Collaborations Between UF and Moffitt (2015-16)

Role of LKB1-CRTC1 on glycosylated COX-2 and response to COX-2 inhibition in lung cancer

C Cao, M Zhang, A Amelio, M Fallahi, Z Chen, Y Gu, C Hu, E Welsh, B Engel, E Haura, D Cress, L Wu, M Zajac-Kaye, FJ Kaye. JNCI, 107(1):358. doi: 10.1093/jnci/dju358. Jan 2015

A sensitive NanoString-based assay to score STK11 (LKB1) pathway disruption in lung adenocarcinoma.

D Cress, L Chen, B Engel, E Welsh, S Yoder, S Brantley, D Chen, C Cao, A Beg, F Kaye, E Haura, M Schabath. J Thoracic Oncol, in press February 2016

cAMP/CREB-regulated LINC00473: potential biomarker and therapeutic target for LKB1-inactivated cancer.

Z Chen, J Li, S Lin, C Cao, N Gimbrone, R Yang, A Fu, M Carper, E Haura, M Schabath, J Lu, A Amelio, D Cress, F Kaye, L Wu. Revised manuscript under peer review

CDK4/6 inhibition stabilizes disease in patients with p16-null lung cancer and is synergistic with mTOR inhibition. P Gopalan, A Gordillo-Villegas, M Pinder-Schenck, A Chiappori, W Hou, M Zajac-Kaye, A Ivey, F Kaye. ms under peer review

Florida Academic Cancer Center Alliance Research Retreat

Aging and Cancer/Inflammation

Defining the FOXO/CRTC1 signaling pathway in anabolic metabolism, cancer, and aging

Frederic Kaye, MD
UF Division Hematology Oncology

Rui Xiao, PhD
UF Department of Aging
and Geriatric Research

SPECIAL ARTICLE

AGING, NATURAL DEATH, AND THE COMPRESSION OF MORBIDITY

JAMES F. FRIES, M.D.

Abstract The average length of life has risen from 47 to 73 years in this century, but the maximum life span has not increased. Therefore, survival curves have assumed an ever more rectangular form. Eighty per cent of the years of life lost to nontraumatic, premature death have been eliminated, and most premature deaths are now due to the chronic diseases of the later years. Present data allow calculation of the ideal average life span, approximately 85 years. Chronic illness may presumably be postponed by changes in life style, and it has been shown that the physiologic and psychologic markers of aging may be modified. Thus, the average age at first infirmity can be raised, thereby making the morbidity curve more rectangular. Extension of adult vigor far into a fixed life span compresses the period of senescence near the end of life. Health-research strategies to improve the quality of life require careful study of the variability of the phenomena of aging and how they may be modified. (N Engl J Med. 1980; 303:130-5.)

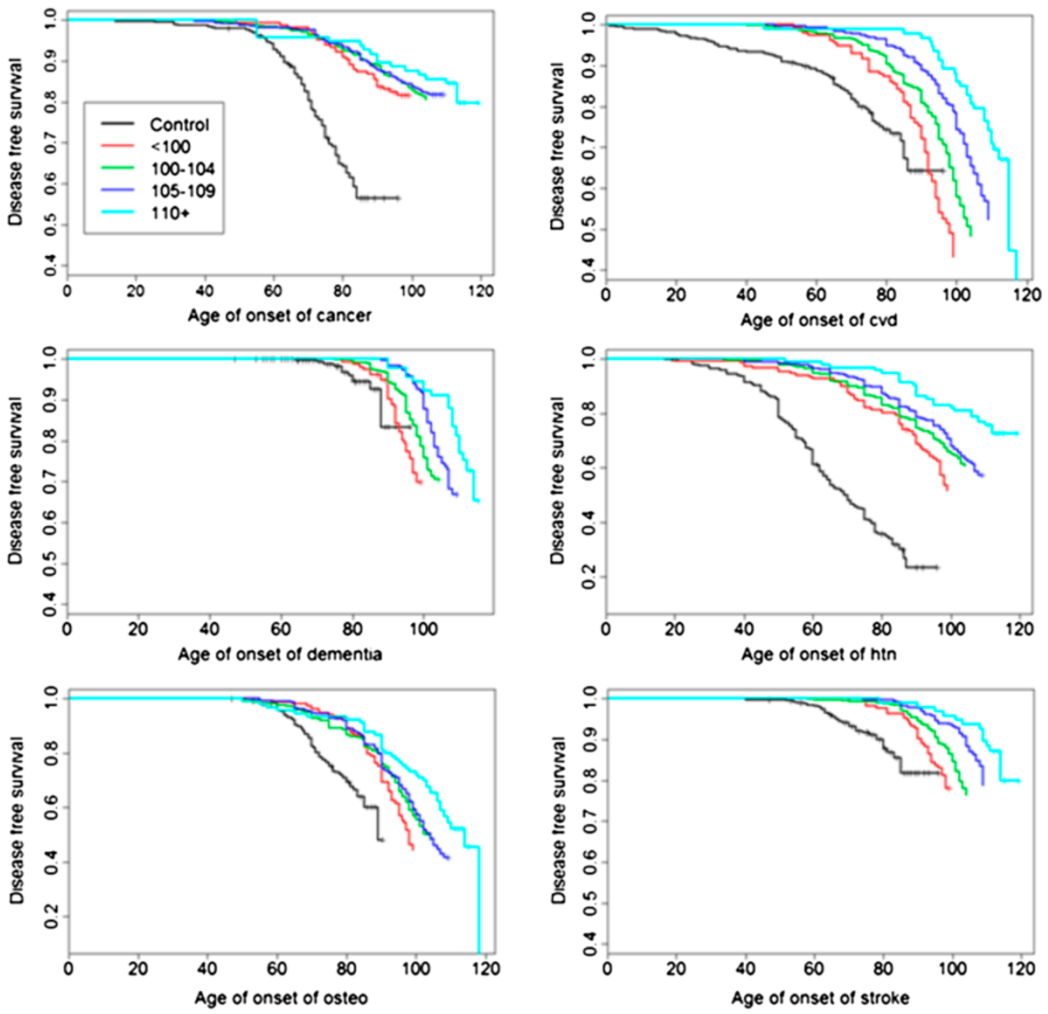
Lifespan is related to health span and this relationship has an important biological message

Several lines of data show that the genetic contribution to human lifespan is most noticeable at the highest median lifespan ages

Special Issue on Extreme Longevity

Health Span Approximates Life Span Among Many Supercentenarians: Compression of Morbidity at the Approximate Limit of Life Span

Stacy L. Andersen,[1] Paola Sebastiani,[2] Daniel A. Dworkis,[3] Lori Feldman,[1] and Thomas T. Perls[1]



New England Centenarian studyof persons aged 100 and over in Boston area

Age related disability And morbidity occurs in the last 20% of the lives of control subjects

But is compressed to last 5% of supercentenarians

GWAS analysis suggests SNPs at APOE and FOXO1/3 genes

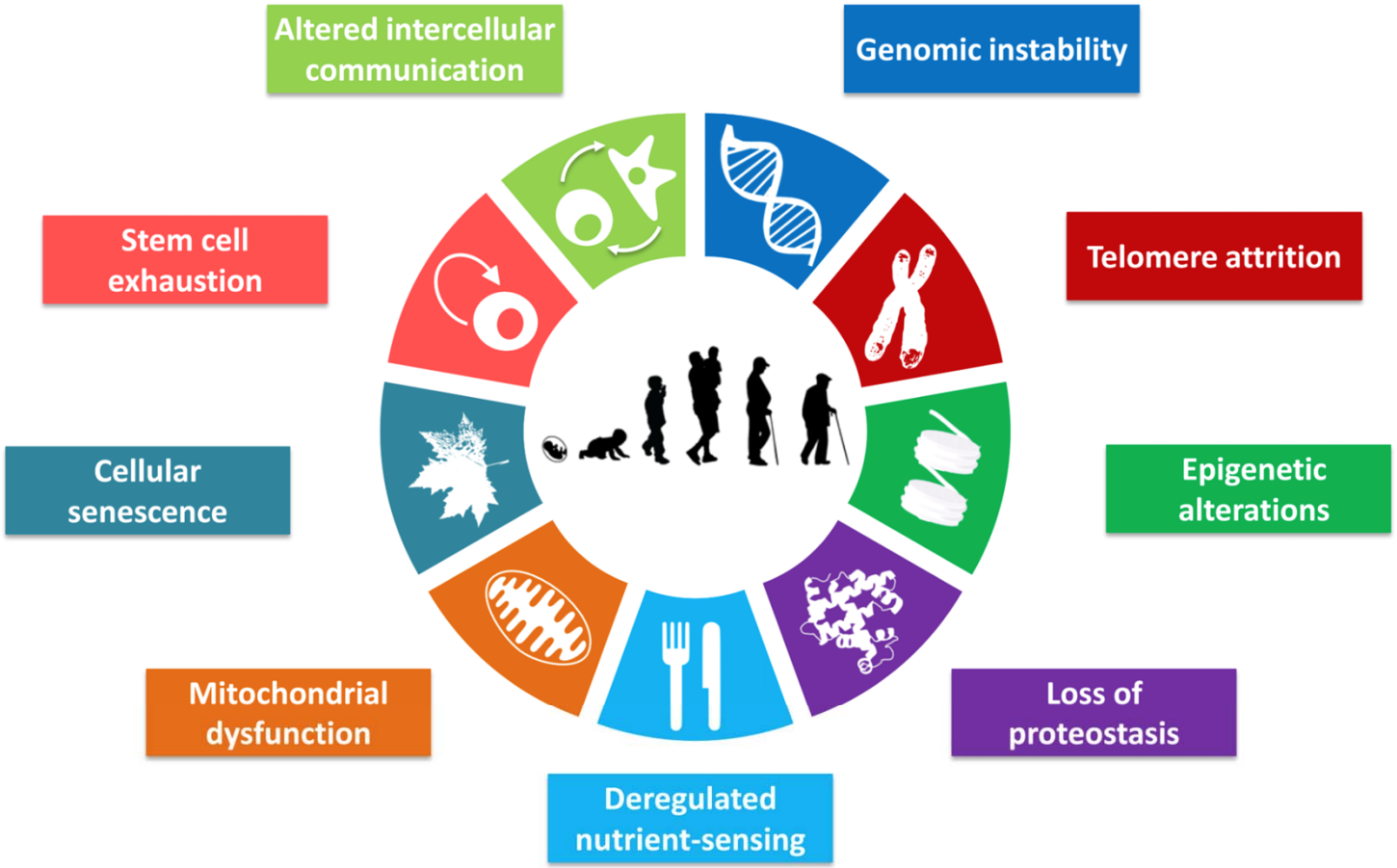


Figure 1. The Hallmarks of Aging

The scheme enumerates the nine hallmarks described in this review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

LETTERS TO NATURE

A *C. elegans* mutant that lives twice as long as wild type

Cynthia Kenyon, Jean Chang, Erin Gensch, Adam Rudner & Ramon Tabtiang

Department of Biochemistry and Biophysics, University of California at San Francisco, San Francisco, California 94143–0554, USA

WE have found that mutations in the gene *daf-2* can cause fertile, active, adult *Caenorhabditis elegans* hermaphrodites to live more than twice as long as wild type. This lifespan extension, the largest yet reported in any organism[1], requires the activity of a second gene, *daf-16*. Both genes also regulate formation of the dauer larva, a developmentally arrested larval form that is induced by crowding and starvation and is very long-lived[2–4]. Our findings raise the possibility that the longevity of the dauer is not simply a consequence of its arrested growth, but instead results from a regulated lifespan extension mechanism that can be uncoupled from other aspects of dauer formation. *daf-2* and *daf-16* provide entry points into understanding how lifespan can be extended.

Daf-2 is an insulin/insulin growth factor receptor

Daf-16 is the single C. elegans FOXO gene

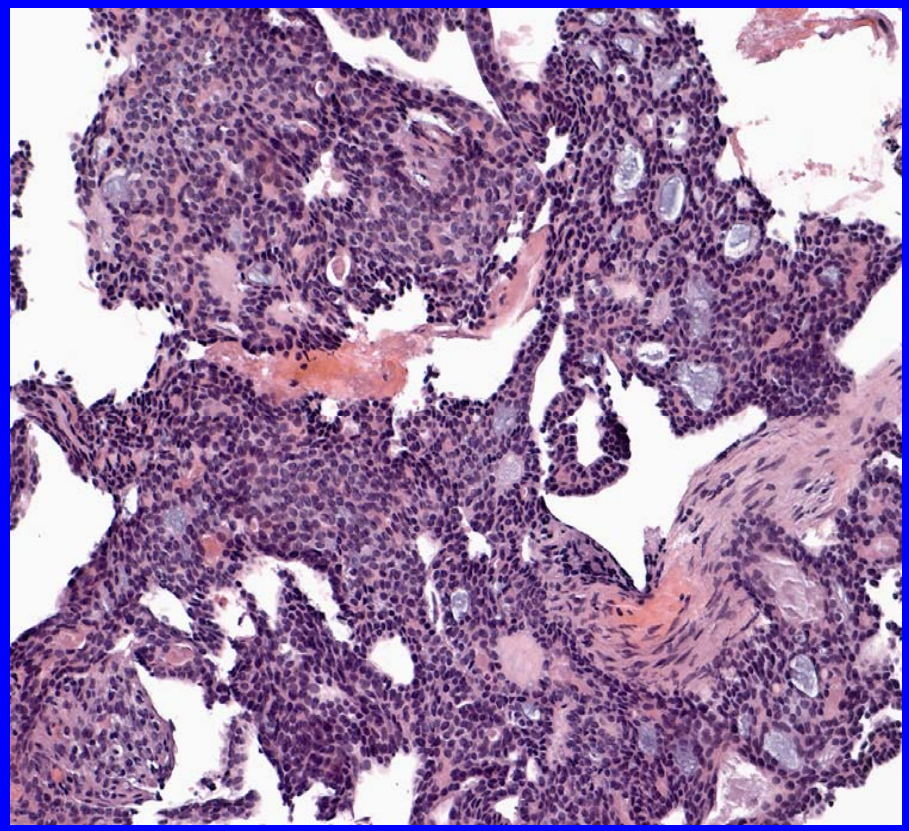
December 1993

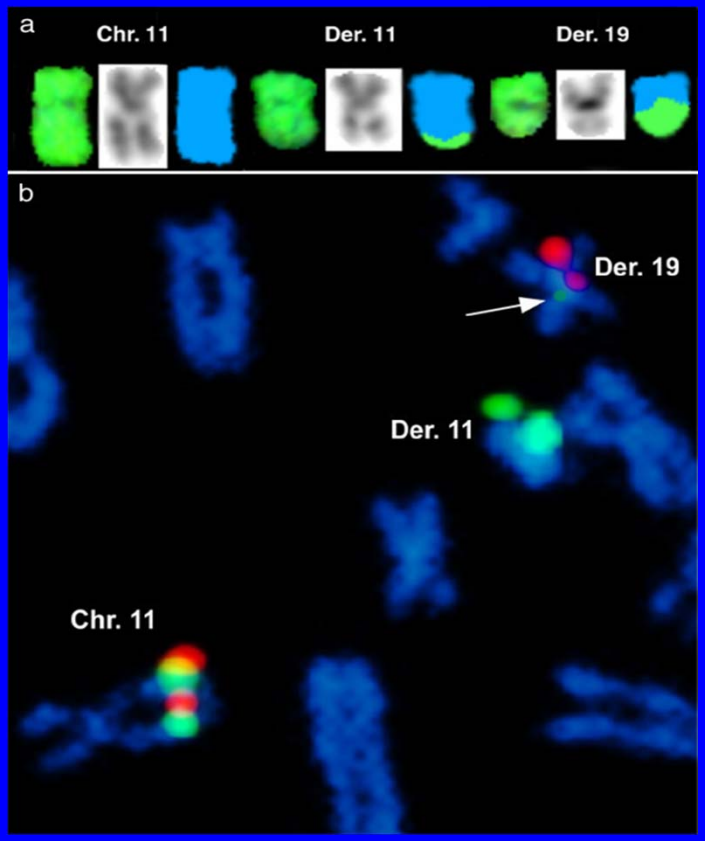
Defining the FOXO/CRTC1 signaling pathway in anabolic metabolism, cancer, and aging

Frederic Kaye, MD
UF Division Hematology Oncology

Rui Xiao, PhD
UF Department of Aging and Geriatric Research

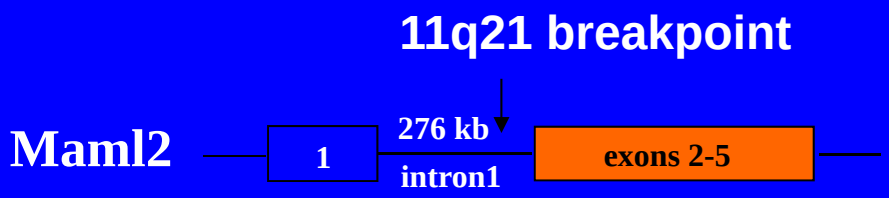
Study of young patients with lung cancer



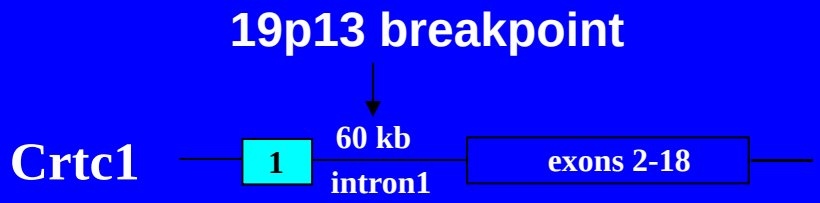


mapping a t(11;19) breakpoint in a
35 yo pt with adeno-squamous lung cancer

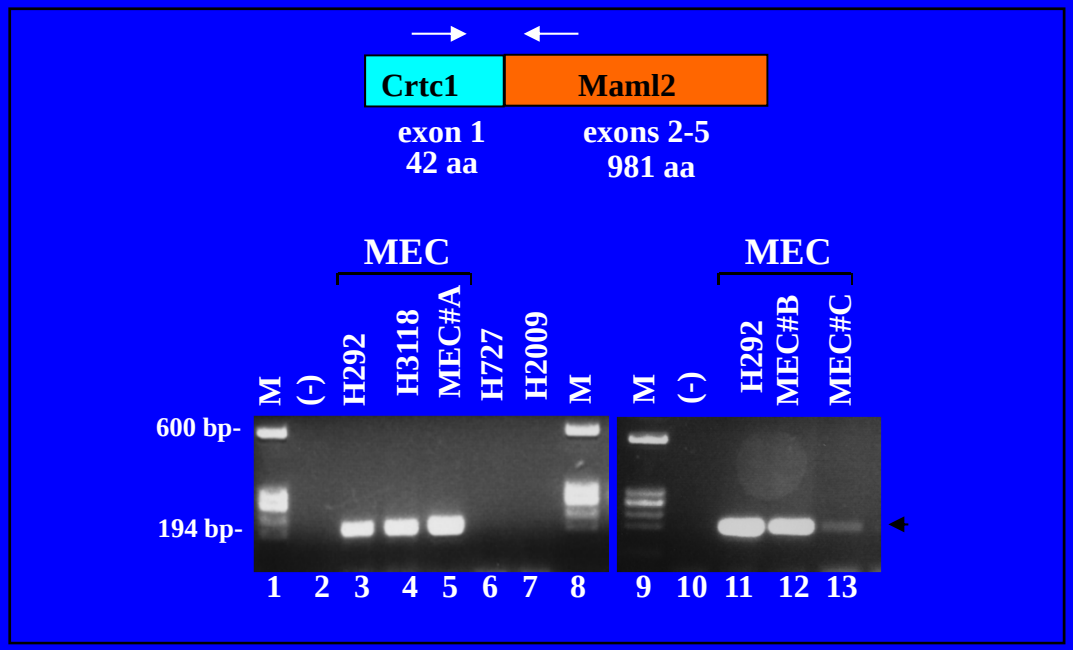
Cloning the t(11;19) breakpoint



Maml2: homolog for an essential NOTCH co-activator



Crtc1: aka Mect1/Torc1 unknown function



Crtc1-Maml2 detected In primary tumors and cell lines

RESEARCH ARTICLES

The Kinase LKB1 Mediates Glucose Homeostasis in Liver and Therapeutic Effects of Metformin

Reuben J. Shaw,[1,2]*† Katja A. Lamia,[1,2] Debbie Vasquez,[2] Seung-Hoi Koo,[3,4] Nabeel Bardeesy,[5] Ronald A. DePinho,[6] Marc Montminy,[3] Lewis C. Cantley[1,2]

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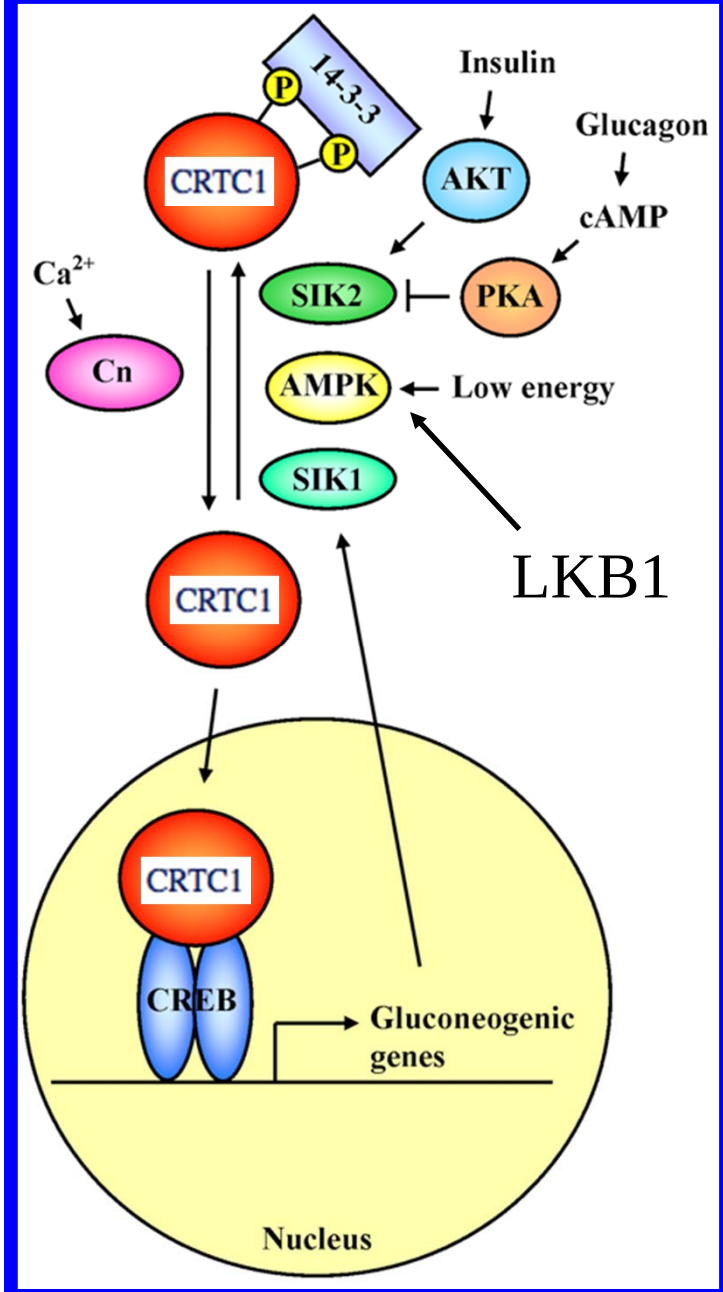
CRTCs are essential CREB co-activator for gluconeogenesis program

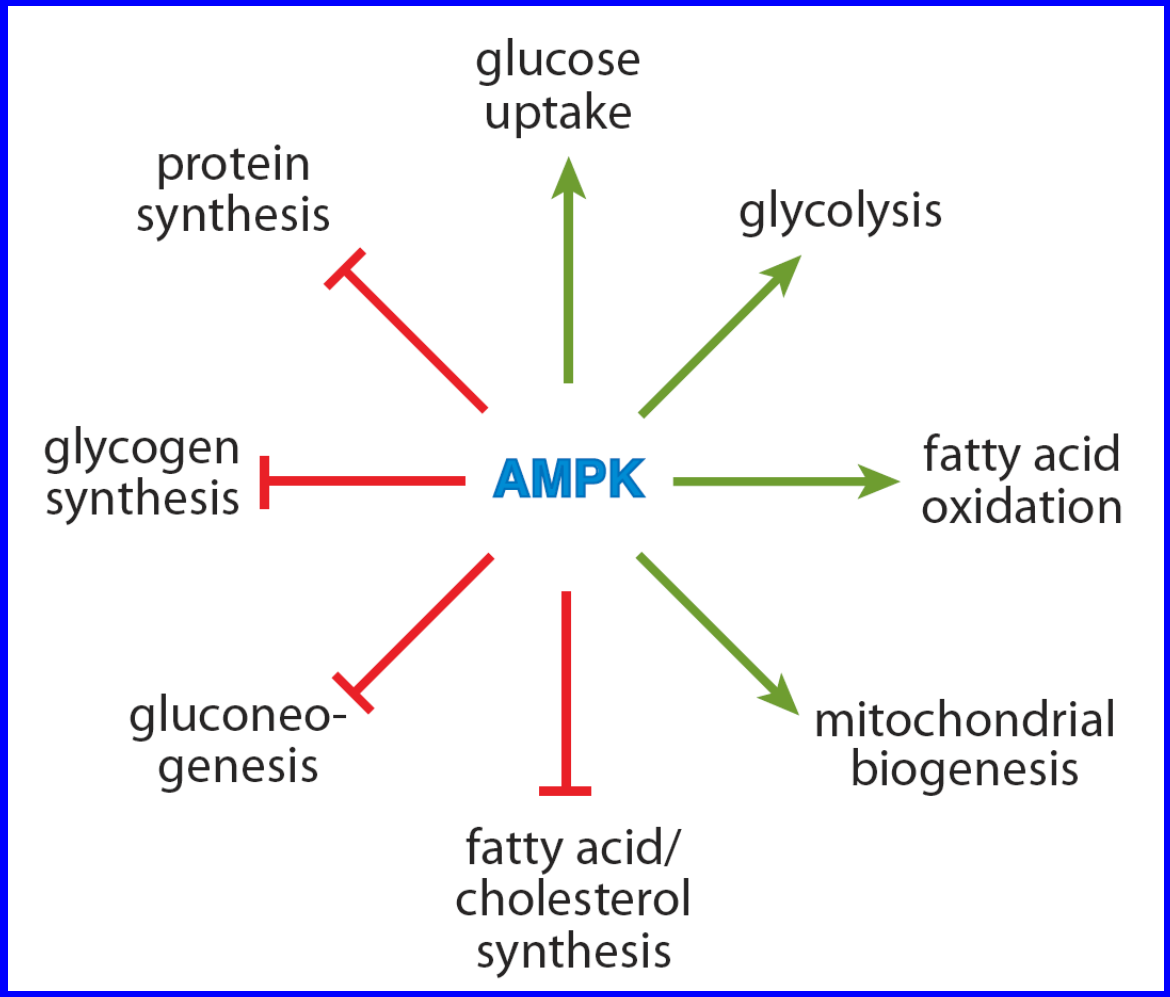
CRTC phosphorylation regulated by calcium flux and signaling through AMPK/SIK kinases



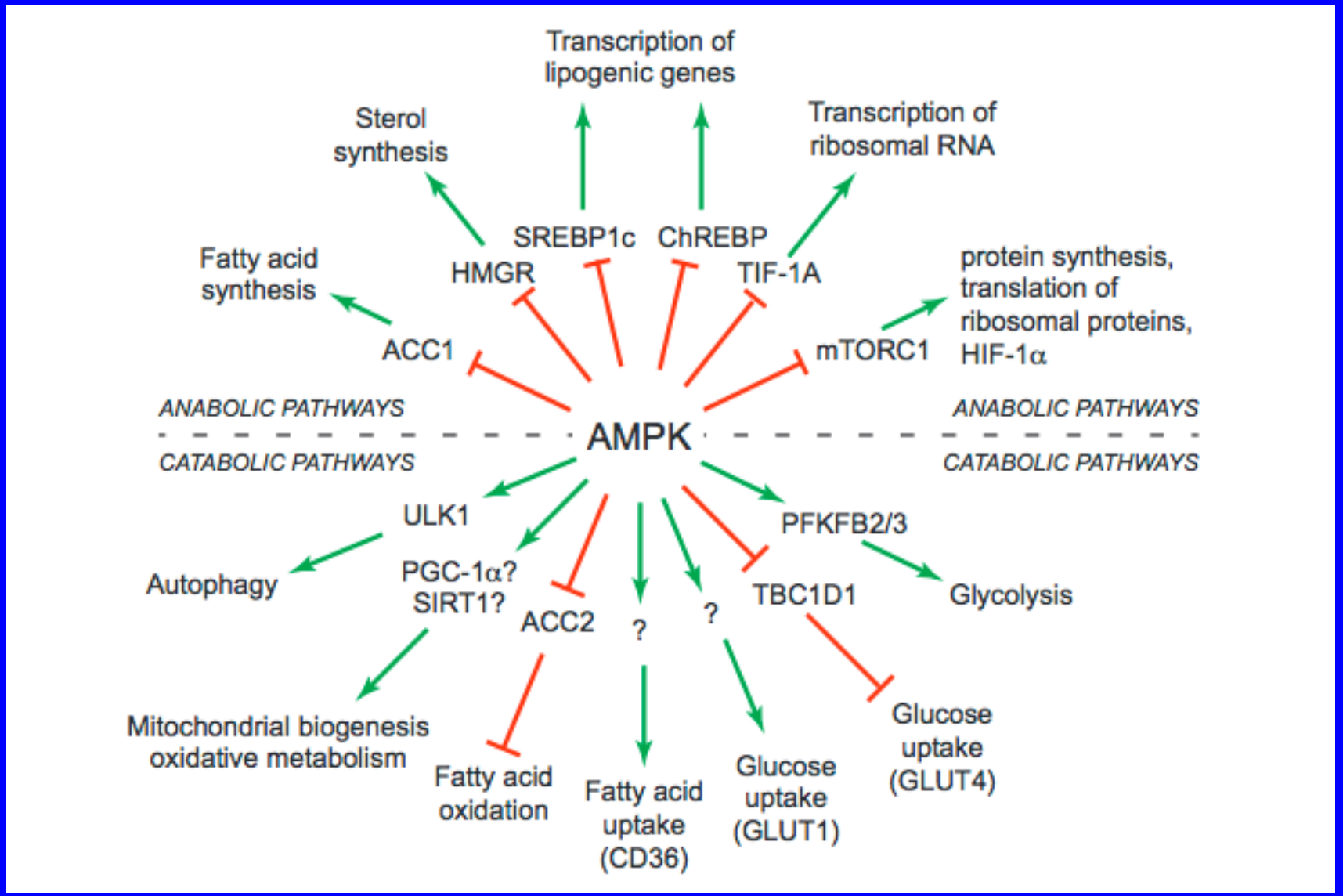
- Crtc2 integrates signals to regulate anabolic metabolism
- LKB1/AMPK signaling inhibit Crtc2 transcriptional activity
- Crtc1: bona fide cancer gene when activated by t(11;19)
- Crtc1 may participate in tumorigenesis when aberrantly activated by loss of LKB1

Cell Metab. 2008 May;7(5):357-8

AMPK pathway senses ATP depletion



AMPK pathway senses ATP depletion

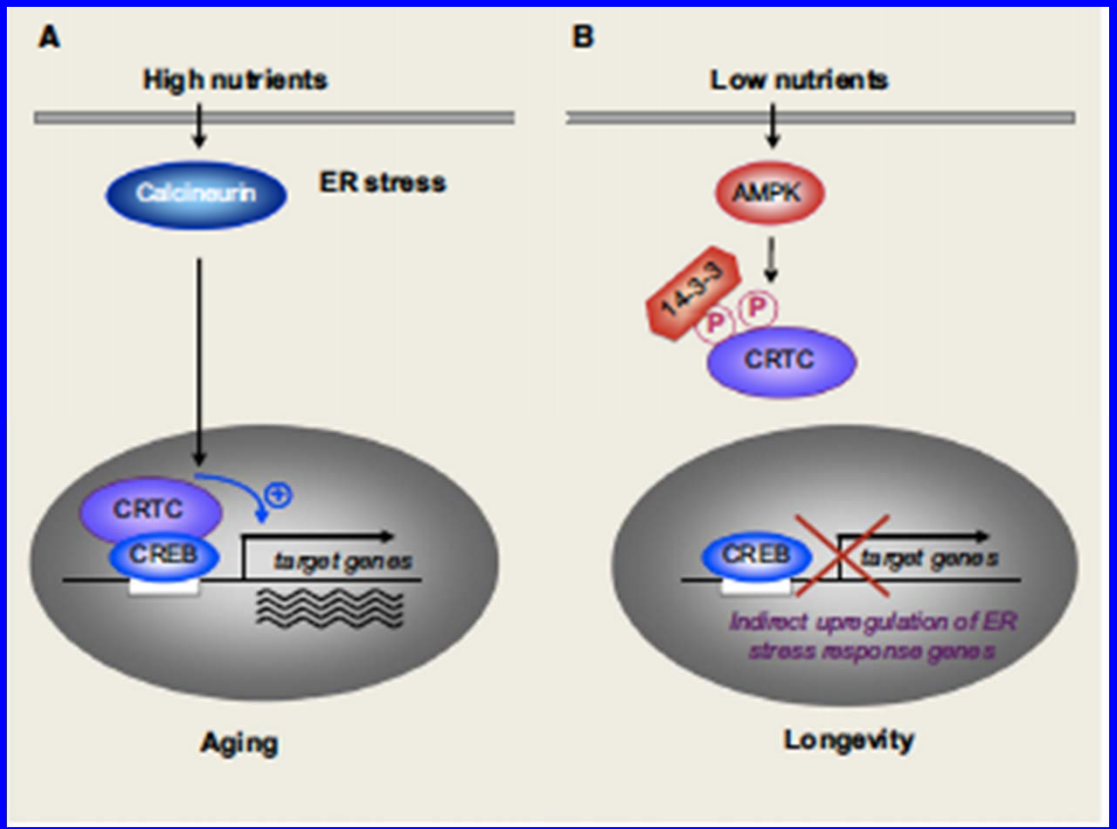


LETTER

doi:10.1038/nature09706

Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB

William Mair[1,2,3], Ianessa Morantte[1,2,3], Ana P. C. Rodrigues[1,4], Gerard Manning[1,4], Marc Montminy[1,3], Reuben J. Shaw[1,2,3] & Andrew Dillin[1,2,3]



Gene targets for mutations in sporadic lung adenocarcinoma

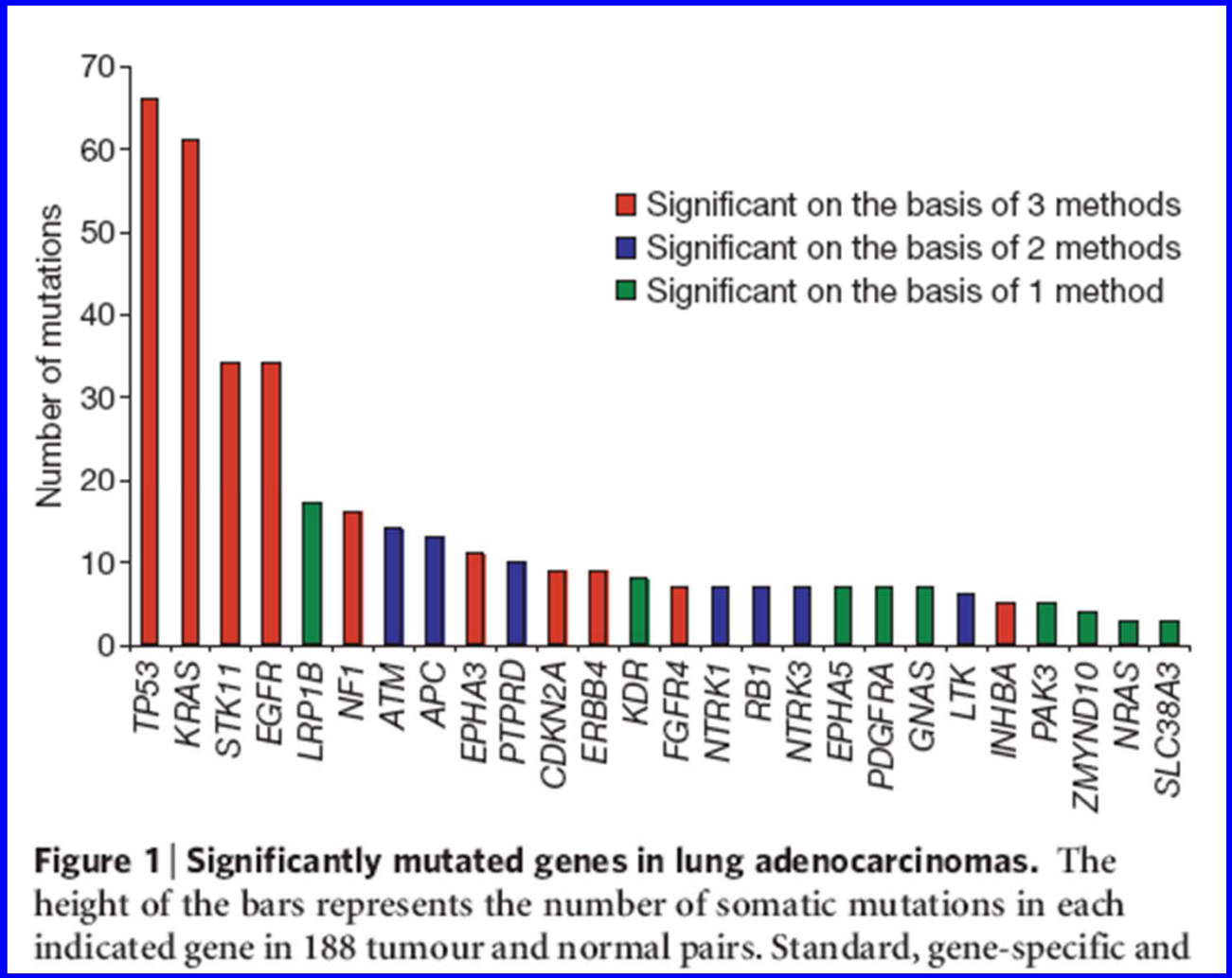


Figure 1 | Significantly mutated genes in lung adenocarcinomas. The height of the bars represents the number of somatic mutations in each indicated gene in 188 tumour and normal pairs. Standard, gene-specific and

Nature. 2008 Oct 23;455(7216):1069-75

STK11/LKB1 target for mutations in sporadic lung cancer

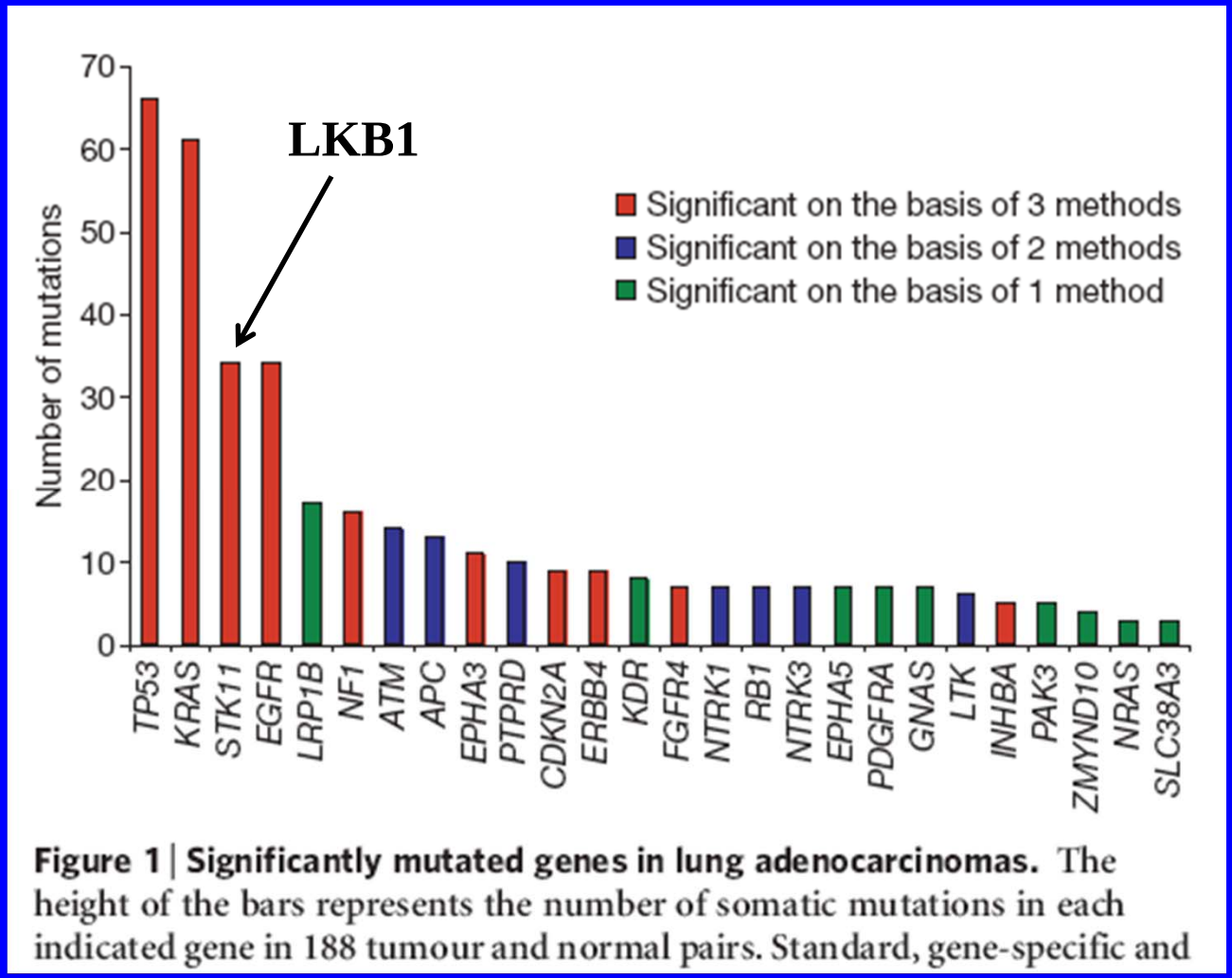
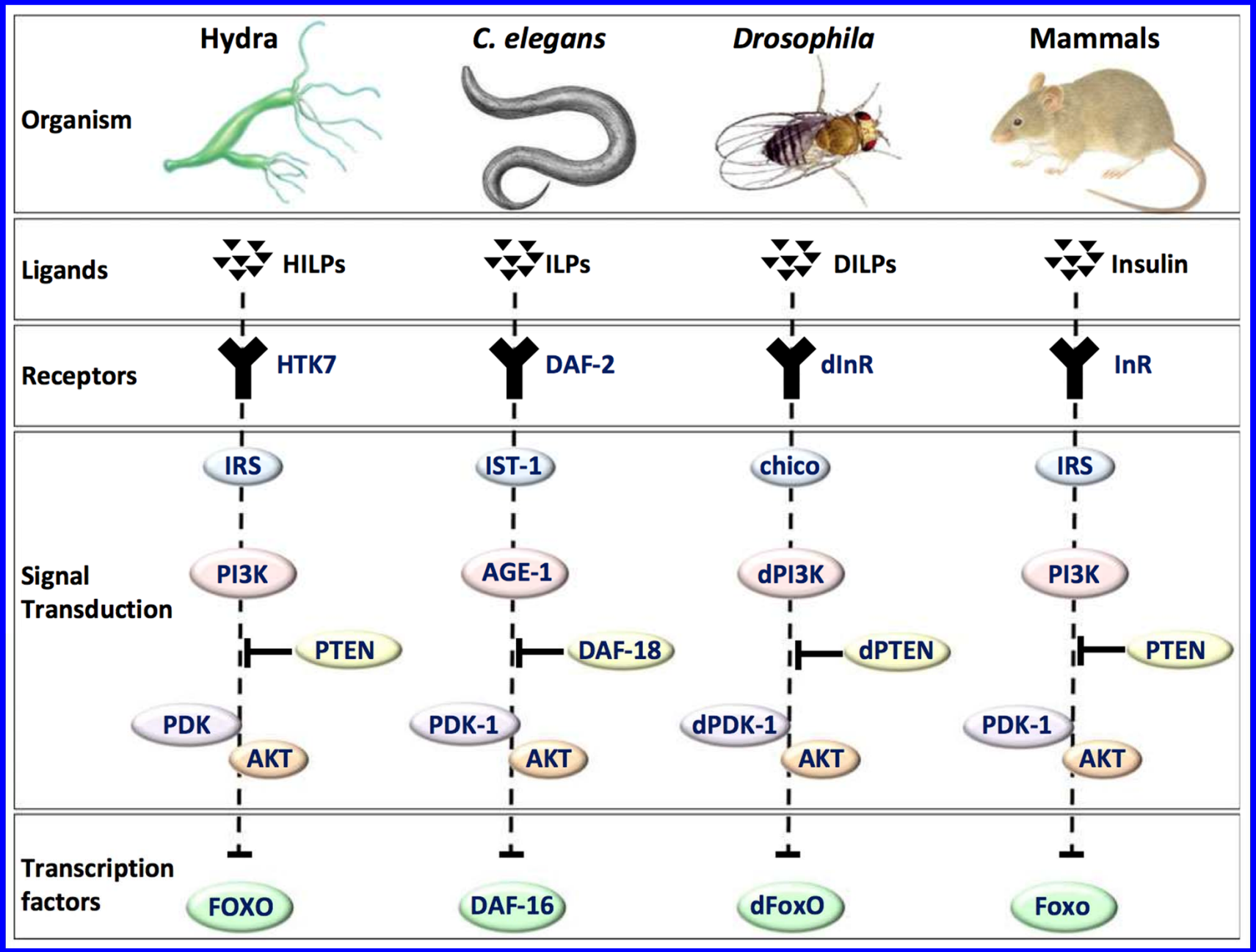
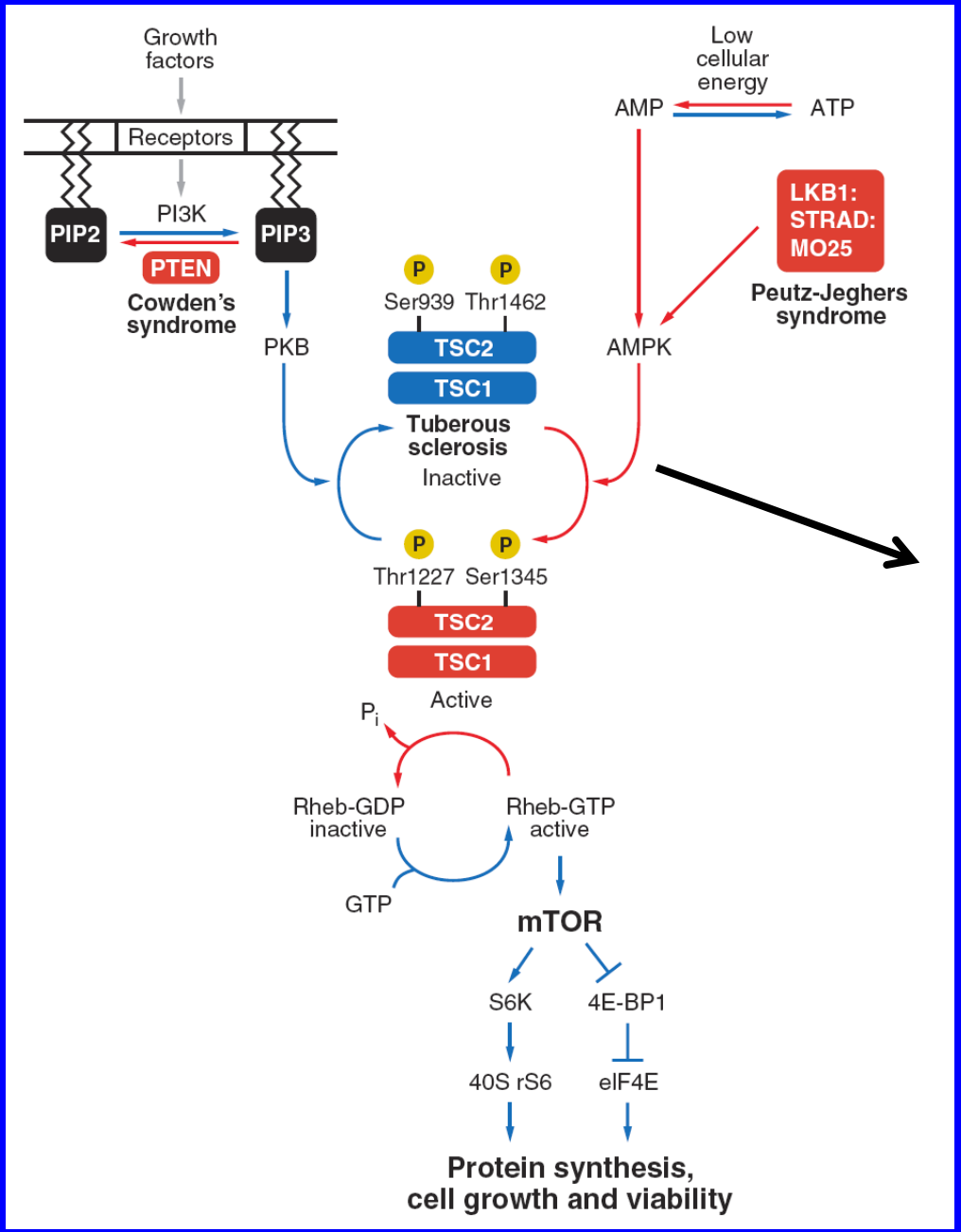


Figure 1 | Significantly mutated genes in lung adenocarcinomas. The height of the bars represents the number of somatic mutations in each indicated gene in 188 tumour and normal pairs. Standard, gene-specific and

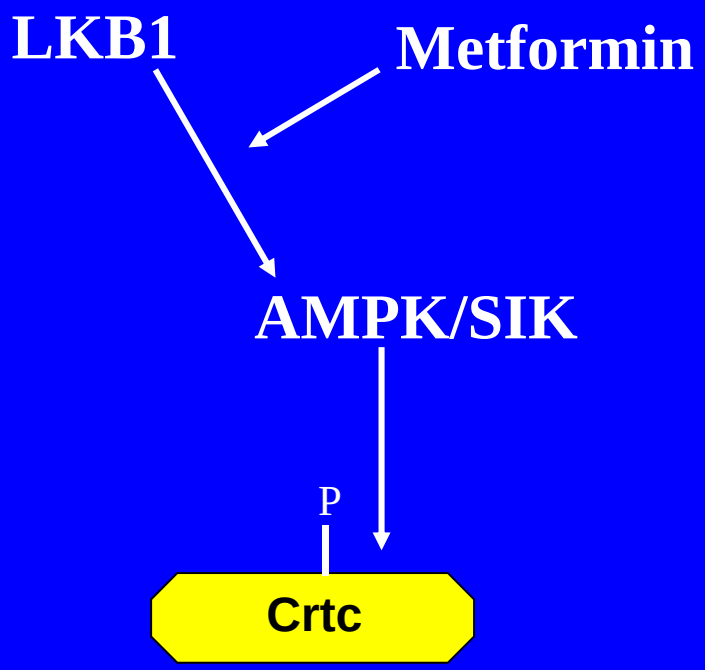
Nature. 2008 Oct 23;455(7216):1069-75

FOXO signaling pathway in aging and cancer





LKB1 links the AMPK pathway to cancer



- glucose/fatty acid metabolism
- aging
- cancer

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