Epigenetics

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A few points about genetics

- DNA contains the blueprint for the body
  - Genes are segments of DNA which code for compounds like proteins, hormones etc
- Your genes are written with a 4 letter alphabet
- You have 99.9% of genes in common with the person sitting next to you
  - The other 0.1% make for all the differences between humans
- DNA can become damaged and it can be repaired
- Your ‘genotype’ is what is in your genes, your ‘phenotype’ is what your genes are expressing
  - Not all genes express themselves; many lie dormant
A mutation is like a spelling or punctuation error.

The body has a ‘spell check’ (DNA Repair Capacity).

Many spelling / punctuation errors do not change the meaning of the sentence whereas some change it profoundly.
It was believed that genes were fixed and that it was good luck or bad luck as to whether genetic tendency for an illness played out.

We now know that factors including environment, lifestyle and mental state all influence how genes express themselves (phenotype): this is epigenetics.

This is due to chemicals (enzymes) which change the gene and switch on and off their activity.
EPIGENETIC MECHANISMS
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

HEALTH ENDPOINTS
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

CHROMATIN

CHROMOSOME

METHYL GROUP

DNA

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Gene

Histone tail

Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Histone

DNA inaccessible, gene inactive

DNA accessible, gene active
Relaxed rats

- Studies on raising baby rats shows that when they are licked and groomed regularly by their mothers (maternal love) in the first week of life they tend to be less stress-prone for the rest of their lives.

- Brains of nurtured rats good at down-regulating stress response because the genes coding for brain cortisol receptors switched on for life.
Happy bunnies (rats)

Lots of nurture leads to more brain serotonin

Stimulates brain to make more of a genetic enzyme to switch on cortisol receptor production

Higher level of cortisol receptors leads to being less stress prone
Not so relaxed rats

- When baby rats are not licked and groomed regularly were far more stress prone later in life (e.g. high levels of CTRH and cortisol)

- These rats do not switch on the genes enough in the brain’s hippocampus to produce the cortisol receptors to down-regulate the stress response

- When baby rats born to less affectionate mothers were transferred to affectionate mothers then they grew up not being stress-prone

Huntington's disease
- Inherited (autosomal dominant) disorder
- Progressive neurodegeneration: uncontrollable movements, loss of motor control and dementia
  - Affects the corpus striatum and cerebral cortex of the brain
- No known cure

Animal studies show that an enriching environment delays the onset of Huntington's Disease
- 1/7 mice with enriched environment failed motor tests compared to 7/7 controls
Putting a rat in an enriched environment (two running wheels and the inside of a toilet roll) led to increased memory due to histone acetylation levels in the hippocampus and cortex.

Experiencing child abuse leads to high levels of stress chemicals (e.g. CTRH and cortisol) for the rest of one’s life even if no longer in a stressful situation.

The brains of suicide victims with a history of child abuse show the same effects on genes and brain stress receptors as seen in the animal experiments:

Maternal stress & schizophrenia

- High levels of schizophrenia a/w stress during pregnancy (loss of husband, severe famine, unwanted pregnancies)

- Women exposed to prenatal stress during the 1940 invasion of Holland c/w women who were pregnant in the previous year or following two yrs

- Risk of schizophrenia in offspring increased by 2.8 times and worst for women in first trimester of pregnancy
  - British Journal of Psychiatry 1998;172:324-6
Stress & genetic expression

- Research suggests that mental state effects genetic function
  - Increases the number of genetic mutations
  - Impairment of the body’s ability to repair mutations

- Implications for carcinogenesis (cancer) and other illnesses
The ability of the cell to repair genetic damage is measured by DNA Repair Capacity (DRC).

Study on healthy medical students confirmed that during high stress periods (exams), c/w low stress periods (vacations), there was a general increase in DRC. This implies an adaptive response to increased DNA damage.

Students with higher/consistent stress and mood disturbance had a reduction in DRC or no change.

Speculative as to whether effects on DRC can be reversed through effective stress management.

Cancer & DNA repair capacity

- Retrospective case-control clinical study compared DRC in women with breast cancer and 47 cancer-free women

- Cancer cases (5.6%) had 36% reduction in DRC compared with the control group (8.7%)
  - Younger breast cancer patients had a more significant reduction in DRC

- “A low DRC is a susceptibility factor for breast carcinoma. A 1% decrease in DRC corresponded to a 22% increase in breast carcinoma risk.”

Dopamine, happiness and addiction

- Stress early in upbringing can affect the brain’s dopamine pathways for life

- Implications for impulsivity, reactivity and addiction

- Increased dopamine release during ‘relaxation response’ associated with the experience of reduced reactivity and impulsivity
Asthma, genes & upbringing

- Study on relationship between early parental behavior and onset of asthma
  - 150 children genetically at risk for asthma
  - Parenting problems and maternal coping assessed during home visit when the infant was 3 weeks old
  - Sample divided into two groups based on concerns about coping and parenting

- “Early problems in coping and parenting were associated with the later onset of asthma. Furthermore, parents of children who developed asthma were more likely to have been having difficulties at the 3-week visit than those whose children developed infectious wheezing.”
TELOMERES

Embryonic Stem Cell

Telomere Long

Telomerase Active

Telomere Short

Telomerase Inactive or Absent

Telomere is a Repeating DNA Sequence

Adult Stem Cell

Google Images modified by Vitetta L. and Sali A.
Stress, telomeres and CVD

- Telomere shortness associated with CVD
- Study on telomerase, stress arousal and CVD risk factors
- Low telomerase activity a/w:
  - Exaggerated autonomic reactivity to acute mental stress
  - Major risk factors for CVD - smoking, poor lipid profile, high BP, high fasting glucose, greater abdominal adiposity (Metabolic Syndrome)
- Short telomere length a/w elevated stress hormones
Telomere length and cancer risk

- Short telomere length at baseline associated with cancer risk independently of other risk factors

- Incidence rates were:
  - 5.1 per 1000 person-years in the longest telomere length group
  - 14.2 in the middle length group
  - 22.5 in the shortest length group

- Short telomere length also associated with high cancer mortality (2.13)

- “there was a statistically significant inverse relationship between telomere length and both cancer incidence and mortality.”
Intrauterine stress and telomere length

- Telomere Length assessed in 94 healthy young adults
  - 45 were offspring of mothers who had experienced a severe prenatal stress
  - 49 subjects were offspring of mothers who had a healthy, uneventful index pregnancy

- Prenatal stress exposure was a significant predictor of subsequent adult telomere length in the offspring
  - Effect unchanged after adjusting for potential confounders and was more pronounced in women
Stress and ageing in children

- Study on associations b/w autonomic nervous system and adrenocorticoid (cortisol) reactivity to lab stressors and telomere length (TL) in 5-6y/o children

- Heart rate and cortisol reactivity inversely related to TL

- Children with high sympathetic activation and parasympathetic withdrawal and high cortisol reactivity had significantly shorter TL – a marker of early biologic aging
In healthy premenopausal women psychological stress (both perception and chronicity) a/w known determinants of cell senescence and longevity:

- higher oxidative stress
- lower telomerase activity
- shorter telomere length

Those with the highest levels of perceived stress c/w low stress have telomeres shorter on average by the equivalent of at least one decade of additional aging

Findings have implications for understanding how stress may promote earlier onset of age-related diseases

Combination of low optimism & high pessimism increases risk for disease and early mortality

Study investigated whether tendency towards optimism or pessimism associated with Telomere Length and IL-6 in healthy post-menopausal women

Pessimism is independently associated with shorter Telomere length and higher Interleukin-6 concentrations

Hostility and ageing

- Study on relationship between cynical hostility and two markers of cellular aging, leukocyte telomere length (TL) and leukocyte telomerase activity (TA)
  - 434 men and women from the Whitehall II study

- High-hostile men had significantly shorter leukocyte TL and elevated TA than low-hostile counterparts
  - Heightened TA in the presence of short telomeres represents a compensatory response in high-hostile individuals

- Relationship between hostility and disease is stronger in men than women – may explain in part shorter life expectancy
Sleep quality and telomere length

- 245 healthy women in midlife

- Sleep duration and onset latency unrelated to LTL

- Poorer sleep quality displayed shorter LTL independent of age, BMI, race, income and perceived psychological stress
Exercise, stress & telomeres

- For non-exercisers a one unit increase in the stress scale related to a 15-fold increase in the odds of having short telomeres (a marker of rapid ageing and chronic illnesses)

- For exercisers, perceived stress was unrelated to telomere length (i.e. exercise buffered against the effects of emotional stress on ageing)
Physical activity categories are based on whether the participant met CDC recommended levels of exercise per week. Perceived stress ratings are based on the Perceived Stress Scale. The relationship between perceived stress and telomere length was significant in sedentary participants only.
Nutrition and telomeres

- Associated with shorter telomeres
  - Smoking
  - Processed meat
  - High BMI
  - High homocysteine

- Associated with longer telomeres
  - Vitamin D
  - Folate
  - Omega-3 f.a.
  - Vitamin C
  - Vitamin E

Lin J, Epel E, Blackburn E. Mutation Research 2011 (in press)
Omega-3 f.a. and telomeres

- Study on the association of omega-3 f.a. levels and changes in telomere length over time
- Individuals in lowest quarter of omega-3 f.a. intake experienced fastest rate of telomere shortening
- Highest quarter experienced slowest rate of telomere shortening
- Each 1-SD increase in omega-3 levels associated with a 32% reduction in the odds of telomere shortening
Ornish program for cancer

- 92 men with early prostate cancer who chose to watch and wait

- Randomised to lifestyle (experimental) group vs. usual treatment (control) group
Ornish lifestyle intervention

- Vegan diet
  - Fruits, vegetables, whole grains, legumes and soy
  - 10% calories from fat
  - Supplemented by soy (tofu), fish oil (3gm daily), vitamin E (400IU daily), selenium (200mcg daily), vitamin C (2gm daily)

- Exercise
  - Walking 30min 6 times weekly

- Stress management
  - Gentle yoga, meditation, breathing and PMR

- Support group 1 hour weekly
2-year follow-up
- 27% (13/49) patients in control group have gone on to require cancer treatment because of disease progression
- 5% (2/43) patients in lifestyle group have gone on to require cancer treatment because of disease progression

Prostate cancer gene expression down-regulated by lifestyle change in men with low-risk prostate cancer who chose to watch and wait

Comprehensive lifestyle change increased telomerase activity
Practicing gene therapy
“This study provides the first compelling evidence that the RR elicits specific gene expression changes in short-term and long-term practitioners. Our results suggest consistent and constitutive changes in gene expression resulting from RR may relate to long term physiological effects.”

Meditation may slow genetic ageing and enhance genetic repair

“...we propose that some forms of meditation may have salutary effects on telomere length by reducing cognitive stress and stress arousal and increasing positive states of mind and hormonal factors that may promote telomere maintenance.”

Meditation, mental health, and telomerase

- Study of effect of brief daily yogic meditation on mental health, cognitive functioning, and immune cell telomerase activity in family dementia caregivers (mean age 60) with mild depressive symptoms
  - Randomized to Kirtan Kriya vs. listening to relaxation music for 12 min/d for 8 weeks

- Meditation group showed significantly lower levels of depressive symptoms and greater improvement in mental health and cognitive functioning c/w relaxation group

- Meditation group showed 43% improvement in telomerase activity c/w 3.7% in the relaxation group
Meditation and health

- 11-year f/u 600,000 non-meditators & 2,000 meditators
- Significant reductions in illness
- An overall 63% reduction in health-care costs
  - 11.4 times less hospital admission for CVD
  - 3.3 times less cancer
  - 6.7 times less mental disorders and substance abuse
- Study not controlled for lifestyle and personality factors
  - Self-selection, healthy lifestyle change and direct physiological benefits would play a part in the results
“The human mind is not capable of grasping the Universe. We are like a little child entering a huge library. … The child knows that someone must have written those books. It does not know who or how.”

Albert Einstein: cited in The Next Thousand Years by A Berry