7.343 Molecular Biology of Aging and Age-related Diseases

Fall 2008. Thursdays, 11 am – 1 pm. (Class time is flexible.) Room 68-151.

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Abstract

Over time, most organisms deteriorate and die in the process called biological aging. The desire of humanity to conquer this process and slow down or reverse aging is depicted in the oldest manuscripts available. The biological basis of aging is now being attacked using modern biological knowledge and sophisticated genetic and molecular tools. It is widely recognized that longevity is genetically controlled. Mouse lifespan is slightly longer than 2 years, the dog has a lifespan of about 15 years, humans about 80 years and some whales can easily reach the 200-year mark. There are also substantial variations within species. Some people look "very old" at the age of 50, while others are still quite energetic and youthful after 85. Scientists have generated a number of mutant and transgenic animals that have extended or shortened lifespans. Many genes that modify lifespan have been identified, and genetic pathways that govern longevity had been defined. What genes control aging, and how do these genes and their products work? In this course, we will discuss the advances that have been made in the field of the biology of aging. We will cover what is known about molecular genetic pathways that govern the rate of aging and longevity. We also will analyze interventions proposed to slow aging or at least delay the onset and severity of age-related diseases.

Course Details

The course will involve a weekly analysis of two scientific papers. It is essential that everyone read the papers before coming to class so the papers can be fully dissected, figure by figure. The success of the class will depend on students' participation in the discussions. The main goal of this course is to familiarize you with how to read and analyze the primary scientific literature. You will practice critical reading and discussion of scientific papers and learn to evaluate data, experimental design and methods. You will also be introduced to a variety of modern techniques in the area of aging. The course is graded pass/fail. A passing grade will be awarded to students who have satisfactory attendance, participate in discussions and have completed class assignments.

Assignments and Field Trip

At the end of each class session, a set of short assignments will be made. These will be directly related to the paper to be discussed during the following session. For example, we will ask you to look up a particular method that is used in the paper, or a reagent, a protein or a gene. You will then prepare to briefly explain that item in sufficient detail to your classmates to help them understand the paper. As our course progresses you will be asked to present more substantial parts of the paper. For example you might be asked to describe an experiment performed by the authors and critique the conclusions the authors derived from it.

Instead of a usual class on October 23rd we will have a **field trip to Sirtris Pharmaceuticals,** a biotechnology company that develops drugs directed against aging and age-related disorders.

Midterm assignment

There will be one written assignment in the middle of the course. Students will write a 2-page 1.5-spaced essay about the role of sirtuins in calorie restriction and longevity control. Sirtuins are genes suspected to control aging in numerous species. We will discuss these topics during the classes of week 6 and 7. We will also visit a biotechnology company that develops and produces sirtuin activators. Students are expected to critically but succinctly assess the arguments for and against linking sirtuins to longevity and present them in 2-page narration due on October 30th. Ideally, students will describe key experiments that led to the assertion that activation of sirtuins might be beneficial for longevity and age-associated diseases. In their essays students should put what they have learned during the course into an evolutionary perspective and speculate why this longevity-control system might have evolved and what role it might play in human beings. The essay also should address the pitfalls of sirtuin theory as well as expected negative side-effects of its activation.

Final assignment

At the end of the course each student will give a short (10-15 min) Power Point presentation. The presentation should briefly describe a primary research article (main finding, techniques used, and broad implications). Students are expected to identify the key figures and tables and the critical experiments described in the article, and discuss whether or not they agree with the conclusions of authors. Each student should choose a paper relevant to the course. The paper should be chosen by week 12 and be approved by the instructor.

Week 1 – September 4

Overview and discussion of syllabus.

Course policies.

Get to know each other.

Literature and database searching (PubMed, isi web of Science).

Reading and analyzing primary scientific papers.

Introduction to some of the techniques to be discussed throughout the course.

Week 2 – September 11

Introduction to Aging: How to identify genes and interventions that affect aging?

We will begin our discussion of the molecular and genetic foundations of aging. We will talk about genetic screening of yeast and the round worm of *C. elegans* that led to the initial identification of some aging genes and pathways. We will consider genetic manipulations that led to the extension of lifespan in model organisms.

B. K. Kennedy, N. R. Austriaco, Jr., J. Zhang and L. Guarente, **Mutation in the silencing gene SIR4 can delay aging in *S. cerevisiae***, *Cell*, 80: 485-96 (1995)

C. Kenyon, J. Chang, E. Gensch, A. Rudner and R. Tabtiang, **A *C. elegans* mutant that lives twice as long as wild type**, *Nature*, 366: 461-4 (1993)

Week 3 – September 18

Trade-offs in longevity and growth.

Insulin is one of the major regulators of growth. Mutations in insulin signaling pathways increase the lifespan of worms, flies and mice. The lifespan extension observed in *C. elegans daf-2* mutants requires the activity of *daf-16*, which encodes a transcriptional factor of the forkhead family. We will talk about the connection between insulin, metabolism and oxidative stress in worms.

K. D. Kimura, H. A. Tissenbaum, Y. Liu and G. Ruvkun, ***daf-2*, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans***, *Science*, 277: 942-6 (1997)

N. Libina, J. R. Berman and C. Kenyon, **Tissue-specific activities of *C. elegans* DAF-16 in the regulation of lifespan**, *Cell*, 115: 489-502 (2003)

Week 4 – September 25

Insulin signaling and its control of aging in mammals

Insulin signaling is believed to be a universal mechanism that control not only growth but also a rate of aging. The longevity benefit of decreased insulin signaling is believed to be mediated by a family of forkhead transcription factors. We will discuss the mechanism of forkhead transcription factor regulation, JNK kinase signaling and insulin signaling in mammals.

M. Holzenberger, J. Dupont, B. Ducos, P. Leneuve, A. Geloen, P. C. Even, P. Cervera and Y. Le Bouc, **IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice**, *Nature*, 421: 182-7 (2003)

M. C. Wang, D. Bohmann and H. Jasper, **JNK extends life span and limits growth by antagonizing cellular and organism-wide responses to insulin signaling**, *Cell*, 121: 115-25 (2005)

Week 5 – October 2

SIR2

The yeast SIR protein complex has been implicated in transcriptional silencing and suppression of recombination. We will discuss how SIR2 homologs regulate aging in two different model organisms , yeast and worms.

H. Aguilaniu, L. Gustafsson, M. Rigoulet and T. Nystrom, **Asymmetric inheritance of oxidatively damaged proteins during cytokinesis**, *Science*, 299: 1751-3 (2003)

H. A. Tissenbaum and L. Guarente, **Increased dosage of a *sir-2* gene extends lifespan in *Caenorhabditis elegans***, *Nature*, 410: 227-30 (2001)

Week 6 – October 9

SirT1 in mammals

Sir2 is an NAD+-dependent deacetylase that is conserved from bacteria to higher eukaryotes. Human SirT1 is the closest mammalian homolog of the yeast SIR2. This week we will talk about identification of Sir2 enzymatic activity and the regulation of p53 by SirT1 through deacetylation. P53 is a main cancer suppressor protein and is directly implicated in longevity.

S. Imai, C. M. Armstrong, M. Kaeberlein and L. Guarente, **Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase**, *Nature*, 403: 795-800 (2000)

H. Vaziri, S. K. Dessain, E. Ng Eaton, S. I. Imai, R. A. Frye, T. K. Pandita, L. Guarente and R. A. Weinberg, **hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase**, *Cell*, 107: 149-59 (2001)

Week 7 – October 16

Caloric restriction

Caloric restriction (CR) refers to a dietary regime low in calories without under-nutrition. CR extends the lifespan of many organisms, including rotifers, spiders, worms, fish, mice and rats. We will discuss how SIR2 links caloric restriction and lifespan extension, and we will talk about the connection between the insulin pathway and caloric restriction.

B. Rogina and S. L. Helfand, **Sir2 mediates longevity in the fly through a pathway related to calorie restriction**, *Proc Natl Acad Sci U S A*, 101: 15998-6003 (2004)

E. Nisoli, C. Tonello, A. Cardile, V. Cozzi, R. Bracale, L. Tedesco, S. Falcone, A. Valerio, O. Cantoni, E. Clementi, S. Moncada and M. O. Carruba, **Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS**, *Science*, 310: 314-7 (2005)

Week 8 – October 23

*Field trip to **SirTriS** pharmaceutical company*

Sirtris is a pharmaceutical company that works towards the design of drugs capable of slowing aging and extending healthy lifespan of humans. The founder of the company is David Sinclair, a former post-doctoral researcher from the laboratory of Dr. Lenny Guarente, an MIT faculty member. The company has made rapid progress since its foundation in 2004. This year the company put its first drug in clinical trials. The overall success prompted an acquisition of Sirtris by pharmaceutical giant GlaxoSmithKline for 720 million dollars earlier this year.

The trip will consist of a 20 min presentation, a 10 min questions section, and a 30 min tour.

Week 9 – October 30

Mid-term assignment paper is due this day by 11.59 pm.

Oxidative stress and mitochondria

Free radicals produced during aerobic respiration cause cumulative oxidative damage to proteins, lipids and DNA. Oxidative damage to mitochondrial and nuclear DNA is implicated in various degenerative diseases and aging. We will discuss animal models that are resistant to oxidative stress and have an extended lifespan and animals with an engineered mutation in a mitochondria-specific gene that age prematurely.

S. E. Schriner, N. J. Linford, G. M. Martin, P. Treuting, C. E. Ogburn, M. Emond, P. E. Coskun, W. Ladiges, N. Wolf, H. Van Remmen, D. C. Wallace and P. S. Rabinovitch, **Extension of murine life span by overexpression of catalase targeted to mitochondria**, *Science*, 308: 1909-11 (2005)

A. Trifunovic, A. Hansson, A. Wredenberg, A. T. Rovio, E. Dufour, I. Khvorostov, J. N. Spelbrink, R. Wibom, H. T. Jacobs and N. G. Larsson, **Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production**, *Proc Natl Acad Sci U S A*, 102: 17993-8 (2005)

Week 10 – November 6

Cellular senescence

Normal human cells undergo a finite number of cell division and ultimately enter a non-dividing state called replicative senescence. It has been proposed that telomere shortening is the molecular clock that triggers senescence. In this class we will discuss the connection between senescence and telomerase expression, and the function of oncogene p63 in the induction of senescence.

A. G. Bodnar, M. Ouellette, M. Frolkis, S. E. Holt, C. P. Chiu, G. B. Morin, C. B. Harley, J. W. Shay, S. Lichtsteiner and W. E. Wright, **Extension of life-span by introduction of telomerase into normal human cells**, *Science*, 279: 349-52 (1998)

W. M. Keyes, Y. Wu, H. Vogel, X. Guo, S. W. Lowe and A. A. Mills, **p63 deficiency activates a program of cellular senescence and leads to accelerated aging**, *Genes Dev*, 19: 1986-99 (2005)

Week 11 – November 13

Werner Syndrome

Werner syndrome is a human autosomal recessive disorder leading to premature aging. The mutations responsible for this disorder have been localized to a gene (WRN) encoding a protein that possesses DNA helicase and exonuclease activities. Patients carrying WRN gene mutations exhibit an elevated rate of cancer, accompanied by increased genomic instability. In this class we

will explore the possible mechanism by which mutation in the WRN gene cause premature aging in Werner Syndrome patients.

M. D. Gray, J. C. Shen, A. S. Kamath-Loeb, A. Blank, B. L. Sopher, G. M. Martin, J. Oshima and L. A. Loeb, **The Werner syndrome protein is a DNA helicase**, *Nat Genet*, 17: 100-3 (1997)

P. R. Laud, A. S. Multani, S. M. Bailey, L. Wu, J. Ma, C. Kingsley, M. Lebel, S. Pathak, R. A. DePinho and S. Chang, **Elevated telomere-telomere recombination in WRN-deficient, telomere dysfunctional cells promotes escape from senescence and engagement of the ALT pathway**, *Genes Dev*, 19: 2560-70 (2005)

Week 12 – November 20

Paper selection for final assignment is due this day.

Alzheimer´s Disease

The most common late-onset human neurodegenerative disease is Alzheimer´s disease which is genetically and pathologically linked to protein aggregation. In AD, formation of aggregation prone peptides A-beta 1-42, by endoproteolysis of the amyloid precursor protein (APP) is associated with the disease through an unknown mechanism. In this class, we will learn about insulin-signalling pathway and insulin growth factor 1 which prevents AD when decreased and try to learn how AD is studied in mouse models.

E. Cohen, J. Bieschke, R. M. Perciavalle, J. W. Kelly and A. Dillin, **Opposing activities protect against age-onset proteotoxicity**, *Science*, 313: 1604-10 (2006)

J. L. Jankowsky, D. J. Fadale, J. Anderson, G. M. Xu, V. Gonzales, N. A. Jenkins, N. G. Copeland, M. K. Lee, L. H. Younkin, S. L. Wagner, S. G. Younkin and D. R. Borchelt, **Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase**, *Hum Mol Genet*, 13: 159-70 (2004)

Week 13 – December 4

*Overview of aging and many processes it affects. General discussion about the articles analyzed in the course.

*Student project presentations.

*Student evaluations.

Each student will give a short (10-15 min) Power Point-assisted oral presentation about the paper they chose using skills developed during the course. Please choose the paper by November 20th, so that we can approve it before you start working on your presentation.

The presentation should be approximately 12 slides long.

- The first slide should present the paper title, authors, their affiliations, the journal, volume, pages, and year it was published.
- The next 2-4 slides should familiarize the audience with background information about the research the authors did. Describe what was known in the field before the research was undertaken, and what are the key molecules and pathways the audience has to know to understand the experimental flow.
- The next 3-4 slides should address the main techniques the authors used to do their experiments.
- The following 4-5 slides should describe the results obtained by authors and their implications. Describe the key experiments? Did they have proper controls and if so, what are they? Critically assess the conclusions that the authors draw from their data. Do they over-interpret their results; can anything else be concluded from the data obtained?
- The final slides should present a brief summary and your conclusion about the paper.

We will have a 5-10 minute discussion after each presentation.