Genetic factors in aging

Moyra Smith M.D., PH.D.
Division of Genetic and Genomic Medicine
UCI
Lecture outline

• Genetic factors impact all cells, tissues and physiological processes
• In considering genetics in aging I will focus on
• Key structures and processes implicated in aging including:
  • Cells, chromosomes, DNA, mitochondria,
  • Metabolism, Nutrition
  • Proteins, homeostasis (balance), folding and abnormal protein aggregation
  • Mechanisms to clear damaged proteins and cells (autophagy)
• I will also briefly consider specific diseases common in aging, their risk factors and pathogenetic processes:
  • Hyperlipidemias and cardio-vascular disease
  • Skeletal and joint disorders
  • Specific Cancer related factors
  • Specific late onset neurodegenerative diseases.
Figure 3. Damage and Aging

Underlying the aging process is a lifelong, bottom-up accumulation of molecular damage. Such damage is intrinsically random in nature, but its rate of accumulation is regulated by genetic mechanisms for maintenance and repair. As cell...

Thomas B.L. Kirkwood

Understanding the Odd Science of Aging

null, Volume 120, Issue 4, 2005, 437–447

http://dx.doi.org/10.1016/j.cell.2005.01.027
Annu. Rev. Biochem. 85:35–64
Aging in mammals is accompanied by a progressive atrophy of tissues and organs, and stochastic **damage accumulation** to the macromolecules DNA, RNA, proteins, and lipids.

The sequence of the human genome represents our genetic blueprint, and accumulating evidence suggests that **loss of genomic maintenance** may causally contribute to aging.

Distinct evidence for a role of **imperfect DNA repair** in aging is that several premature aging syndromes have underlying genetic DNA repair defects.

Accumulation of DNA damage may be particularly prevalent in the central nervous system owing to the low DNA repair capacity in postmitotic brain tissue (most neurons do not undergo division to give rise to new neurons).

Telomeres in aging and disease.

Telomerase (TERT) is responsible for maintaining telomeres.

Telomeres and telomerase as therapeutic targets to prevent and treat age-related diseases

Christian Bär¹ and Maria A. Blasco 2016
Telomeres, the protective ends of linear chromosomes, shorten throughout an individual’s lifetime.
Telomere shortening is a hallmark of molecular aging and is associated with premature appearance of diseases associated with aging

Telomeres are heterochromatic structures located at the ends of linear chromosomes formed by DNA tandem repeats bound by specialized protein complexes, which exert a protective function.

A proper telomere structure prevents chromosome ends from being recognized as DNA strand breaks.

In vertebrates, telomeric DNA is composed of up to thousands of TTAGGG hexanucleotide repeats that are bound by a six-protein complex known as shelterin.
Fig. 1. Overview of the DNA damage theory of ageing. A variety of intrinsic and extrinsic sources can result in DNA damage. An array of complex DNA repair mechanisms evolved to repair DNA damage, yet these are not perfect. DNA lesions in cells can lead to muta...

Alex A. Freitas, João Pedro de Magalhães

A review and appraisal of the DNA damage theory of ageing

Mutation Research/Reviews in Mutation Research, Volume 728, Issues 1–2, 2011, 12–22

http://dx.doi.org/10.1016/j.mrrev.2011.05.001
Fig. 1 Overview of epigenetic changes during aging.

Modifications of DNA


Published by AAAS
Loss of DNA methylation leads to activation of normally silenced DNA sequences like the transposable elements. However, DNA methylation also increases in a non-stochastic manner over the CpG islands of certain genes, correlating with their heterochromatinization and silencing.

Figure 1. Model of Parkin-Induced Mitophagy

Dysfunctional mitochondria (yellow mitochondrion) fail to import and degrade PINK1 stabilizing it on the outer mitochondrial membrane (OMM). After PINK1 accumulation, PINK1 phosphorylates ubiquitin and Parkin to activ...

Alicia M. Pickrell, Richard J. Youle

The Roles of PINK1, Parkin, and Mitochondrial Fidelity in Parkinson's Disease

null, Volume 85, Issue 2, 2015, 257–273

http://dx.doi.org/10.1016/j.neuron.2014.12.007
Fig. 1. The sedentary elderly mitochondrion. Schematic shows key mitochondrial changes in a sedentary elderly individual. Solid arrows indicate likely casual relationships, whereas dashed arrows are more speculative relationships. Green boxes indicate those pr...

Brendan A.I. Payne, Patrick F. Chinnery

Mitochondrial dysfunction in aging: Much progress but many unresolved questions

Biochimica et Biophysica Acta (BBA) - Bioenergetics, Volume 1847, Issue 11, 2015, 1347–1353

http://dx.doi.org/10.1016/j.bbabio.2015.05.022
DNA glycosylases are the first DNA repair enzymes recruited to oxidative lesions and there are 11 glycosylases in humans.

Fig. 1. Oxidative damage repair of ROS-induced DNA damage in normal aging and neurological diseases. Amyloid beta precursor protein (AβPP) aggregates, α-synuclein deposits and ischemic reperfusion can cause mitochondrial dysfunction and increase cellular ROS...

Chandrika Canugovi, Magdalena Misiak, Leslie K. Ferrarelli, Deborah L. Croteau, Vilhelm A. Bohr

The role of DNA repair in brain related disease pathology

DNA Repair, Volume 12, Issue 8, 2013, 578–587

http://dx.doi.org/10.1016/j.dnarep.2013.04.010
Figure 3. Mechanisms of proteostasis impairment. (A) Homeostasis. The capacity of the chaperone network is sufficient to correctly fold most newly synthesized proteins. The limited fraction of proteins that cannot be successfully folded on synthesis (~5–10% of...
Molecular chaperones are key players in the cellular proteostasis network and serve to maintain a balanced proteome.

David Balchin et al. Science 2016;353:aac4354
The ubiquitin (Ub)-proteasome pathway (UPP) of protein degradation.

Stewart H. Lecker et al. JASN 2006;17:1807-1819
Figure 1. Simplified Diagram of Autophagy Pathways. Macroautophagy is initiated by recruitment of ULK and PI3K complex to the phagophore assembly site (PAS). The ULK complex is composed of ULK1/2, FIP200, and ATG13. The PI3K complex is made up of Vps34, Vps15,...

Damaged cells and cells with damaged DNA are removed in a process defined as autophagy.
Metabolism
**MTOR (TORC1)**
Key regulator of growth and cell proliferation
Is stimulated by intake of nutrients glucose, amino acids, lipids
Dietary restriction (DR), a moderate reduction in food intake, improves health during aging and extends life span across multiple species.

Aging is defined as an accumulation of cellular damage over time, promoting disease and death.

Genetic or pharmacological inhibition of TORC1 signaling extends lifespan in yeast, worms, flies and mice

Importantly, rapamycin delays the onset of age-related disease and extends lifespan even in old mice
Cornu et al, 2012

There is evidence that MTOR inhibits autophagy
Environment influences neurodegeneration through age modifiers and proteostasis networks.

Peter M. Douglas, and Andrew Dillin J Cell Biol 2010;190:719-729
The most frequent form of monogenic hypercholesterolemia, also known as **Familial Hypercholesterolemia (FH)**, is characterized by plasma accumulation of cholesterol transported in Low Density Lipoproteins (LDLs). FH has a co-dominant transmission with a gene-dosage effect.

FH heterozygotes have levels of plasma LDL-cholesterol (LDL-C) twice normal and present xanthomas and coronary heart disease (CHD) in adulthood.

Most FH patients are carriers of mutations of the LDL receptor (LDLR);

a minority of them carry either mutations in the Apolipoprotein B (ApoB), the protein constituent of LDLs which is the ligand for LDLR,

or gain of function mutations of PCSK9, the protein responsible for the intracellular degradation of the LDLR.

(Fellin e tl., 1015)
LDL in FH: A comparative look.

Prashant Nair PNAS 2013;110:14829-14832
Genetic basis of common polygenic triglyceride (TG) phenotypes
Lewis, Hegele, 2015

Clinically relevant abnormalities of plasma TG levels appear to require a polygenic foundation of common variants.

These create a background state of predisposition that can interact with additional rare heterozygous variants or nongenetic secondary factors, then forcing expression of a more extreme TG phenotype

Forty-Five Single Nucleotide Polymorphism Loci Associated With Plasma TG Levels Either Independently or in Conjunction With Other Plasma Lipid Traits

There is convincing evidence that hypertriglyceridemic states are associated with accelerated atherosclerosis and cardio-vascular disease (CVD)

Nongenetic, Aggravating Causes of hypertriglyceridemia (HTG): Insulin Resistance, Nephrotic Syndrome, Alcohol Consumption
Complex genetic basis of HTG. Elevated plasma TG levels are typically due to interactions between genetic susceptibility factors: an increased burden of rare heterozygous variants of large effect in the genes indicated plus a high cumulative burden of common single nucleotide polymorphisms of small effect from >40 loci from across the genome (Table 2). The presence of any one of several secondary nongenetic factors can exacerbate the biochemical phenotype, as discussed in the text. Among individuals with plasma TG levels between 2 and 10 mmol/L, the underlying genetic architecture appears indistinguishable in terms of burden of TG-raising genetic variants.
Age-related degenerative disorders of the spine and synovial joints

Basic understanding of the age-related changes in joint tissue is needed to combat the adverse effects of aging on joint health.

Aging is caused at least in part by time-dependent accumulation of damaged organelles and macromolecules, leading to cell death and senescence

In addition there is the eventual loss of multipotent stem cells and tissue regenerative capacity.
Cancer related factors

**Intact and normal p53 protein function is important in preventing cancer**

Aberrant p53 or abnormal p53 function is one of the most common defects found in cancer.

p53 has an important role in determining the response of cells to numerous types of stress — such as DNA damage, hypoxia and nutrient fluctuation — by both supporting cell survival and promoting cell death.

p53 activity can result in a permanent inhibition of cell proliferation, through the induction of cell death, senescence and differentiation. There are various mechanisms through which p53 can support cell survival, including the role of p53 in enabling metabolic adaptation.

Flore Kruiswijk, Christiaan F. Labuschagne & Karen H. Vousden

*Nature Reviews Molecular Cell Biology | Review*

2015
In the case of repairable damage or transient stress, a reversible process is activated that allows for damage repair and/or adaptation in response to the change in environment.

However, when the stress stimulus is persistent and irreparable, the affected cell is permanently removed from the pool of proliferating cells through cell death, senescence or the induction of terminal differentiation.

Approximately 50% of all tumours harbour mutations in the tumour suppressor gene \textit{TP53}.
The 127 SMGs from 20 cellular processes in cancer identified in 12 cancer types.

Attempts to reactivate expression of normal p53 in cancer

• Among the tumor suppressor genes, p53 is one of the most studied. It is widely regarded as the "guardian of the genome", playing a major role in carcinogenesis. In fact, direct inactivation of the TP53 gene occurs in more than 50% of malignancies, and in tumors that retain wild-type p53 status, its function is usually inactivated by overexpression of negative regulators (e.g., MDM2 and MDMX).

• Hence, restoring p53 function in cancer cells represents a valuable anticancer approach. Ribeiro et al., 2016 presented an updated overview of the most relevant small molecules developed to restore p53 function in cancer cells through inhibition of the p53-MDMs interaction, or direct targeting of wild-type p53 or mutated p53. In addition, optimization approaches used for the development of small molecules that have entered clinical trials will be presented.
Common mutations in cancer

The most frequently mutated gene in the Pan-Cancer cohort is TP53 (42% of samples). Its mutations predominate in serous ovarian (95%) and serous endometrial carcinomas (89%) (Fig. 2). TP53 mutations are also associated with basal subtype breast tumours. PIK3CA is the second most commonly mutated gene, occurring frequently (>10%) in most cancer types except OV, KIRC, LUAD and AML. PIK3CA mutations frequented UCEC (52%) and BRCA (33.6%), being specifically enriched in luminal subtype tumours. Tumours lacking PIK3CA mutations often had mutations in PIK3R1, with the highest occurrences in UCEC (31%) and GBM (11%).

Mutational landscape and significance across 12 major cancer types

Telomeres and telomerase in Cancer

A hallmark of advanced malignancies is the ability for continuous cell divisions that almost universally correlates with the stabilization of telomere length by the reactivation of telomerase. The repression of telomerase and shorter telomeres in humans may have evolved, in part, as an anticancer protection mechanism. Although there is still much we do not understand about the regulation of telomerase, it remains a very attractive and novel target for cancer therapeutics.

In summary, telomerase and its regulation of telomere length is an important target both for cancer therapy and for the treatment of age-related disease. The telomerase gene will likely have many important applications in the future of medicine and cellular engineering.

*Cancer Discov.* 2016 Role of Telomeres and Telomerase in Aging and Cancer. Shay JW¹.
All somatic normal human cells display progressive telomere shortening with increased cell divisions.

Jerry W. Shay Cancer Discov 2016;6:584-593
It is now widely accepted that new neurons continue to be added to the brain throughout life including during normal aging. The finding of adult neurogenesis in the hippocampus, a structure involved in the processing of memories, has favored the idea that newborn neurons might subserve cognitive functions, Verret et al. 2007. Strategies aimed at promoting neurogenesis may also contribute to improve cognitive deficits caused by normal or pathological aging.

Adult hippocampal neurogenesis is a complex multi-step process that originates from multipotent precursor cells in the SGZ of the dentate gyrus. The sequence is composed of proliferation of progenitor cells, commitment to a neuronal phenotype, morphological and physiological maturation, and functional synaptic integration into the pre-existing hippocampal circuitry.

Hippocampal neurogenesis is finely tuned and influenced by a wide range of intrinsic factors such as neuronal activity in the local environment, neurotransmitters, growth factors and hormones (Overstreet-Wadiche and Westbrook, 2006). Extrinsic factors such as environmental enrichment, physical activity, stress or caloric restriction also regulate adult hippocampal neurogenesis.
Human umbilical cord plasma proteins revitalize hippocampal function in aged mice
Castellano et al., (Nature 2017)

We thus created a youth-associated protein list by overlapping human and mouse age-related plasma changes. Given the unexplored role of TIMP2 in CNS plasticity and cognition, we further pursued TIMP2 and confirmed elevations in cord plasma.

We detected an age-related decline in TIMP2 protein in hippocampal lysates by immunoblotting.

To investigate whether systemic TIMP2 was sufficient to improve hippocampal-dependent learning and memory, we administered TIMP2 over 2 weeks, leading to significant improvements in several functional outcomes.

The necessity of TIMP2 for the beneficial activity of cord plasma and its ability to improve aspects of hippocampal function at an age when TIMP2 expression has declined suggest that it may be a critical mediator in mechanisms governing synaptic plasticity.

Here we show that human cord plasma treatment revitalizes the hippocampus and improves cognitive function in aged mice. Tissue inhibitor of metalloproteinases 2 (TIMP2), a blood-borne factor enriched in human cord plasma, young mouse plasma, and young mouse hippocampi, appears in the brain after systemic administration and increases synaptic plasticity and hippocampal-dependent cognition in aged mice. Depletion experiments in aged mice revealed TIMP2 to be necessary for the cognitive benefits conferred by cord plasma. We find that systemic pools of TIMP2 are necessary for spatial memory in young mice, while treatment of brain slices with TIMP2 antibody prevents long-term potentiation, arguing for previously unknown roles for TIMP2 in normal hippocampal function. Our findings reveal that human cord plasma contains plasticity-enhancing proteins of high translational value for targeting ageing- or disease-associated hippocampal dysfunction.
<table>
<thead>
<tr>
<th>Neurodegenerative Disease</th>
<th>Pathology</th>
<th>Component Proteins</th>
</tr>
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<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Senile plaques, Neurofibrillary tangles, Lewy bodies, Neuronal inclusions</td>
<td>Ab amyloid, Tau, a-Synuclein</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Lewy bodies</td>
<td>a-Synuclein</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Neuronal inclusions</td>
<td>TDP-43, FUS/TLS, SOD1</td>
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<tr>
<td>Huntington's disease</td>
<td>Neuronal intranuclear inclusions</td>
<td>Huntington</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Lewy bodies, Senile plaques, Neurofibrillary tangles</td>
<td>a-Synuclein, Ab amyloid, Tau</td>
</tr>
<tr>
<td>Frontotemporal diseases</td>
<td>Neuronal and glial inclusions</td>
<td>Tau, TDP-43, FUS</td>
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<td>Multiple system atrophy</td>
<td>Gliarial cytoplasmic inclusions</td>
<td>a-Synuclein</td>
</tr>
<tr>
<td>Prion diseases</td>
<td>Senile plaques</td>
<td>PrP protein</td>
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NOTES: FUS/TLS = fused in sarcoma/translocated in liposarcoma; PrP = prion protein; SOD1 = superoxide dismutase 1; TDP-43 = TAR DNA-binding protein 43.
Proteolytic Processing of Amyloid Precursor Protein (APP) by β- and γ-Secretases to Generate Amyloid β (Aβ) Protein When APP undergoes nonamyloidogenic proteolytic cleavage by α- and γ-secretases, p3 instead of Aβ is generated. A small number of APP molecules is proteolytically processed by β-secretase and generates an N-terminal soluble APP and a 12-kDa C-terminal stub of APP, which is cleaved by γ-secretase to yield Aβ and amyloid intracellular domain. The PS1 and PS2 genes carry the active site of γ-secretase complex. Proteins encoded by multiple risk genes associated with late-onset Alzheimer disease are involved in Aβ clearance. The SORL1, PICALM, and CD2AP genes regulate APP endocytosis (vs retromer-mediated APP recycling) and Aβ generation in endosome-lysosomes.
Figure 1. Rare and common variants contribute to Alzheimer's disease risk. GWAS, genome-wide associated studies. (Updated and modified with permission from Guerreiro et al. [149].)

Celeste M. Karch, Alison M. Goate

Alzheimer's Disease Risk Genes and Mechanisms of Disease Pathogenesis

Biological Psychiatry, Volume 77, Issue 1, 2015, 43–51

http://dx.doi.org/10.1016/j.biopsych.2014.05.006
Schematic overview of frequency and conferred risk of genes and genetic loci associated with the development of familial and idiopathic PD/parkinsonism.

Ravindran Kumaran, and Mark R. Cookson Hum. Mol. Genet. 2015;24:R32-R44

Published by Oxford University Press 2015. This work is written by (a) US Government employee(s) and is in the public domain in the US.
Figure 1. Model of Parkin-Induced Mitophagy

Dysfunctional mitochondria (yellow mitochondrion) fail to import and degrade PINK1 stabilizing it on the outer mitochondrial membrane (OMM). After PINK1 accumulation, PINK1 phosphorylates ubiquitin and Parkin to activ...
Figure 1. Clinical, Genetic, and Pathological Overlay of ALS and FTD

A) ALS and FTD represent a continuum of a broad neurodegenerative disorder with each presenting as extremes of a spectrum of overlapping clinical symptoms (ALS in red and FTD in purple). Major...

Shuo-Chien Ling, Magdalini Polymenidou, Don W. Cleveland

Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis


http://dx.doi.org/10.1016/j.neuron.2013.07.033
Abnormal intracellular protein aggregates comprise a key characteristic in most neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

The seminal discoveries of accumulation of TDP-43 in most cases of ALS and the most frequent form of FTD, frontotemporal lobar degeneration with ubiquitinated inclusions, followed by identification of FUS as the novel pathological protein in a small subset of patients with ALS and various FTD subtypes provide clear evidence that these disorders are related.

Smn also associates with components not included in the classical SMN complex like RNA-binding proteins FUS, TDP43,

**Therapeutic reduction of ataxin-2 extends lifespan and reduces pathology in TDP-43 mice**
From
Neurodegenerative disease: Two-for-one on potential therapies
Ke Zhang & Jeffrey D. Rothstein
Nature 544, 302–303 (20 April 2017) | doi:10.1038/nature21911

a. Toxic mutations in the gene that encodes ataxin 2 cause transcriptional dysregulation in neurons called Purkinje cells, disrupting their function. This leads to the neurodegenerative disease spinocerebellar ataxia type 2. Scales et al.1 studied mice that harboured the disease-causing human gene, injecting them with an antisense oligonucleotide (ASO) molecule that binds to ataxin 2 messenger RNA and inhibits its translation. The treatment ameliorates the effects of the disease. b. Ataxin 2 also promotes the assembly of cytoplasmic RNA-protein complexes called stress granules, in which the protein TDP-43 aggregates to form toxic clumps. This aggregation is thought to contribute to the neurodegenerative disease amyotrophic lateral sclerosis (ALS). Becker et al.2 show that an ataxin 2
Figure 1. Model of Parkin-Induced Mitophagy: Dysfunctional mitochondria (yellow mitochondrion) fail to import and degrade PINK1 stabilizing it on the outer mitochondrial membrane (OMM). After PINK1 accumulation, PINK1 phosphorylates ubiquitin and Parkin to activ...
Healthy neurons efficiently remove damaged mitochondria by mitophagy as a quality control mechanism to ensure cell survival. Excess mitochondrial damage (from trig...