The Critical Connection Between Protein, Cancer, Aging and TOR

Ron Rosedale M.D.
The Answer First...
Your health and likely your lifespan will be determined by the proportion of fat versus sugar you burn over a lifetime.
Your health and likely your lifespan will be determined by the proportion of fat versus sugar you burn over a lifetime...and that will be determined by the communication of nutrient sensors.
The Answer First...

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

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

...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
Evolution of Life in Reverse
Is Cancer A Genetic Disease, caused by the accumulation of 2-3 oncogenetic mutations?
“...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
Hyperinsulinemia adversely affects 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

abstract
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. Finally, we highlight the novel therapeutic and imaging applications that are emerging as a result of our improved understanding of the role of glutamine metabolism in cancer.

"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, which ultimately provides "fuel" for the tumor to grow and even metastasize.

This revealing symbiotic process, which is similar to how muscle and brain cells communicate with the body, could prove useful for developing new drugs to prevent and treat cancers. In this simple model, our bodies provide nourishment for the cancer cells, via chronic inflammation.

"People think that inflammation drives cancer, but they never understood the mechanism," said Michael P. 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.

“At the researchers see that lactate is like ‘candy’ for cancer cells. And cancer cells are addicted to this supply of ‘candy.’”
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 gluconeogenic substrate by other cells and tissues. However, within the fermenting cell itself, lactate is thought to be produced to replenish NAD+ and then secreted. Here we explore the possibility that cytosolic lactate is metabolized by the mitochondria of fermenting mammalian cells. We found that fermenting HeLa and H460 cells utilize exogenous lactate carbon to synthesize 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.
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 metastatic 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 not consumed in normal 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.
SUMMARY
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 (FAO) in cancer is limited. Prolyl hydroxylase domain proteins hydroxylate substrate proline residues and have been linked to fuel switching. Here, we reveal that PHD3 rapidly triggers repression of FAO in response to nutrient abundance via hydroxylation 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.

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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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Mitochondrial dysfunction and longevity in animals: Untangling the knot

Ying Wang and Siegfried Hekimi

SCIENCE; 4 DECEMBER 2015 • VOL 350

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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
“...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).”
The role of insulin and IGF-1 signaling in longevity


M. Katic and C. R. Kahn

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Received 8 July 2004; received after revision 25 August 2004; accepted 17 September 2004

Abstract. There are many theories of aging and parameters that influence lifespan, including genetic instability, telomerase activity and oxidative stress. The role of caloric restriction, metabolism and insulin and insulin-like growth factor-1 signaling in the process of aging is especially well conserved throughout evolution. These latter factors interact with each other, the former factors and histone deacetylases of the SIR family in a complex interaction to influence lifespan.

Key words. Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; gluthatione; thiorphotoxidation; calorie restriction; insulin; IGF-1; growth hormone; signaling; Sir; FOXO; p66; klotho; animal models; S. cerevisiae; C. elegans; 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?

Social scientists have raised other considerations: Do we want to live longer? And if so, how much longer? Is increasing 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 focus especially on the role of metabolism and insulin and 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
The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn
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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 increasing 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?

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We will focus especially on the role of metabolism and insulin and insulin-like growth factor-1 (IGF-1) signaling in this process.

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

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)
...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 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."
Reduced function mutations in the insulin/IGF-I signaling pathway increase maximal lifespan and health span in many species. Calorie restriction (CR) decreases serum IGF-1 concentration by ~40%, protects against cancer and slows aging in rodents. However, the long-term effects of CR with adequate nutrition on circulating IGF-1 levels in humans are unknown. Here we report data from two long-term CR studies (1 and 6 years) showing that severe CR without malnutrition did not change IGF-1 and IGF-1:IGFBP-3 ratio levels in humans. In contrast, total and free IGF-1 concentrations were significantly lower in moderately protein-restricted individuals. Reducing protein intake from an average of 1.67 g kg⁻¹ of body weight per day to 0.95 g kg⁻¹ of body weight per day for 3 weeks in six volunteers practicing CR resulted in a reduction in serum IGF-1 from 194 ng mL⁻¹ to 152 ng mL⁻¹. These findings demonstrate that, unlike in rodents, long-term severe CR does not reduce serum IGF-1 concentration and IGF-1:IGFBP-3 ratio in humans. In addition, 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 correspond to longevity in these species. 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.

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

Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans
Luigi Fontana John O. Holloszy

"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."
Insulin analogues and cancer risk: cause for concern or cause célèbre?

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 choices. In this respect, metformin may be protective, whereas insulin and insulin analogues can function as growth factors and therefore have theoretical potential to promote tumour proliferation. Analogues causing inappropriate prolonged stimulation of the insulin receptor, or excess stimulation of the IGF-1 receptor, are the most likely to show mitogenic properties in laboratory studies. Some recent epidemiological studies appear to be consistent with these experimental 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.
Leptin
Central nervous system control of food intake and body weight


...genetic and pharmacological studies suggest a more critical role for leptin than insulin in mammalian energy homeostasis"
The role of leptin in leptin resistance and obesity.
Physiol Behav, 88(3): 249-56  2006
Zhang Y, Scarpace PJ

Abstract:
Although the presence of hyperleptinemia with leptin resistance and

“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.”

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.

Language:
Leptin regulates proinflammatory immune responses

FASEB 12 January 98

Departments of Medicine, †Molecular Microbiology and Immunology, ‡Surgery, and §Biological Chemistry, Johns Hopkins University, Baltimore, Maryland 21205, USA

ABSTRACT Obesity is associated with an increased incidence of infection, diabetes, and cardiovascular disease, which together account for most obesity-related morbidity and mortality. Decreased expression of leptin or of functional leptin receptors results in hyperphagia, decreased energy expenditure, and obesity. It is unclear, however, whether defective leptin-dependent signal transduction directly promotes any of the conditions that frequently complicate obesity. Abnormalities in tumor necrosis factor-α (TNF-α) expression have been noted in each of the above comorbid conditions, so leptin deficiency could promote these complications if leptin had immunoregulatory activity. Studies of rodents with genetic abnormalities in leptin or 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 contributes 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: obesity, macrophage, cytokine, phagocytic function, TNF-α, lipopolysaccharide

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 decreased 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-α)2 was documented in adipose tissues of obese rodents and humans (4, 5) and implicated in the pathogenesis of
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.

Spector found that the white blood cells of the youngest women had telomeres that were around 7500 base pairs long. Their length declined at an average rate of 27 base pairs per year.

When lifestyle factors were taken into account, however, dramatic differences emerged. The difference between being obese and being lean corresponds to 8.8 years of extra ageing, Spector told a press conference in London.

Intriguingly, the link between high leptin concentrations and telomere shortening was even stronger than the link with obesity, as measured by the body mass index. Leptin is an appetite-inhibiting hormone, but obese people are resistant to it and have higher than normal levels.

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)

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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 cancer by maintaining a healthy weight. The results of both studies will be reported December 22 online in the Journal of Clinical Oncology (JCO).

"The primary role of obesity in prostate cancer is still unclear, but it appears to induce the development of more aggressive tumors," said Christopher L. Amling, MD, of the Naval Medical Center's Department of Urology in San Diego and lead author of one of the studies. "I would advise patients to maintain a normal body weight to limit the possibility that they would develop clinically significant, more aggressive prostate tumors."

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,"
Aging is associated with a metabolic decline characterized by the development of changes in fat distribution, obesity, and insulin resistance. Dysfunctional humoral and cell-mediated immune responses occur with age, and these aberrations have been implicated in the increased incidence of infectious diseases, hyporesponsiveness to vaccination, and the etiology of numerous chronic degenerative diseases. All these metabolic and immune alterations are associated with a variety of age-related diseases that subsequently result in increased mortality. Leptin can modulate many of the metabolic alterations characteristic of aging. Leptin resistance has been implicated in the pathogenesis of obesity-related complications involving abnormalities of lipid metabolism that resemble those of old age. Increased plasma leptin levels with aging suggest resistance to 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.

"Leptin’s failure may be considered for the metabolic decline seen with aging."
Hormone levels and cataract scores as sex-specific, mid-life predictors of longevity in genetically heterogeneous mice.

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 cataract severity, were evaluated as predictors of life span in a population of genetically 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

“amino acids precursors of citric acid cycle intermediates potently stimulate per se basal leptin secretion, insulin having an additive effect”
Medical researchers at the University of Sheffield have defined the structure of a key part of the human obesity receptor—an essential factor in the regulation of body fat—which could help provide new treatments for the complications of obesity and anorexia. This major advance in research, published in the journal Structure, will greatly enhance the ability to generate drugs which can both block and stimulate the receptor for the obesity hormone leptin. This could have life-changing effects on people suffering from the complications of obesity and malnutrition.

Researchers have solved the challenging crystal structure of the leptin-binding domain of the obesity receptor using state-of-the-art X-ray crystallography, helping them to work out how to block or stimulate the receptor. Leptin, the obesity hormone, is produced by fat and excess leptin predisposes overweight people to conditions such as multiple sclerosis, cancer, and heart disease. A deficiency in leptin, as occurs in malnutrition, results in infertility and immunodeficiency. Blocking the 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.
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 receptors, or inactivation of the tumor suppressor gene, PTEN, that normally negatively regulates this pathway. Akt is a crucial kinase in this pathway that is activated by phosphorylation in the activation domain (T308) and in the hydrophobic motif (S473). Once active, Akt exerts its cellular effects through the phosphorylation of downstream substrates that regulate the apoptotic machinery, cell cycle progression, gene expression, metabolism, and protein translation. Of all downstream Akt substrates, mTOR is probably the best studied, perhaps due to the availability of drugs that specifically inhibit mTOR.

Is PI3K/Akt/mTOR Pathway Important in Many Types of Cancer?
Yes. The measurement of active Akt and other pathway components in human tumors has revealed that pathway activation is one of the most common molecular alterations in human cancer. Using activation state specific antibodies in immunohistochemical (IHC) analyses of parafilm-embedded, formalin-fixed tissues, active Akt and other pathway components have been detected in at least 12 types of human cancers in vivo, with prevalence as high as 90%. The importance of pathway activation in situ has been demonstrated when IHC analysis of tumor tissues has been linked to clinical outcomes. Akt activation is a poor prognostic factor for breast cancer, prostate cancer, non-small cell lung cancer (NSCLC), endometrial cancer, gastric cancer, pancreatic cancer, glioblastoma multiforme, melanoma, and acute myelogenous leukemia. Thus, constitutive activation of this pathway is common and important in many cancers.

Pathway Inhibitors Prevent Cancer in Preclinical Model Systems
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 kinase that integrates a multitude of extracellular signals and intracellular cues to drive growth and proliferation. mTOR activity is altered in numerous pathological conditions, including metabolic syndrome and cancer. In addition to its well-established role in regulating mRNA translation, emerging studies indicate that mTOR modulates mitochondrial functions. In mammals, mTOR coordinates energy consumption by the mRNA translation machinery and mitochondrial energy production. mTOR inhibits autophagy, which is a process that can eliminate [damaged] mitochondria.
mTORC1 controls fasting-induced ketogenesis and its modulation by ageing

“inhibition of mTORC1 is required for the fasting-induced activation of PPARα, the master transcriptional activator of ketogenic genes"
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 amino acid-driven mammalian target of rapamycin (mTOR) pathway to control the growth and development of the organism. Insulin regulates mTOR function through a recently described canonical signaling pathway, which is initiated by the activation of 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.

Unicellular eukaryotes use the mammalian target of rapamycin (mTOR)/raptor/G-protein-α-subunit-like protein (G!L) pathway in a cell-autonomous manner (1); however, with the rise of metazoans and humoral systems, the insulin-controlled 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.
Nutrient-sensing mTOR-mediated pathway regulates leptin production in isolated rat adipocytes

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Boston University School of Medicine, Boston, Massachusetts 02118

"mTOR is activated by free amino acids"

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

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 80 S6 potassium (Thr<sup>38</sup>), 70 S6 kinase (Thr<sup>42</sup>), and 4E-BP-1 PHAS-1 (Ser<sup>70</sup>) were from Cell Signaling (Beverly.

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The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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 the diet, mediates extension of life span. We here demonstrate that extension of life span by DR in Drosophila is not attributable to the reduction in calorie intake. 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. 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 dictates whether it maintains health and longevity remain unanswered. Here, the Geometric Framework, a state-space nutritional modeling method, was used to measure interactive effects of dietary energy, protein, fat, and carbohydrate on food intake, cardiometabolic phenotype, and longevity in mice fed one of 25 diets ad libitum. Food intake was regulated primarily by protein and carbohydrate content. Longevity and health were optimized when protein was replaced with carbohydrate to limit compensatory feeding for protein and suppress protein intake. These consequences are associated with hepatic mammalian target of rapamycin (mTOR) activation and, in turn, related to circulating branched-chain amino acids and glucose. Calorie restriction achieved by high-protein diets or dietary dilution had no beneficial effects on lifespan. The results suggest that longevity can be extended in ad libitum-fed animals by manipulating the ratio of macronutrients to inhibit mTOR activation.

INTRODUCTION

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

“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.
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 the regulation of mitochondrial genes and open new avenues of inquiry into the interplay between mitochondrial function, diet and energy metabolism.

Mitochondria act as the "powerhouse" of the cells. It is well known that mitochondrial function worsens with age in many species and in humans with Type II diabetes and obesity. "Our study shows that dietary restriction can enhance mitochondrial function hence offsetting the age-related decline in its performance," said Buck faculty member Pankaj Kapahi, PhD, lead author of the study.

The research provides the first genome-wide study of how proteins are translated under dietary restriction in any organism. The researchers report the unexpected finding that while there is a reduction in protein synthesis globally with the low protein diet, the activity of specific genes involved in generating energy in the mitochondria are increased, Kapahi said. That activity, which takes place at the level of conversion of RNA to protein, is important for the protective effects of dietary restriction, Kapahi said. "There have been correlative studies that show mitochondria change with dietary restriction, this research provides a causal 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

"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 OrA L 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
The protein content in breast milk is about 1g/100ml and the daily protein intake approximately 1g/kg/day.
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, 25% protein, and 60% fat. Recommended sources of fat included raw nuts, avocados, olives and olive oil, flax oil and cod liver oil. The intake of protein was limited to 1.0 - 1.25 grams/kg lean body mass per day (increased for exercise to 1.25 grams/day). Recommended sources of protein included sardines, fish, eggs, tofu, chicken, turkey, wild meats, non-fat cheeses (cottage, ricotta, cream), and seafood. Only non-starchy, fibrous vegetables were acceptable. Nutritional supplements recommended were: L-carnitine 2000mg, alpha-lipoic acid 400mg, coenzyme Q10 100 mg, 1 tbsp cod liver oil, magnesium 300mg, potassium 300mg, vitamin C 1000mg, vitamin E 800mg daily, and a multivitamin. Medications were adjusted if needed. The mean duration of follow-up was 91.5 days (range 36-211).

Thirty-one patients were identified with baseline and follow-up body weight, and fasting laboratory tests. The mean age of patients was 57.6 years, 53% were female. 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.

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