Hormetins as Drugs for Healthy Ageing

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Understanding ageing – biogerontological perspective…

Ageing – a progressive loss of ability to function independently, increase in frailty, and increase in the chance of emergence of diseases and death – happens after the essential lifespan of the species.
Essential lifespan (ELS) is the time that a species needs in its natural environment to assure reproduction and continuation of generations.
Ageing occurs at all levels of biological organisation, but differently…
Usain Bolt – 26 years, in 2012

Some of us can...

Hidekichi Miyazaki- 105 years, in 2015
There are no real gerontogenes with a specific task of causing ageing and death.

Genes “determine” ELS – longevity assurance genes, vitagenes
Ageing is the progressive failure of maintenance and shrinkage of the homeodynamic space.
Survival is a constant struggle….

**Oxygen metabolites**
*ROS, other free radicals*

**Nutritional metabolites**
glyoxal, methylglyoxal, carbonyls acids, aldehydes

**Biochemical infidelity**
errors, modifications, misfolding

**Sources of damage**

**Maintenance and repair systems**

- Genomic stability
- Epigenomic stability
- Protein stability
- Macromolecular turnover
- Free radical counteraction
  + higher order systems
Life is Homeodynamic and not Homeostatic

- **Homeodynamic space**
- **Vulnerability zone**

**Growth, maturation & development**
Characteristics of the Homeodynamic Space
Ageing is the shrinkage of the homeodynamic space.
Accumulation of molecular damage is the mechanistic explanation for the shrinkage of the homeodynamic space.

**DNA damage**
- mutations, epimutations, base modifications, strand breaks...

**RNA damage**
- base modifications, miscoding, missplicing...

**Protein damage**
- Amino acid modifications, misincorporations, misfolding...

**Other macromolecular damage**
- Lipid-protein conjugates, advanced glycation endproducts (AGE)...


Instead of adopting an “enemy-oriented” anti-ageing approach, a “friend-oriented” approach is to strengthen the homeodynamic processes for healthy ageing.
Hormesis in ageing is based on the view that deliberate and repeated challenging of the biological systems can stimulate compensatory, adaptive, and reparative processes.
Phenomenon: HORMESIS

Causative agent: HORMETIN

Field of study: HORMETICS

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Improving human cellular functionality by hormesis – our labs’ studies

• Ageing, health-span and longevity
• Wound healing and migration
• Differentiation
• Angiogenesis
• Tolerance, robustness and resilience

Stressors used:
• Heat shock
• Phytochemicals
• Serum starvation
• Hydrocortisol
• Nanoparticles
Some examples from our labs

Repeated mild heat shock slows down cellular ageing

Mild heat shock improves angiogenesis

Curcumin improves wound healing
Intermittent fasting of human skin fibroblasts
(low serum for 24 hr, once a week)

Stimulation of lysosomal autophagy and mitochondrial activity

Extension of proliferative lifespan

Lysosomal staining - 10%, 5%, 2% serum

LONGEVITY CURVE

0 50 100 150 200 250
DAYS IN CULT

0 10 20 30 40 50 60
LONGEVITY CU

A

B
Once a week serum starvation extends longevity of human skin fibroblasts.
Hydrocortisol (HC) has biphasic hormetic effects on stem cell differentiation and cell migration / wound healing
Table 1: Major pathways of stress response in human cells

<table>
<thead>
<tr>
<th>Stress response</th>
<th>Stressors</th>
<th>Effectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat shock response (HSR)</td>
<td>Heat, heavy metals, antibiotics, protein denaturation</td>
<td>Heat shock proteins, proteasome, and other proteins</td>
</tr>
<tr>
<td>Unfolded protein response (UPR)</td>
<td>Unfolded and misfolded proteins in endoplasmic reticulum</td>
<td>Chaperones and co-chaperones</td>
</tr>
<tr>
<td>Autophagic response</td>
<td>Food limitation, hypoxia, damaged organelles</td>
<td>Lysosomes</td>
</tr>
<tr>
<td>DNA-repair response</td>
<td>Radiation, oxidants, free radicals</td>
<td>DNA-repair enzymes</td>
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<tr>
<td>Antioxidant response</td>
<td>Free radicals, reactive oxygen species, pro-oxidants</td>
<td>Nrf-2, heme oxygenase, FOXO</td>
</tr>
<tr>
<td>Sirtuin response</td>
<td>Energy depletion</td>
<td>Sirtuins</td>
</tr>
<tr>
<td>NFκB inflammatory response</td>
<td>Pathogens, allergens, damaged macromolecules</td>
<td>Cytokines, nitric oxide synthase</td>
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</tbody>
</table>
Normal human cells in culture
- Fibroblasts
- Keratinocytes
- Endothelial cells
- Osteoblasts
- Myocytes
- Neuronal cells
- Stem cells

Test material

Early stress responses
- Heat shock response – HSF1 activation
- Oxidative stress response – Nrf2 activation
- Autophagic response – LC3 I and II ratio
- Unfolded protein response – ATF activation
- Energy depletion response – NAD+/NADH ratio
- Inflammatory response – NFκB activation
- DNA damage response – ATRIP activation

Prospective hormetin for testing at tissue, organ, and organismal level

Late stress response effectors
- Heat shock response – HSPs
- Oxidative stress response – HO-1, antioxidants
- Autophagic response – Lysosomal activity
- Unfolded protein response – Chaperones
- Energy depletion response – Sirtuins
- Inflammatory response – Cytokines and interleukins
- DNA damage response – Cell cycle checkpoint

Cell type-specific functional assays
- Fibroblasts – motility, wound healing
- Keratinocytes – differentiation
- Endothelial cells – angiogenesis
- Osteoblasts – osteocalcin, matrix
- Myocytes – muscle fibers
- Neuronal cells – dendrite, synapses
- Stem cells – differentiation

Potential hormetin
HORMESIS-BASED ANTI-AGING PRODUCTS: A CASE STUDY OF A NOVEL COSMETIC

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Application of hormesis in aging research and interventions is becoming increasingly attractive and successful. The reason for this is the realization that mild stress-induced activation of one or more stress response (SR) pathways, and its consequent stimulation of repair mechanisms, is effective in reducing the age-related accumulation of molecular damage. The potential for applying hormetic principles in drug development has tremendous implications for the field of anti-aging research.
HORMETINS

Physical hormetins
exercise, heat, cold, radiation...

Nutritional hormetins
spices, micronutrients, fasting

Psychological hormetins
Social and mental engagement, focussed attention (meditation)
Creating stress response profiles

**Stressor: Heat Shock**

Stressor: Nutritional deprivation

Heat shock proteins

Autophagy markers
Stress response profiles: theoretical and real
Challenges for developing “drugs” FOR health

1. Changing the paradigm –
   - from “anti-ageing” to “pro-health”;
   - from disease-oriented to health-oriented, &
   - from large and immediate inhibitory / killing effects to small and cumulative hormetic effects
Challenges for developing “drugs” FOR health

1. Changing the paradigm

2. Measurable markers of health and homeodynamics at:
   - Molecular level
   - Cellular level
   - Physiological level
   - Mental/psychological level (well-being)
3. Establishing protocols for single and multiple hormetins for health maintenance, recovery and improvement