Dynamics of ageing: a silent transformation caused by “noise”

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The Silent Transformations of Ageing

Silent transformation of the body

Silent transformation of society
Recent trends in life expectancy (2006-2013)

Source: http://data.worldbank.org
Transformation of Population Structures

Source: Statistics Finland www.stat.fi
Transformation even in the poorest regions

Photo: Immigration hut at border between Burkina Faso and Ghana
Unexpected Continuation of Growth in Life Expectancy

Declining early/mid-life mortality

Declining later-life mortality

Oeppen & Vaupel Science 2002
Understanding the silent transformations of ageing

- Why and how does ageing occur?
- What is the relationship between ageing and disease?
- What explains the continuing increase in life expectancy?
- What accounts for the individuality of ageing?
- Changing the mind-set
Why There is No Genetic Programming FOR Ageing

• Animals in nature mostly die young.

• There is neither need nor opportunity to evolve a program.

• Programmed ageing, if it existed, would be ‘unstable’.

Kirkwood & Melov *Current Biology* 2011
Life – a Sexually Transmitted Condition with an Invariably Fatal Outcome
Immortal Germ-Line – Mortal Soma

August Weismann
Molecular integrity, cell generation $t+1$

The margin of safety is increased (reduced) by increasing (reducing) the energy invested in molecular proofreading and error elimination.

Reducing the margin of safety to a minimal level saves considerable energy but leaves the cell highly vulnerable to accumulation of defects.

Cellular Stability and Instability

Kirkwood & Holliday *J Mol Biol* 1975
THE CENTRAL PROBLEM OF ALLOCATING METABOLIC RESOURCES

DISPOSABLE SOMA THEORY

Period of longevity assured by maintenance and repair

Protected

Wild

Survival

Age

Kirkwood *Nature* 1977
Mechanistic Implications of Disposable Soma Theory

- Maintenance & repair high in germ-line; reduced in soma
- Ageing caused primarily by damage
- Longevity regulated by resistance/repair

- Inherently stochastic
- Multiple mechanisms; Complexity
- Plasticity and trade-offs
"Accuracy in the germ line is vital but a high level of accuracy in somatic cells may be a luxury our genes do better to forego.

Ageing may, therefore, be the result of … switching off the mechanisms responsible for high accuracy at or around the time of differentiation of somatic cells from the germ line."

Kirkwood Nature 1977
Germ Cells are Special – Embryonic Stem Cells Lose this Status as they Undergo Differentiation

Embryoid Bodies

ES  EBs d2  d4  d6

AO defence, DNA repair, chaperones

‘Noise’ Drives the Ageing Process

- Copying errors, Telomere shortening
- Mutations e.g. ROS
- Transcription errors
- Translation errors
- Damage, denaturing e.g. ROS
- Antioxidants
- Refolding
- Chaperones
- Degradation or aggregation (e.g. β-amyloid)

Processes:
- DNA → RNA → PROTEIN
- DNA
- RNA
- PROTEIN
- mtDNA

Factors:
- ROS, etc
- ATP
The Importance of a Systems Approach

Phenotypic outcome

Underlying causes

Reduction
Integration
Each cell division is accompanied by inevitable somatic mutation.

Age-Related Increase in Frequency of Hprt Mutations in Mice

Odagiri et al Nat Genet 1998
Senescent Cell (human fibroblast)

- DNA damage foci
- Telomeres
- Overlap of damage foci with telomeres
- Mitochondria with high membrane potential
- Mitochondria with low membrane potential
Cellular Responses to Damage – Apoptosis

- Apoptosis acts to **delete unwanted cells**.
- Cells may be unwanted during development (tissue shaping), haematopoiesis (auto-reactive immune cells), or because they become **damaged with increased risk of adverse consequences**, e.g. malignancy.
- Frequency of apoptosis increases with age, because **age is associated with damage**.
- Enhancing pro-apoptotic pathways in transgenic mice confers increased protection against cancer but **accelerates aging** through more rapid loss of tissue cellularity.
Ageing of Human Fibroblasts *in vitro*: The Hayflick “limit”

replicative senescence

1 month                  3 months                  6 months           1 year                  2 years
PD 10                   PD 25                          PD 50                       PD 50                              PD 50

PD: population doublings – measure of cell multiplication
Mitochondrial Dysfunction Accounts for the Stochastic Heterogeneity in Telomere-Dependent Senescence

Sozou & Kirkwood 2001

Multiple mechanisms:
• Telomere shortening
• Mitochondrial dysfunction
• Nuclear mutation
• Stochastic simulation

Data

Smith & Whitney 1980

Systems Modelling ↔ Experiment
Combining *in-silico* interactome analysis and functional target gene inhibition, stochastic modelling and live cell imaging, we found that there exists a dynamic feedback loop that is triggered by molecular damage and which locks the cell into an actively maintained state of cellular senescence.

The essential feature of the loop is that long-term activation of the checkpoint gene CDKN1A (p21) induces mitochondrial dysfunction and production of reactive oxygen species (ROS) via serial signalling through GADD45-MAPK14(P38MAPK)–GRB2-TGFBR2-TGFb.

Passos et al *Mol Systems Biol* 2010
Senescence is a regulated response to damage mediated by a positive feedback loop between DNA damage and mitochondrial ROS generation. Passos et al. *Mol Sys Biol* 2010.

Cellular senescence is causally implicated in generating age-related phenotypes and removal of senescent cells can prevent or delay tissue dysfunction. Baker et al *Nature* 2011.
Correlation Between Cellular Stress Resistance and Mammalian Species Life Span

Kapahi, Boulton, Kirkwood  Free Rad Biol Med 1999
Understanding the silent transformations of ageing

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Intrinsic Ageing is the Primary Driver of Chronic Disease

AGEING

- Sarcopenia
- Diabetes
- Cancer
- Stroke
- CVD
- CKD
- COPD/ Pulmonary Fibrosis
- Neurodegeneration
- Dementias
- Blindness
- Arthritis
- Osteoporosis

US National Institute on Aging
Risk Factors for Age-Related Diseases

**Alzheimer’s Disease**
- Sex
- Diabetes
- Phys Inact
- ApoE
- Smoking

**Heart Disease**
- Hypertension
- Smoking
- Cholesterol
- Diabetes

**Cancer**
- Tobacco
- Alcohol
- Diet
- Infection

**Alzheimer’s Disease**
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- Aging
Intrinsic Ageing and Age-Related Disease
Accumulation of Molecular and Cellular Damage

Initiating Processes

Intrinsic Ageing

End-Stage Pathology

Disease A

Disease B

Disease C

Likely Effectiveness of Interventions
Fundamental Mechanisms Shared by Intrinsic Ageing and Age-Related Chronic Diseases

- Macromolecular dysfunction
- Replicative senescence
- Apoptosis
- Stem cell dysfunction
- Inflammation (chronic, low-grade, sterile)
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HUMAN AGEING AND ITS MALLEABILITY
Kirkwood *Cell* 2005

Age-related Frailty, Disability, and Disease

Accumulation of Cellular Defects

Random Molecular Damage

INFLAMMATION

ANTI-INFLAMM.

GOOD LIFESTYLE

GOOD NUTRITION

STRESS

ENVIRONMENT

BAD NUTRITION
Understanding the silent transformations of ageing

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Factors Influencing Health Trajectories in Old Age

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude
Genetics of Human Longevity

Twin Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Coefficient of heritability</th>
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<tbody>
<tr>
<td>McGue et al (1993)</td>
<td>0.22</td>
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<tr>
<td>Herskind et al (1996)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ljungquist et al (1998)</td>
<td>&lt;0.33</td>
</tr>
</tbody>
</table>

Genes account for about 25% of what determines human longevity.

The relevant genes are numerous, mostly of small individual effect, and they influence somatic maintenance and metabolism.

Schachter, Cohen, Kirkwood *Hum Genet* 1993
Kirkwood, Cordell, Finch *Trends Genet* 2011
Beekman et al *Aging Cell* 2013
Deelen et al *Hum Mol Genet* 2014
Nutrition and Survival: The EPIC-Ageing Study

76,707 men and women aged 60+
Followed for 7.5 years

Adherence to Mediterranean diet assessed on 10-point scale:
0 (poor)...9 (high)

2 unit increase in ‘Mediterraneanness’ of diet results in 8% reduction of overall mortality

Trichopoulou A et al. (2005) BMJ 330, 991-997
A few minutes on the Newcastle metro can take years off your life ...

Age of expected onset of limiting long-term condition for 55 yr old person

Courtesy Prof Peter Gore/Prof Carol Jagger/ONS
Factors Influencing Health Trajectories in Old Age
Newcastle 85+ Study; prospective study in 1000+ individuals born in 1921

Comprehensive study of the complex biological, medical and psychosocial factors affecting ageing trajectories of 85+ year olds.

Domains of assessment: health (nurse assessment and GP record review); cognitive and physical function; nutrition; activity; sleep; sensory function; psychology; socioeconomics; biological markers; genetics.

Exceptionally high rates of recruitment and retention through nurse-led development and refinement of procedures.
No one has perfect medical health at age 85. Yet, 78% rated their health compared with others of the same age as “good” (34%), “very good” (32%) or “excellent” (12%).

Collerton et al British Medical Journal 2009
A quarter of men and a sixth of women have no important functional limitation at age 85.

Jagger et al. *BMC Geriatrics* 2011
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The bad news is we are living even longer
Oracle founder Larry Ellison has proclaimed his wish to live forever and donated more than $430 million to anti-aging research. “Death has never made any sense to me,” he told his biographer, Mike Wilson. “How can a person be there and then just vanish, just not be there?”

Larry Page, who is now 41 and chief executive of Google, has made the biggest bet on longevity yet, founding Calico, short for California Life Company, a secretive anti-aging research center, with an investment of up to $750 million from Google.

Bill Gates has been very vocal in his praise of the generosity of Silicon Valley’s newly minted billionaires, but in January 2015 he expressed misgivings about their priorities. He wrote, “It seems pretty egocentric while we still have malaria and TB for rich people to fund things so they can live longer.”
The Life Course Trajectory of Mental Capital and Wellbeing

Mental Capital & Wellbeing

Lifestage

Childhood  Adulthood  Older

Government Office for Science - Foresight: Mental Capital and Wellbeing Project.
Key Questions and Implications

■ Can we identify the precise factors contributing to the malleability of longevity and health in old age?

■ Can we improve understanding of age-related multimorbidity?

■ Can we use such knowledge further to promote health in old age and to reduce frailty and dependency?

■ What mechanisms do we need to set in place to track trends in incidence of age-related diseases?
Common misconceptions about population ageing

- Old age is inevitably a period of poor quality existence
- Population ageing is the main cause of increased health costs
- Population ageing threatens dangerous growth in the size of the world’s population
- Older people are an unsupportable economic burden
Thank you

Centre for Integrated Systems Biology of Ageing and Nutrition

Newcastle 85+ Study team

Institute for Ageing and Health (now NUIA)