and afferent neural signals, information regarding nutrient status and energy stores is communicated to the brain where it is integrated with cognitive, visual, olfactory and taste cues—all happening unconsciously, before the first bite is taken.

Here we describe CNS mechanisms that regulate food intake, and review evidence that in response to reduced body fat stores, adaptive changes occur in neuronal systems governing both food-seeking behaviour (important for meal initiation) and satiety perception (important for meal termination). The net effect is that in response to weight loss, both the motivation to find food and the size of individual meals tend to increase until energy stores are replenished (Fig. 1), and mutation of any of several key molecules involved in this process has been shown to cause severe obesity in both animal models and humans. Despite this progress, the many fundamental questions remaining unanswered represent rich opportunities for future study.

Energy homeostasis

Obesity, by definition, results from ingesting calories in excess of ongoing requirements. Although environmental and lifestyle factors contribute to obesity pathogenesis, homeostatic adaptations to weight loss induced by voluntary caloric restriction are robust in both lean and obese individuals. In addition, normal-weight individuals are protected against expansion of body fat stores induced by

contribute to common forms of obesity and, hence, the global obesity pandemic.

Adiposity negative feedback. Introduced more than 50 years ago, the 'adiposity negative-feedback' model of energy homeostasis is founded on the premise that circulating signals inform the brain of changes in body fat mass and that in response to this input, the brain mounts adaptive adjustments of energy balance to stabilize fat stores[1]. Proposed criteria for a negative-feedback signal include: (1) that it circulates at levels proportionate to body fat content and enters the brain; (2) that it promotes weight loss by acting on neuronal systems implicated in energy homeostasis; and (3) that blockade of these neuronal actions increases food intake and body weight. Although many nutrients (for example, free fatty acids and glucose), cytokines (for example, interleukin-6, tumour necrosis factor-α) and hormones (for example, glucocorticoids) fulfill some of these criteria, only leptin and insulin satisfy all of them[4].

Studies in primitive organisms such as the nematode, *Caenorhabditis elegans*, and the fruitfly, *Drosophila melanogaster*, implicate insulin as a key ancestral negative-feedback regulator of body fuel stores[5,6]. By comparison, leptin has not been detected in invertebrates and probably evolved more recently[7]. Although genetic and pharmacological studies[8,9] suggest a more critical role for leptin than insulin in mammalian energy homeostasis, cross-talk between these hormones with respect to both the neuronal subsets and signal transduction pathways on which they act offers evidence of their shared evolutionary past.

Although leptin administration causes weight loss in diverse mammalian species, enthusiasm surrounding leptin as a therapeutic agent diminished rapidly with the discovery that leptin resistance is common among obese individuals[10]. Because obesity has long been associated with insulin resistance in peripheral tissues, it is perhaps not surprising that in obese rats, the hypothalamus develops resistance to insulin[11] as well as leptin[12]. Although reduced neuronal signalling by either hormone induces hyperphagia and weight gain

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The role of leptin in leptin resistance and obesity.

Physiol Behav, 88(3): 249-56 2006

Zhang Y , Scarpace PJ

Physiol Behav, 88(3): 249-56 2006

Abstract:

Although the presence of hyperleptinemia with leptin resistance and signaling capacity; and (3) leptin resistance confers increased susceptibility to diet-induced obesity. In essence, the augmented leptin accompanying obesity contributes to leptin resistance, and this leptin resistance promotes further obesity, leading to a vicious cycle of escalating metabolic devastation.

"chronically elevated central leptin decreases hypothalamic leptin receptor expression and (receptor) protein levels and impairs leptin signaling...In essence, the augmented leptin accompanying obesity contributes to leptin resistance, and this leptin resistance promotes further obesity, leading to a vicious cycle of escalating metabolic devastation."

Language:

Leptin regulates proinflammatory immune responses

FASEB 12 January 98

S. LOFFREDA, S. Q. YANG, H. Z. LIN, C. L. KARP, M. L. BRENGMAN, D. J. WANG, A. S. KLEIN, G. B. BULKLEY, C. BAO, P. W. NOBLE, M. D. LANE, A. M. DIEHL

*Departments of Medicine, †Molecular Microbiology and Immunology, ‡Surgery, and §Biological Chemistry, Johns Hopkins University,

"These results identify an important and novel function for leptin: up-regulation of inflammatory immune responses, which may provide a common pathogenetic mechanism that contributes to several of the major complications of obesity."

leptin receptors revealed obesity-related deficits in macrophage phagocytosis and the expression of proinflammatory cytokines both in vivo and in vitro. Exogenous leptin up-regulated both phagocytosis and the production of proinflammatory cytokines. These results identify an important and novel function for leptin: up-regulation of inflammatory immune responses, which may provide a common pathogenetic mechanism that con-tributes to several of the major complications of obesity.—Loffreda, S., Yang, S. Q., Lin, H. Z., Karp, C. L., Brengman, M. L., Wang, D. J., Klein, A. S., Bulkley, G. B., Bao, C., Noble, P. W., Lane, M. D., Diehl, A. M. Leptin regulates proinflammatory immune responses. *FASEBJ.* 12, 57–65 (1998)

Key Words: obesitymacrophagecytokine phagocyticfunctionTNFlipopolysaccharide

LEPTIN, THE PROTEIN ENCODED by the ob gene, is known to regulate appetite and energy expenditure. Obese/obese (ob/ob) mice, homozygous for a spontaneous mutation in the ob gene, fail to produce leptin and exhibit hyperphagia and obesity. Treatment of such mice with recombinant leptin results in de-creased food intake and weight loss (1–3). It is not known whether leptin deficiency per se explains other aspects of the ob/ob phenotype, such as diabetes and hyperlipidemia. Recently, ectopic expression of tumor necrosis factor alpha (TNF-a)2 was documented in adipose tissues of obese rodents and humans (4, 5) and implicated in the pathogenesis of

Obesity may accelerate the ageing process

From The Lancet

14 June 2005

Rowan Hooper

Obesity accelerates the ageing process even more than smoking, according to the largest ever study of the "chromosomal clock" in human cells.

Tim Spector of St Thomas' Hospital in London, UK, measured the length of the ends of chromosomes, called telomeres, in the white blood cells of 1122 women aged 18 to 76.

Each time a cell divides, its telomere loses a small chunk of DNA. When it becomes too short, cells can no longer divide. In effect, telomere shortening acts as a kind of chromosomal clock, counting down the cellular generations.

S[illegible]base p[illegible] W[illegible] a[illegible] I[illegible]an appetite-inhibiting hormone, but obese people are resistant to it and have higher than normal levels.

> "Intriguingly, the link between high leptin concentrations and telomere shortening was even stronger than the link with obesity"

Fat smokers

Smoking was the other big factor. "Smokers were on average biologically older than lifetime non-smokers by 4.6 years," Spector says. "For a heavy smoker on 20 cigarettes a day for 40 years, that equals 7.4 years of extra biological ageing."

And there is a synergistic effect. "Fat smokers are at the highest risk of all. An obese smoker is on average at least 10 years older than a lean non-smoker," says Spector. "It's not just about heart disease or lung cancer, the whole chromosomal clock is going faster. That's the public health message."

And the effects appear to be permanent. Quitting smoking or losing weight reduces the rate of telomere loss but cannot restore them.

The damage to telomeres is probably done by free radicals. Smoking causes oxidative stress - a source of free radicals - as does obesity, says Abraham Aviv of the University of Medicine and Dentistry of New Jersey, US. Free radicals can cause mutations in DNA, and there is some evidence that mutations in telomeres cause larger chunks than normal to be lost during cell division.

"Telomere age difference"

But the findings do not necessarily prove that, say, obese people will die nearly nine years early. For one thing, Spector looked only at white blood cells, and it remains to be seen if obesity and smoking have as dramatic an effect on other tissues.

For another, while the link between telomere length and cell division is well established, the effect of shortened telomeres on the overall lifespan of organisms composed of trillions of cells is less clear. Men do have shorter telomeres than women, and intriguingly the "telomere age difference" of about seven years is about the same as the length of time women live longer than men.

But animal studies have failed to reveal any simple relationship between telomere length and lifespan. Some studies suggest that the rate of loss may be the most important factor, others that the crucial factor is not telomere length per se but a protein cap found on telomeres. It could even be that shortened telomeres are merely a sign of how much free radical damage cells have suffered, rather than a direct cause of ageing.

Spector now plans to look at the effect of other lifestyle factors on telomere length, such as exercise, diet and occupation.

Journal reference: *The Lancet* (DOI: 10.1016/S0140-6736(05)66630-5)
Printed on Thu Aug 18 15:05:18 BST 2005

Obesity Linked To Aggressive Prostate Cancer

American Society Of Clinical Oncology :2003-12-24

Obese men with prostate cancer are more likely to have aggressive tumors and to experience cancer recurrence after surgery compared to men of normal weight or those who are overweight but not obese, according to two new studies. Although more research is needed, the findings suggest that men may be able to modify their risk of aggressive prostate

"Proteins and hormones stored in body fat – such as leptin and insulin-like growth factor-1 may promote prostate tumor growth in obese men."

Both Drs. Amling and Freedland suggest that proteins and hormones stored in body fat – such as leptin and insulin-like growth factor-1 – may promote prostate tumor growth in obese men. Also, obese men typically have lower testosterone levels and higher estrogen levels, which may encourage the growth of cancer.

Both studies examined the relationship between obesity and prostate cancer recurrence in large samples of men with localized prostate cancer who had undergone surgery to remove the prostate – a procedure called radical prostatectomy. While obesity rates in the general adult population are similar between African-American and Caucasian men, both studies found that obese patients in the study groups were more likely to be African American. This finding may help explain why African-American men with prostate cancer generally have more aggressive tumors and worse outcomes compared to Caucasians.

"We suspect that worse outcomes among African-American men with prostate cancer are related to obesity rather than race. If we can target obesity in the African-American community, we may be able to reduce the burden of prostate cancer among black men,"

PPARa activators may be good candidates as antiaging agents

Medical Hypotheses (2005)

Adnan Erol *
Silivri City Hospital, Internal medicine, Ali Cetinkaya Cad, 34930 Silivri, Istanbul, Turkey

Received 26 January 2005; accepted 27 January 2005

Summary

Aging is associated with a metabolic decline characterized by the development of changes in fat distribution, o

"… the cellular damage in aging is, at least in part, the result of FA excess secondary to leptin resistance. So, we may come to a conclusion that youth is a leptin-sensitive state, and that resistance to leptin occurs with aging."

me

in increased mortality. Leptin can modulate many of the metabolic alterations characteristic of aging. Leptin resis s of lipid ce to

"Leptin's failure may be considered for the metabolic decline seen with aging."

leptin action and may explain why elderly subjects have abdominal obesity and insulin resistance. Leptin's failure may be considered for the metabolic decline seen with aging. Peroxisome proliferator-activated receptor (PPAR)-a, the transcription factor for the mitochondrial and peroxisomal enzymes of b-oxidation, and its target enzymes, are upregulated by hyperleptinemia. PPARa has been shown to mediate the action of the hypolipidemic drugs of the fibrate class on lipid and lipoprotein metabolism. PPARa activators furthermore improve glucose homeostasis and influence body weight and energy homeostasis. The administration of agents capable of activating the PPARa was found to restore the cellular redox balance, evidenced by a lowering of tissue lipid peroxidation, an elimination of constitutively active NF-*j*B, loss in spontaneous inflammatory cytokine production, and ailing in the aging immunity.

Hormone levels and cataract scores as sex-specific, mid-life predictors of longevity in genetically heterogeneous mice.

Mech Ageing Dev 2003 Jul;124(7):801-10

Harper JM; Wolf N; Galecki AT; Pinkosky SL; Miller RA

Department of Pathology, School of Medicine, University of Michigan, Ann Arbor, MI, USA.

Serum levels of thyroxine (T4), **leptin**, and insulin-like growth factor I (IGF-I), as well as [illegible] heterogeneous mice (UM-HET3). Long **life span** was predicted by low levels of **leptin** at age 4 months in females, and by low levels of IGF-I at age 15 months and high levels of T4 at age 4 months, in males. Cataract severity at either 18 or 24 months was also a significant predictor of **life span** in females only, but in contrast to what has been reported in human studies, relatively severe cataract was correlated with longer **life span**. Additional work is needed to evaluate the role of these hormones as potential modulators of the aging process, and to resolve the conflicting data obtained for cataract severity as a predictor of **life span**.

"Long life span was predicted by low levels of leptin"

Regulation of Leptin Secretion from White Adipocytes by Insulin, Gycolytic Substrates, and Amino Acids

Am J Physiol Endocrinol Metab March 1, 2005

Philippe G. Cammisotto, Ludwig Bukowiecki

Université de Montréal 2900 Edouard Montpetit, R-822, C.P. 6128 Succ. Centre Ville, Montréal (Qué), Canada H3C

"amino acids precursors of citric acid cycle intermediates potently stimulate *per se* basal leptin secretion, insulin having an additive effect"

New drug to tackle fat problems

26 April 2012 News Release

"Leptin, the obesity hormone, is produced by fat and excess leptin predisposes overweight people to conditions such as multiple sclerosis, cancer and heart disease. 'Because we now know the precise atomic structure of the receptor we can begin to design drug molecules that can alter its activity.'"

receptor, and therefore the excessive actions of leptin, could prevent the complications of obesity and stimulating the receptor may improve fertility and the immune response. Professor Richard Ross, Professor of Endocrinology at the University of Sheffield said: "This pioneering research gives us the potential to generate new drugs that could treat conditions and diseases associated with obesity such as Multiple Sclerosis, diabetes and cardiovascular disease. "Modulating the actions of the obesity receptor provides a novel approach to the treatment of conditions associated with both obesity and anorexia and has the potential to make a massive difference to millions of people whose quality of life and health is hindered by obesity or malnutrition."

Protein...

Increases IGF-1

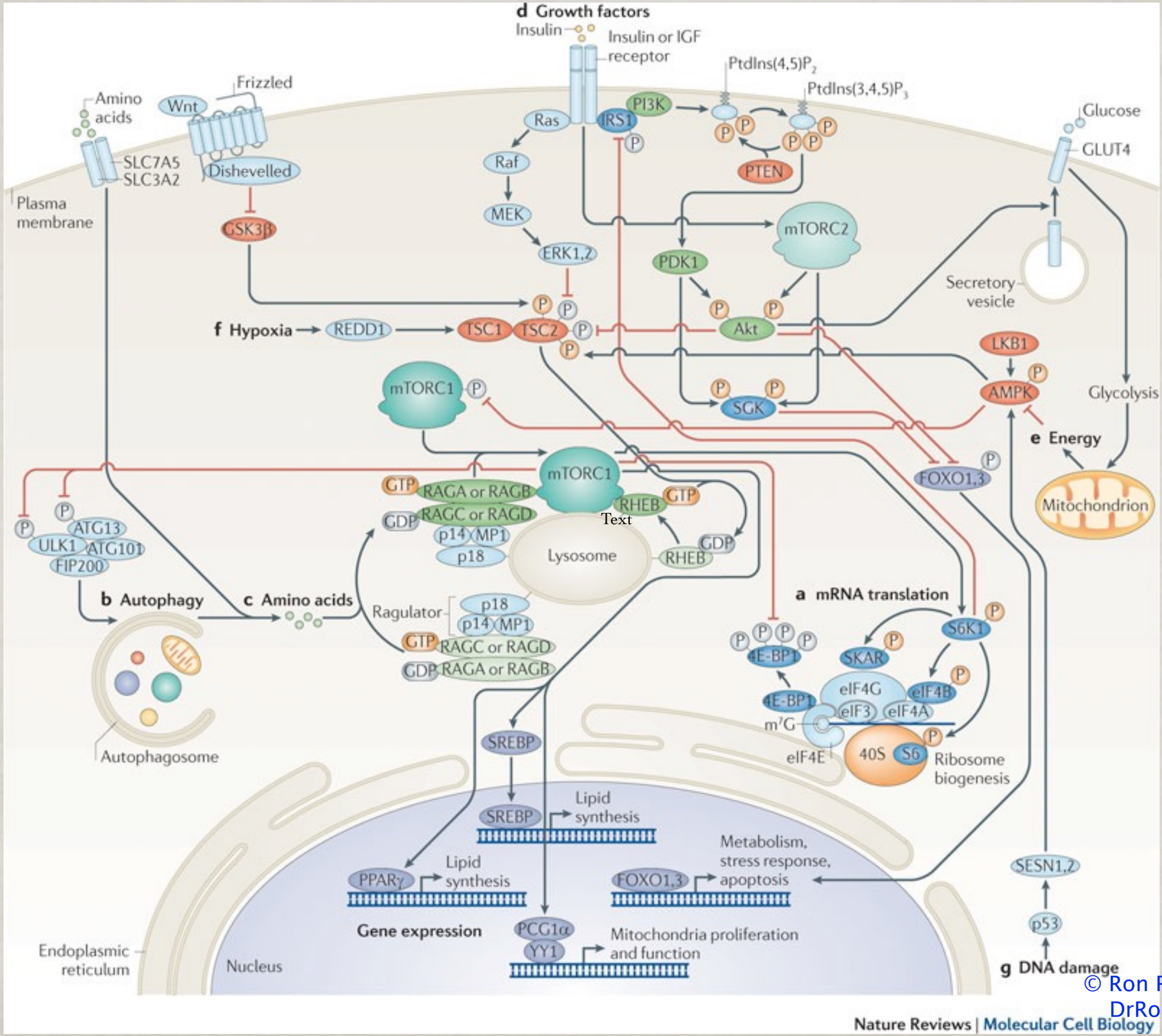
Increases Leptin

it appears that

High Protein Accelerates Aging

Reducing Protein Extends Life

mTOR



TOR signalling and control of cell growth

Professor Michael N. Hall
Winner of the 2009 Louis-Jeantet Prize for medicine

"TOR (Target of Rapamycin)...was originally discovered in [bacteria] but is conserved in all eukaryotes including plants, worms, flies and mammals. Mammalian TOR (mTOR) controls growth in response to nutrients (e.g., amino acids), growth factors (e.g., insulin, IGF-1)...As a central controller of cell growth and metabolism, TOR plays a key role in development and aging, and is implicated in many major diseases including cancer, cardiovascular disease, inflammatory disease, and metabolic disorders. Indeed,it has been calculated that mTOR is upregulated in 70% of all tumors."

TOR is found in two structurally and functionally distinct multiprotein complexes, TORC1 and TORC2 (mTORC1 and mTORC2 in mammals), each of which signals via a different set of effector pathways (figure 1). mTORC1 is composed of raptor, mLST8 and mTOR, and is sensitive to the immunosuppressive and anti-cancer drug rapamycin. Rapamycin, in complex with the intracellular protein FKBP12, binds and inhibits mTORC1 directly. mTORC2 consists of rictor, mSIN1, PRR5, mLST8 and mTOR, and is rapamycin insensitive. The best-characterized phosphorylation substrates of mTOR are S6K and 4E-BP1, via which mTORC1 controls protein synthesis, and Akt/PKB via which mTORC2 controls cell survival and other processes. Like TOR itself, the two TOR complexes and the overall architecture of the TOR signalling network are conserved from yeast to human. Thus, the two TOR complexes constitute an ancestral signalling network conserved throughout eukaryotic evolution to control the fundamental process of cell

PI3K/Akt/mTOR Pathway: The Main Cancer Breakthrough

John Kim on Wed, Jul 18, 2012
AG Scientific, Inc.

Activation of signal transduction pathways is a key mechanism to increase proliferation and survival, and inhibitors of specific kinases that are key components in signaling pathways are under intense investigation as cancer therapeutics. Perhaps the best studied pathway that promotes cellular survival and therapeutic resistance is the PI3K/Akt/mTOR pathway. It is activated by oncogenes such as ras or erbB2, receptor tyrosine kinases, G protein coupled

"Is PI3K/Akt/mTOR Pathway Important in Many Types of Cancer? Yes. …that pathway activation is one of the most common molecular alterations in human cancer."

Although pathway inhibitors that target individual components such as PI3K, PDK-1, Akt, and mTOR are being developed, mTOR inhibitors are the most mature. mTOR inhibitors include rapamycin, which is FDA-approved as an immunosuppressant, and analogues such as RAD001 and CCI779 that are in late phase clinical trials with cancer patients. mTOR inhibitors have been effective in preclinical models of lung tumorigenesis, breast tumorigenesis, and prostate tumorigenesis.

What do we do with PI3K/Akt/mTOR pathway for future?

Out of pathway inhibitors, mTOR inhibitors are most available, but what are the consequences of mTOR inhibition? Rapamycin is well tolerated at low doses given daily in transplant patients, but in light of possible immunosuppression in otherwise healthy people at risk for cancer, does this meet the high bar set for tolerability in the prevention setting? What is the optimal dosing regimen for prevention that maximizes effectiveness and minimizes toxicity? Would pulsatile vs. daily dosing reveal differences in efficacy or tolerability? A hypothetical disadvantage of mTOR inhibitors as single agents is possible feedback activation of Akt, which has been reported in in vitro studies. Although the study by Liu et al. and others demonstrated decreased Akt activation

mTOR coordinates protein synthesis,mitochondrial activity and proliferation

Cell Cycle 14:4, 473--480; February 15, 2015, Masahiro Morita

Abstract;
Protein synthesis is one of the most energy consuming processes in the cell. The mammalian/mechanistic target of rapamycin (mTOR) is a serine/threonine

..emerging studies indicate that mTOR modulates mitochondrial functions. In mammals, mTOR coordinates energy consumption… and mitochondrial energy production.

mTOR coordinates energy consumption by the mRNA translation machinery and

mTOR inhibits autophagy,
which is a process that can eliminate [damaged] mitochondria.

mTORC1 controls fasting-induced ketogenesis and its modulation by ageing

NATURE | VOL 468 | 23/30 DECEMBER 2010

"inhibition of mTORC1 is required for the fasting-induced activation of PPARa, the master transcriptional activator of ketogenic genes"

Amino acids mediate mTOR/raptor signaling through activation of class 3 phosphatidylinositol 3OH-kinase

14238–1424 PNAS October 4, 2005 vol. 102 no. 40

Takahiro Nobukuni Fried J. T. Zwartkruis

During the evolution of metazoans and the rise of systemic hormonal regulation, the insulin-controlled class 1 phosphatidylinositol 3OH-kinase (PI3K) pathway was merged with the primordial

class 1 PI3K. However, how the amino acid input is integrated with that of the insulin signaling pathway is unclear. Here we used a number of molecular, biochemical, and pharmacological approaches to address this issue. Unexpectedly, we found that a major pathway by which amino acids control mTOR signaling is distinct from that of insulin and that, instead of signaling through components of the insulin!class 1 PI3K pathway, amino acids mediate mTOR activation by signaling through class 3 PI3K,

"we found that a major pathway by which amino acids control mTOR signaling is distinct from that of insulin"

Unicellular eukaryotes use the mammalian target of rapamycin (mTOR)!raptor!G-protein-!-subunit-like protein (G!L) pathway in a cell-autonomous manner (1); however, with the rise of metazoans and humoral systems, the insulincontrolled PI3K signaling pathway was merged with the mTOR signaling pathway to maintain cellular homeostasis. The clinical importance of mTOR has been underscored by the use of rapamycin and its derivatives in a number of pathological settings, including organ transplantation, restenosis, rheumatoid arthritis, and more recently the treatment of solid tumors

AmJ Physiol Endocrinol Metab 284: E322–E330, 2003.
First published October 1, 2002; 10.1152/ajpendo.00230.2002.

Nutrient-sensing mTOR-mediated pathway regulates leptin production in isolated rat adipocytes

CECILIA ROH, JIANRONG HAN, ALEXANDROS TZATSOS, AND KONSTANTIN V. KANDROR
Boston University School of Medicine, Boston, Massachusetts 02118

tin production by these cells, suggesting that postprandial

tant to actinomycin D, and insulin administration does

"mTOR is activated by free amino acids"

secreted protein, its biosynthesis is compartmentalized on the endoplasmic reticulum. To analyze mTOR signaling in

a posttranscriptional level. Mammalian cells possess an important nutrient-sensing pathway that controls pro-

"We proposed that mTOR may be an appropriate nutrient sensor for leptin expression in adipose cells."

leptin mRNA is compartmentalized on the endoplasmic reticulum, and leucine activates translation of these messages via the mTOR/4E-BP/PHAS-I-mediated signaling pathway.

mammalian target of rapamycin

LEPTIN IS PRODUCED mainly by adipose cells and regulates food intake and whole body energy balance (36). Pursuant to this physiological role, circulating leptin levels rapidly increase after feeding (20) and decrease after food deprivation (9). Because leptin mRNA levels in adipose tissue also follow this pattern (3, 34), it has been generally accepted that leptin expression is controlled at the level of transcription (1). Although this

In agreement with this hypothesis, we found that addition of leucine to isolated rat adipocytes significantly stimulated leptin secretion in a rapamycin-sensitive and an actinomycin D-resistant fashion. Thus dietary leucine may increase leptin production via activation of mTOR and subsequent activation of leptin mRNA translation. This mechanism may provide a long-sought-after connection between food intake and leptin levels in blood.

MATERIALS AND METHODS

Antibodies. Affinity-purified polyclonal antibodies against phosphorylated S6 ($Ser^{235/236}$), p70 S6 kinase (Thr^{389}), and 4E-BP1/PHAS-I (Ser^{65}) were from Cell Signaling (Beverly,

Address for reprint requests and other correspondence: K. V. Kandror, Boston Univ. School of Medicine, Dept. of Biochemistry, K124D, 715 Albany St., Boston, MA 02118 (E-mail: kandror@biochem.bumc.bu.edu).

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Calories Do Not Explain Extension of Life Span by Dietary Restriction in Drosophila

PLOS Biology July 2005 | Volume 3 | Issue 7

William Mair, Matthew D. W. Piper, Linda Partridge
Centre for Research on Ageing, University College London, Department of Biology, London, United Kingdom

Dietary restriction (DR) extends life span in diverse organisms, including mammals, and common mechanisms may be at work. DR is often known as calorie restriction, because it has been suggested that reduction of calories, rather than of particular nutrients in th
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bu

"Reduction of either dietary yeast or sugar can reduce mortality and extend life span, but by an amount that is unrelated to the calorie content of the food, and with yeast having a much greater effect per calorie than does sugar [yeast is mostly protein]. Calorie intake is therefore not the key factor in the reduction of mortality rate by DR in this species."

Introduction

Dietary restriction (DR), the extension of life span by reduction of nutrient intake without malnutrition, is often used as a benchmark comparison for interventions that extend life span [1–3]. Since McCay's pioneering experiments in rats 70 years ago [4], some form of food restriction has been shown to increase life span in commonly used model organisms such as yeast [5,6], nematodes [7], fruit flies [8,9], and mice [10], along with many species less often used for laboratory research such as water fleas, spiders, fish (see [3] for review), and dogs [11]. Preliminary data also suggest that DR may extend life span in nonhuman primates [12,13] and potentially give health benefits in humans [14]. Despite the finding that restricting diet increases longevity in such a diversity of species, the mechanisms responsible remain to be fully elucidated in any of them. It is therefore as yet unclear whether these mechanisms are evolutionarily conserved across taxa or if instead life extension during DR is an example of convergent evolution.

The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice

Cell Metabolism 418–430, March 4, 2014

SUMMARY
The fundamental questions of what represents a macronutritionally balanced diet and how this
consequences are associated with hepatic mammalian target of rapamycin (mTOR) activation

Longevity and health were optimized when protein was replaced with carbohydrate to limit compensatory feeding for protein and suppress protein intake.

The results suggest that longevity can be extended in ad libitum-fed animals by manipulating the ratio of macronutrients to inhibit mTOR activation.

Resolving the effects of dietary macronutrients on aging and
health remains a fundamental challenge, with profound implica

The Tor Pathway Regulates Gene Expression by Linking Nutrient Sensing to Histone Acetylation

MOLECULAR AND CELLULAR BIOLOGY, Jan. 2003, p. 629–635 Vol. 23, No. 2

John R. Rohde and Maria E. Cardenas

Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, North Carolina 27710

Rap1 and Abf1. Genetic and biochemical evidence identifies Rpd3 as the major histone deacetylase responsible for reversing histone H4 acetylation at RP gene promoters in response to Tor inhibition by rapamycin or nutrient limitation. Our results illustrate that the Tor pathway links nutrient sensing with histone acetylation to control RP gene expression and cell growth.

"We therefore find it intriguing that, in mammalian cells, rapamycin treatment results in a gene expression profile that resembles one seen with amino acid limitation (32)."

such as sodium toxicity and carbon starvation (2, 4, 6, 9, 13, 19). In contrast, inhibition of Tor results in the rapid repression of genes involved in ribosome biogenesis, including tRNAs and rRNAs transcribed by Pol I and Pol III as well as ribosomal proteins expressed by Pol II (6, 25, 35, 49). Significant progress has been made in understanding how the genes that are induced by Tor inhibition are controlled. In these cases, under optimal nutrient conditions the Tor pathway prevents the nuclear import of the corresponding transcription factors, including Gln3, Gat1, Msn2, Msn4, Rtg1, and Rtg3 (2, 4, 19). However, the molecular mechanism(s) by which Tor regulates expression of the RP genes remains poorly understood.

The RP genes are subject to stringent regulation in order to couple protein synthesis and growth to the availability of nutrients and the physiological status of the cell (48). In addition to the Tor pathway, two other important signaling pathways regulate RP gene expression. The nutrient-sensing protein kinase A (PKA) pathway is required to activate RP gene expression while the PKC pathway mediates repression of RP genes in response to perturbations of the cell integrity pathway (18, 31). Additional signaling programs are also thought to regulate RP gene expression in response to nutrients (30). The majority of RP gene promoters contain binding sites for two transcription factors of partially overlapping function: Abf1 and Rap1

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Esa1 histone acetylase and transcription from RP gene promoters (37). Furthermore, recruitment of Esa1 to RP gene promoters requires a binding site for Rap1 and/or Abf1 (37). Esa1 is the catalytic subunit of the NuA4 histone acetylase complex that acetylates histones H4 and H2A (1). The NuA4 complex is recruited to DNA by acidic activators such as VP16 and Gcn4 (5).

In this work we examined whether Tor signaling is required for the occupancy of known regulatory factors at the RP gene promoters by using chromatin immunoprecipitation assays. We found that Tor signaling is required for the maintenance of Esa1 at RP gene promoters. Repression of RP genes in response to nutrient depletion or rapamycin treatment requires components of the Rpd3-Sin3 histone deacetylase complex. Our results establish a link between Tor-mediated nutritional signaling and histone acetylation and illustrate a novel mechanistic paradigm by which the Tor pathway controls gene expression.

MATERIALS AND METHODS

***Saccharomyces cerevisiae* strains, plasmids, and growth conditions.** Strain MCY47 was obtained by introducing a three-hemagglutinin (HA) epitope-tagged Esa1 in a two-step gene replacement (with plasmid YIplac211 HA-Esa1, a generous gift from Kevin Struhl) into strain MLY41 Σ1278b *MAT*a *ura3-52* (37). Strains JRY16a, JRY17a, and JRY18a were derived from MLY41a by replacing the entire open reading frame of *RPD3*, *SIN3*, and *SAP30*, respectively, with *kanMX*. Gene disruptions were all verified by PCR.

Chromatin immunoprecipitation and quantitative PCR. Exponentially growing cultures of strain MCY47 containing HA_3 epitope-tagged Esa1 were treated with 100 nM rapamycin for 0, 15, 30, and 60 min. Cultures were adjusted to 1% formaldehyde and incubated for 20 min at room temperature with gentle shak-

Metabolism 1994 Apr;43(4):462-7

Effects of dietary protein restriction on glucose and insulin metabolism in normal and diabetic humans.

Lariviere F, Chiasson JL, Schiffrin A, Taveroff A, Hoffer LJ

McGill Nutrition and Food Science Centre, McGill University, Montreal, Quebec, Canada.

McGill Nutrition and Food Science Centre, McGill University, Montreal, Quebec, Canada.

"We conclude that severe protein restriction decreases insulin requirements in type I diabetes and fasting hepatic glucose output and basal insulin levels in normal subjects. This effect appears to be mediated in part by decreased hepatic gluconeogenesis, but a contributory influence of increased insulin sensitivity is not ruled out."

preprandial and average daily blood glucose concentrations ($P < .01$); this occurred despite a concurrent 25% decrease in both basal and bolus insulin dosages ($P < .001$). Protein restriction decreased the postabsorptive glucose Ra ($P < .05$) and insulin concentrations ($P < .01$) of normal subjects by 20%, and increased their fasting glucagon concentrations by 24% ($P < .01$). We conclude that severe protein restriction decreases insulin requirements in type I diabetes and fasting hepatic glucose output and basal insulin levels in normal subjects. This effect appears to be mediated in part by decreased hepatic gluconeogenesis, but a contributory influence of increased insulin sensitivity is not ruled out.

PMID: 8159104, UI: 94211139

'Anti-Atkins' Low Protein Diet Extends Lifespan In Flies

Oct. 2, 2009 Science Daily
From ***Cell*** **October 2 2009**

Oct. 2, 2009 — Flies fed an "anti-Atkins" low protein diet live longer because their mitochondria function better. The research, done at the Buck Institute for Age Research, shows that the molecular mechanisms responsible for the lifespan extension in the flies have important implications for human aging and diseases such as obesity, diabetes and cancer.

The findings, which appear in the October 2 edition of *Cell*, also provide a new level of understanding of

"Flies fed an "anti-Atkins" low protein diet live longer because their mitochondria function better. The molecular mechanisms responsible for the lifespan extension in the flies have important implications for human aging and diseases such as obesity, diabetes and cancer....In flies, we see that the long-lived diet is a low protein diet and what we have found here is a mechanism for how that may be working...TOR. A recent study appearing in the Nature showed that feeding rapamycin to mice inhibited TOR and extended their lifespan."

relationship between diet and mitochondrial function," he said.

The study describes a novel mechanism for how mitochondrial genes are converted from RNA to protein by a particular protein (d4EBP). Flies fed a low protein diet showed an uptick in activity of d4EBP, which is involved in a signaling pathway that mediates cell growth in response to nutrient availability called TOR (target of rapamycin). The research showed that d4EBP is necessary for lifespan extension upon dietary restriction. When the activity of the protein was genetically "knocked out" the flies did not live longer, even when fed the low protein diet. When the activity of d4EBP was enhanced, lifespan was extended, even when the flies ate a rich diet.

Novartis drug Afinitor® helps women with advanced breast cancer live significantly longer without their disease progressing

Press Release

Sep 25, 2011

Novartis International AG / Novartis drug Afinitor® helps women with advanced breast cancer live significantly longer without their disease progressing . Processed and transmitted by Thomson Reuters

"Everolimus targets mTOR in cancer cells, a protein that acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism. Resistance to hormonal therapy in breast cancer has been associated with over-activation of the mTOR pathway"

"Everolimus is the first drug to show significant efficacy when combined with hormonal therapy in women with ER+HER2- advanced breast cancer, where there continues to be a critical unmet need," said Hervé Hoppenot, President, Novartis Oncology. "The magnitude of benefit seen in these patients, despite their resistance to previous hormonal therapies, shows everolimus represents a potential important new treatment approach."

BOLERO-2 (Breast cancer trials of OraL EveROlimus-2) examined the safety and efficacy of everolimus in combination with exemestane versus exemestane alone in postmenopausal women with ER+HER2- advanced breast cancer who recurred or progressed while on or following previous treatment with hormonal therapies, letrozole or anastrozole[1]. Findings from the trial will be presented today during a Presidential Symposium at the 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden.

At a pre-planned analysis, the trial met its primary endpoint of PFS showing treatment with everolimus improved PFS to 6.9 months compared to 2.8 months (hazard ratio 0.43 [95% confidence interval (CI): 0.35 to 0.54]; p<0.0001) by local investigator assessment. This significant improvement was consistent across all subgroups including number of prior therapies, presence of visceral disease, bone metastases

The best drug to reduce mTor signalling, to slow aging and the chronic diseases associated with it, is already available...

Avoid high protein

Lower TOR

Increase Autophagy/Mitophagy

Eat and Recycle Your Own Damaged Proteins

What's High?

Above 1 gm/Kg/Day (estimated lean mass)

.75/Kg lean mass/day better

.6/kg lean mass/day may be even better after adaption to treat DM, Cancer

Protein and Energy Requirements in Infancy and Childhood.

Nestlé Nutr Workshop Ser Pediatr Program, vol 58, pp 121–131, 2006

Irene Axelsson

Department of Pediatrics, University of Lund, Lund, Sweden

The protein content in breast milk is about 1g/100ml and the daily protein intake approximately 1g/kg/day.

standard from birth to 6 months. During the breastfeeding period the protein intake is low in the human being compared too many other animals. The protein content in breast milk is about 1 g/100 ml and the daily protein intake approximately 1 g/kg/day. When other foods are introduced during the weaning period the protein intake increases remarkably to 3–4 g/kg/day in spite of the fact that the protein requirement is decreasing. The long-term consequences of this phenomenon are obscure. A high protein intake has endocrine effects, such as the high levels of insulin and insulin-like growth factor-1. Furthermore, the metabolic effects with high levels of urea in serum and urine, and the high levels of many amino acids may exceed the capacity of the hepatic and renal systems to metabolize and excrete the excess of nitrogen. This may lead to acidosis and hypernatremic dehydration during periods of fever and diarrhea. Whether the risk of obesity later in life is decreased because of a low intake of protein during the breastfeeding period is still obscure.

During the breastfeeding period, protein intake is low in the human being compared too many other animals. The protein content of breast milk is about 1 g/100 ml and the daily protein intake approximately 1 g/kg/day. During the weaning period, protein intake increases remarkably, even after the first year of life. There is a shift from about 1 to 3–4 g/kg/day in spite of the fact that the protein requirement is decreasing. The long-term consequences of this phenomenon are obscure. A high protein intake may have both endocrine, metabolic, physiologic effects and may increase the risk of obesity.

Studies in humans are still surrounded by a number of uncertainties. Few studies have addressed the nutritional needs of infants at the time of weaning and the long-term consequences of the changes in the diet.

The First “Fasting Mimetic Diet”

Clinical Experience of a Diet Designed to Reduce Aging

J Appl Res. 2009 January 1; 9(4): 159–165

Ron Rosedale MD, Eric C. Westman MD MHS

The Rosedale Center, Denver CO, Department of Medicine, Duke University Medical Center

Abstract **A retrospective chart review of patients attending an outpatient metabolic management program involving instruction in a high-fat, adequate-protein, low-carbohydrate diet, the use of nutritional supplements, and periodic individual visits. The general dietary recommendation was approximately 15% carbohydrate, 35% protein, and**

Over a mean follow-up of 91.5 days, body weight decreased 8.2% ($p<0.01$), fasting serum glucose decreased 8.3% ($p=0.001$). There were 50% reductions in insulin, leptin, fasting serum triglyceride, and triglyceride/HDL ratio ($p<0.001$). Free T3 decreased 7% ($p<0.001$), while TSH did not change significantly.

leptin, fasting serum triglyceride, and triglyceride/HDL ratio (p<0.001). Free T3 decreased 7% (p<0.001), while TSH did not change significantly.

We conclude that a high-fat, adequate-protein, low-carbohydrate diet with nutritional supplementation led to improvements in serum factors related to the aging process in adherent patients. Further research regarding this nutritional approach and its relationship to aging is in order.

"Your health and lifespan will mostly be determined by the proportion of fat versus sugar you burn over a lifetime"

Ron Rosedale M.D.

"Your health and lifespan will mostly be determined by the proportion of fat versus sugar you burn over a lifetime"
Ron Rosedale M.D.

….and that will be determined by the communication of insulin/IGF, leptin and especially mTOR

Cancer is not glucose driven.
Nor is it driven by mitochondrial dysfunction.
It is driven by growth signals, particularly mTOR

Life is not in the parts…we are all made of the same stuff…it is what you do with the parts that determines health and life…and that is largely determined by mTOR