What Causes Frailty?

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15 October 2013
Biology of Intrinsic Ageing

What happened? Why?
What Causes Ageing?

• Ageing is associated with progressive increase in age-specific death rate from early teens onwards (approximate doubling every 8 years).

• Ageing is widespread across the “tree of life” but not universal.

• Ageing is not actively programmed; the body is programmed for survival but not well enough to last forever (“disposable soma” theory).

• Intrinsic ageing is driven by damage.

• Genetic influences on human longevity arise through the actions of many genes, individually of small effect; these genes influence the body’s maintenance and repair systems?
Functional Impairments in Organs and Tissues leading to Age-related Frailty, Disability, and Disease

Accumulation of Cellular Defects

Random Molecular Damage

The Ageing Process
Status Report on a Senescent Human Cell

- DNA damage foci
- Telomeres
- Overlap of damage foci with telomeres
- Mitochondria with high membrane potential
- Mitochondria with low membrane potential
AGEING PROCESS AND ITS MALLEABILITY

Kirkwood *Cell* 2005

**Age-related Frailty, Disability, and Disease**

**Accumulation of Cellular Defects**

**Random Molecular Damage**

**GOOD NUTRITION**

**GOOD LIFESTYLE**

**ANTI-INFLAMM.**

**INFLAMMATION**

**STRESS**

**ENVIRONMENT**

**BAD NUTRITION**
Nutrition and Survival: The EPIC-Ageing Study

76,707 men and women aged 60+
No CHD, stroke or cancer at enrolment
Median follow up 89 months (4047 deaths)

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

2 unit increment in ‘Mediterranean-ness’ of diet results in 8% reduction of overall mortality

Trichopoulou A et al. (2005) BMJ 330, 991-997
Cardiovascular fitness and mortality


6213 consecutive men referred for treadmill exercise testing

Quintiles of maximal exercise capacity

Relative risk of death

No Cardiovascular disease

With Cardiovascular disease

1.0 – 5.9

6.0 – 7.9

8.0 – 9.9

10.0 – 12.9

>13.0

>10.7

1.0 – 4.9

5.0 – 6.4

6.5 – 8.2

8.3 – 10.6

>13.0

>10.7

46,405 men and 15,282 women without known MI or stroke at baseline
All Cause Mortality per 10,000 person years

P = 0.001

<60

P = 0.02

20

Cancer Mortality per 10,000 person years

P = 0.005

>60

P = 0.007

40

80

120

160

Lower 3\textsuperscript{rd}

Middle 3\textsuperscript{rd}

Upper 3\textsuperscript{rd}

Tertiles of muscular strength

8762 men

Factors Influencing Health Trajectories in Old Age

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude

These factors and their interactions are being studied in the Newcastle 85+ Study; a 5-year prospective study in more than 1000 individuals born in 1921 of the biological, clinical and psychosocial factors associated with healthy ageing.
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
Targeting Age-Related Disease
Accumulation of Molecular and Cellular Damage

Initiating Processes

End-Stage Pathology

Likely Effectiveness of Interventions

Disease A

Disease B

Disease C
So What is Frailty?

• Is frailty just extreme ageing?

• Frailty is notoriously elusive to define:
  
  – Linda Fried: a clinical syndrome – a cluster of specific symptoms and signs including weight loss, exhaustion, low physical activity, muscle weakness and slow walking speed.

  – Ken Rockwood: a cumulative index of health deficits – the individual deficits can include diseases, symptoms and signs, function tests and laboratory tests. Provided enough deficits are included in the index, their exact nature seems unimportant.
The Quest for Measures of Frailty

• Can we define frailty in terms of things that can be measured in individual people (biomarkers, functional tests)?

• Can we use such tests to distinguish frail individuals from those who are not frail even though they may be experiencing age-related multi-morbidity?

• Can we use such tests to establish measures that can be applied to individuals to evaluate the effectiveness of interventions specifically targeting frailty?
Biomarker Domains in Newcastle 85+ Study

Anthropometry, blood pressure and physical function
- Weight, body fat percentage, body fat mass, fat free mass and total body water
- Diastolic and systolic blood pressures
- Right and left hand-grip strength
- Timed Up-and-Go (TUG) test; 7 day continuous activity monitoring
- Respiratory function

Blood-based candidate biomarkers
- Haematology and biochemistry:
- Nutritional markers:
- Inflammatory response:
- Lymphocyte subpopulations
- Telomere length
- DNA Damage and Repair:
- Plasma Isoprostanes
Biomarker Findings from Base-line Analyses

- Low BMI (or fat) is protective for multimorbidity and disability, but a risk factor for mortality.
- High blood pressure is a risk factor in younger populations, but in an 85 year old population was shown previously not to be a risk factor for mortality. We found low blood pressure to be associated with risk for cognitive impairment and disability.
- Hand grip strength, TUG and FEV are established biomarkers of aging in younger populations. We confirm their usefulness in the oldest old.
- Anemia is highly prevalent. The associations between low RBC and multimorbidity and disability support a role for severe anemia as a marker of decline.
- High B-natriuretic peptide (BNP) marks CVD risk. However, high BNP has been shown to be a predictor of mortality in the oldest old independent of specific cardiac diagnoses. High BNP also associates with low cognitive function in our population.
- Low Apolipoprotein B (ApoB) levels were associated with disability and mortality. High HDL appeared protective against disability, and low total cholesterol associated with increased multimorbidity. Low total cholesterol and LDL associated with increased risk of death and might be signs of unidentified co-morbidity and/or rapid decline.
- Low values of vitamins B6 and D were associated with increased risk for two outcomes each.

Martin-Ruiz et al Mech Ageing Dev 2011
Unexpected negative biomarker findings

- Inflammation - high levels of high-sensitivity C-reactive protein (hsCRP) and serum interleukins have been associated with various age-related outcomes. High levels of hsCRP were associated with multi-morbidity, disability and mortality risk, however, only the association with disability remained in a multivariate approach.

- Short telomeres have been repeatedly shown to be associated with cognitive dysfunction, various age-associated diseases and mortality. However, we and others previously observed no association between telomere length and morbidity/mortality in another group of the oldest-old. This result is now confirmed.

- A low CD4/CD8 T-lymphocyte ratio is a central feature of an ‘immune risk profile’, associated with low survival in Swedish longitudinal studies of 80- and 90-year olds. We did not find any significant association of the extreme percentiles of the CD4/CD8 ratios with 1.5-year survival or any other of the outcome measures tested.

Frailty in the Newcastle 85+ Study

- Using cross-sectional data from the Newcastle 85+ Study (n=845, aged 85), frailty was operationalized by the Fried and Rockwood models and biomarker associations explored using regression analysis.
- We confirmed the importance in the very old of inflammatory markers (IL-6, TNF-alpha, CRP, neutrophils) in frailty, previously established only in the younger old. Limited evidence was found for immunosenescence in frailty.
- No association was found of frailty with immune risk profile, and associations with memory/naïve CD8 T and B cell ratios were in the opposite direction to that expected. Nor was there significant association of frailty with CMV sero-positivity, telomere length, markers of oxidative stress, or DNA damage and repair.
- The Fried and Rockwood frailty models measure different, albeit overlapping, concepts, yet biomarker associations were generally consistent between models. Difficulties in operationalizing the Fried model, due to high levels of co-morbidity, were found to limit its utility in the very old.
Campus for Ageing and Vitality

Newcastle Initiative on Changing Age (www.ncl.ac.uk/changingage)