Why is Age the Most Significant Risk Factor for All Chronic Diseases?

A 7-Minute Webinar Presented By
Jeffrey Bland, PhD
President, Personalized Lifestyle Medicine Institute
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Number and proportion of older people globally in 2015, 2030, 2050

- Number 60+ 901 million 12.3% of total worldwide population
- Number 60+ 1402 million 16.5% of total worldwide population
- Number 60+ 2092 million 21.5% of total worldwide population

Source: United Nations

(a)

Age-related diseases raise exponentially:
This is not a coincidence!

**Treat aging**

Prolonging the healthy years of life:
Improving lifespan and healthspan!

(b)

Deregulated nutrient sensing
Mitochondrial dysfunction
Oxidative stress
Systemic inflammation
High or low autophagy
Senescence
Telomere shortening

(c)

Aging

Diabetes
Cardiovascular diseases
Cancer
Neurodegenerative diseases
Figure 2: Senescence and aging. Aging is characterized by senescent cell accumulation into the body. Senescence can be achieved replicatively or induced by stress. Once activated, the p16 and p53/p21 pathways converge with each other, regulating the Rb mechanism, leading to cell cycle arrest, and consequently, the senescence. This results in the release of cytokines and chemokines, driving towards a systemic inflammatory condition that lead to aging and age-related diseases. The senescent cells are characterized by a high lysosomal β-galactosidase activity and, in association with others characteristic factors, consist the gold standard for the senescence characterization.
Myeloid cell contributions to cardiovascular health and disease

Matthias Nahrendorf

Recent advances in cell tracing and sequencing technologies have expanded our knowledge on leukocyte behavior. As a consequence, inflammatory cells, such as monocyte-derived macrophages, and their actions and products are increasingly being considered as potential drug targets for treatment of atherosclerosis, myocardial infarction and heart failure. Particularly promising developments are the identification of harmful arterial and cardiac macrophage subsets, the cells' altered, sometimes even clonal production in hematopoietic organs, and epigenetically entrained memories of myeloid progenitors and macrophages in the setting of cardiovascular disease. Given the roles of monocytes and macrophages in host defense, intricately understanding the involved cellular subsets, sources and functions is essential for the design of precision therapeutics that preserve protective innate immunity. Here I review how new clinical and preclinical data, often linking the cardiovascular, immune and other organ systems, propel conceptual advances to a point where cardiovascular immunotherapy appears within reach.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Modifiable?</th>
<th>Therapy</th>
<th>Link to innate immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>Yes</td>
<td>Lifestyle modification, statins, fibrates, PCSK9</td>
<td>Increased hematopoiesis[^2][^4], modulation of macrophage phenotype, trained immunity[^2]</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>Lifestyle modification</td>
<td>Adipose tissue harbors inflammatory macrophages, increased hematopoiesis[^2]</td>
</tr>
<tr>
<td>Diet</td>
<td>Yes</td>
<td>Lifestyle modification</td>
<td>Via microbiome?</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Lifestyle modification, antihypertensive drugs</td>
<td>Leukocytes increase in vascular wall and in the hypertrophic myocardium[^2]</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Yes</td>
<td>Lifestyle modification</td>
<td>Via modulation of leukocyte phenotypes and hematopoiesis?</td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td>Yes</td>
<td>Lifestyle modification</td>
<td>Increased hematopoiesis via sympathetic signaling, altered leukocyte number and phenotype[^4]</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>Lifestyle modification</td>
<td>Leukocytosis and altered leukocyte phenotype?</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>Diet, oral antihyperglycemic agents, insulin</td>
<td>Increased hematopoiesis via RAGE ligands, etc.[^70]</td>
</tr>
<tr>
<td>Age</td>
<td>No</td>
<td>Currently none, possibly targeting aging hematopoietic and immune system in future</td>
<td>Via clonal hematopoiesis[^5] and myeloid bias? Via altered tissue resident macrophage repertoire in heart[^36] and vasculature?</td>
</tr>
<tr>
<td>Sex</td>
<td>No</td>
<td>N/A</td>
<td>Via sex hormone signaling to HSPC and leukocytes?</td>
</tr>
<tr>
<td>Family history and genetics</td>
<td>No</td>
<td>Currently none, possibly gene editing in future</td>
<td>Via hyperlipidemia and possibly hematopoiesis, etc.</td>
</tr>
</tbody>
</table>
The Connection of Heart Disease to the Hematopoietic-Derived Immune System
DNA damage-induced immune response: Micronuclei provide key platform

Nelson O. Gekara
The Laboratory for Molecular Medicine Sweden, Department of Molecular Biology, Umeå University, Umeå, Sweden

Figure 1. Micronuclei serve as a source of immunostimulatory DNA. Cell division after DNA damage leads to micronuclei formation. cGAS sensing of micronuclei DNA triggers gene activation, which may lead to autoinflammation or antitumor immunity. Micronuclei can be cleared via autophagy.
The Nobel Committee has recognized this breakthrough by the awarding of the 2016 Nobel Prize in Physiology or Medicine for research in autophagy to Yoshinori Ohsumi.
Calorie restriction increases telomerase activity, enhances autophagy, and improves diastolic dysfunction in diabetic rat hearts

LETO = Control Hearts
White Columns Ad Lib

OLETF = Obese Diabetic Hearts
Black Columns Calorie Restricted
Mediterranean diet and telomere length in Nurses’ Health Study: population based cohort study

Estimated least squares mean telomere length z scores (and standard errors) by Mediterranean diet score categories (Alternate Mediterranean Diet score) in Nurses’ Health Study (n=4676)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>≤2 (n=891)</th>
<th>3 (n=795)</th>
<th>4 (n=909)</th>
<th>5 (n=880)</th>
<th>≥6 (n=1201)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted</td>
<td>-0.028 (0.033)</td>
<td>-0.039 (0.035)</td>
<td>-0.011 (0.033)</td>
<td>0.029 (0.033)</td>
<td>0.054 (0.029)</td>
<td>0.016</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>-0.038 (0.035)</td>
<td>-0.049 (0.036)</td>
<td>-0.010 (0.033)</td>
<td>0.039 (0.034)</td>
<td>0.072 (0.030)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, pack years of smoking, physical activity, and total caloric intake.

Multivariable adjusted least square means of leukocyte telomere length z scores (and their corresponding confidence intervals) by diet score quarters. All dietary patterns are represented: prudent pattern, Western pattern, Alternative Healthy Eating Index (AHEI) score, and Alternate Mediterranean Diet (AMED) score.