Is "Garb-aging" a More Precise Description?

Consider this: on the broad scale of human evolution, population-wide longevity is relatively new. Up until recently, we have hardly realized that biological aging and chronological aging are different—and that biological aging is modifiable. In order to successfully modify it on an individual basis, though, we need to understand which specific behaviors will shift which validated biomarkers of aging (another fertile area of study!).

In 2000, immunologist/gerontologist Dr. Claudio Franceschi and colleagues coined the term "inflamm-aging" to describe how excessive oxidative stress and the resulting chronic immune response interact with genetic variations to contribute to age-related dysfunction. In 2017, Dr. Franceschi et al added further consideration of long-term imbalance between generation and disposal of molecular/cellular ‘garbage’, including metabolic waste products, microbes and their products, debris from injury or immune response, toxins, altered or misplaced molecules, excess nutrients, etc. In robust health, cellular and mitochondrial housekeeping programs (autophagy and mitophagy) regularly remove this ‘waste,’ but in “garb-aging,” these programs are not sufficiently activated, leading to cellular signaling of distress and an unresolved immune response that is amplified over time and may constitute a form of auto-immunity.

An important mention by these and other researchers is the validation of biomarkers for attributing and tracking particular causes of biological aging. There are many candidates, but some include:

- functional testing (e.g., for lung, cardiovascular, and cognitive function)
- laboratory -omics tests
- gene variants (e.g., mutations in DNMT3A and other genes that regulate stem cell
In this FMU, PLMI President Dr. Jeff Bland explains how "inflamm-aging" links biological aging processes with chronic disease, and he describes the critical importance of functional balance; for example, between temporary inflammation to increase resistance and antiinflammatory processes that keep immunity focused. Last, he shows that individuals’ management of what passes through the gut (and its indwelling immune tissues that monitor environmental conditions) is the first-line approach for maintaining adaptive immune balance and controlling pro-inflammatory messaging in the body. With effective integration of these concepts into medical practice, it will be possible for individuals to realize which behaviors contribute to which axes of their own biological aging and impact specific aspects of their own health—and which personal choices can cultivate positive wellness for them.

Living in Space is a Rough Ride for DNA and Metabolism

While space agencies have long studied the effects of outer space on humans, having the first twin astronauts has provided NASA (the National Aeronautics and Space Administration) the perfect opportunity to minutely compare alterations in health, function, cell signaling, and DNA as experienced by one living in space while the other stays on Earth—and it is clear that the challenges of space station living are felt on numerous levels in the body. Considered individually, the effects of space living are not entirely exotic—reduced cellular oxygen delivery, heightened inflammation, bone changes, and altered gene expression are also known to occur as a result of aging, smoking, obesity, and unhealthy diet and lifestyle habits. But in this n=2 twins experiment, these and other alterations were seen despite the space-living participant pursuing a vigorous program of exercise and caloric restriction.

NASA has shared a few details about the physiological and gene-related differences seen between Scott and Mark Kelly. Scott, who has since retired from NASA, received extensive testing while living on the International Space Station for one year, and brother Mark received the same tests on Earth. One particularly fascinating finding was that the protective telomeres on Scott’s chromosomes within his white blood cells lengthened substantially while he was in space, which is extremely compelling in and of itself and would seem to indicate a strong defensive response to space life. NASA researchers felt that it might relate to Scott’s exercise regimen, reduced calorie intake, and improved dietary delivery of folate while he was in space and note its coincidence with the loss in body mass he showed. Even more remarkably, though, Scott’s telomeres shortened within about two days after arriving back on Earth and then returned to almost pre-mission lengths. Mark’s telomeres, in contrast, remained fairly stable during the same time period. And while Scott’s cognitive function did not significantly change relative to Mark’s during the mission, Scott experienced decreases in speed and accuracy after coming back to the planet.

Scott additionally showed elevated indications of inflammation in space and after returning to Earth, including carotid vascular thickening. Though NASA has provided little detail regarding the lipid metabolites and cytokines involved, changes in C-reactive protein and insulin-like growth factor levels were apparently seen. NASA also reports an overall drop in DNA methylation in Scott’s white blood cells (likely indicating more widespread reading and activation of cellular programs) as well as alterations in DNA repair and in gene expression related to mitochondrial and hypoxic stress signaling. NASA has estimated that about 93% of these gene-related changes returned to normal after Scott’s return to Earth but that hundreds of them remain altered. Scott also
experienced a reversal in microbiome balance between Firmicutes and Bacteroidetes phylum members during the mission, though NASA hasn’t explicitly shared which phylum was dominant during the mission or on Earth.

Longer time in space has been shown to narrow the midline space between the right and left hemispheres of the brain and in areas where cerebrospinal fluid circulates. It also affects eye structure and can cause irreversible visual impairments in male astronauts, which NASA feels is partially explained by altered folate/methyl metabolism but also relates to intracranial hypertension and changes in vasopressin, natriuretic peptide, insulin-like growth factor, and markers of inflammation in these men. It is possible that these 2012 findings increased NASA’s interest in epigenetic influences on mission-critical physiological functions. Astronauts’ increased exposure to radiation also relates to cellular and functional changes they experience, and NASA recognizes that radiation exposure represents a major risk to them. In one preclinical study, animals with cognitive impairments induced by limited simulated space radiation show heightened methylation (generally indicating gene silencing) in the hippocampus (a brain area central to cognition, mood, and the stress response), while irradiated animals given a methylation inhibitor showed learning behaviors and methylation activity much more comparable to that of controls.

What does this mean to us on Earth? While the environment of space is extreme, research conducted for NASA states that “spaceflight simulates vascular aging”—the latter of which is not, after all, so uncommon. Even on the planet’s surface, we are subject to genetic variations that affect functions and responses, and to thinning of the atmospheric layer of ozone that protects against greater radiation. We pursue activities and experience circumstances that increase or decrease telomerase activity and biological aging. We adapt to a greater or lesser degree to rapid flux in climate and environment and to voluntary and involuntary stresses stemming from lifestyles, social and financial pressures, diet, and the unpredictability of 21st century life. These affect everyone and can cause cellular distress and dysfunction in ways similar to that induced by life in space—and all present opportunities to explore individual and collective choices that impact health. Perhaps learning how radiation, vascular challenge, diet, gender, physical activity, and epigenetics impact astronauts’ performance of mission objectives will translate into greater resolve to address analogous issues confronting the earthbound.

SNiPPets

How significant to health are particular single nucleotide polymorphisms, also known as SNPs? SNiPPets is a ongoing exploration of this topic. This column is produced by Jeffrey Bland, PhD and the Personalized Lifestyle Medicine Institute.

These SNPs Can Alter Cells’ Priorities, Especially (But Not Only) Around Pregnancy

Choline is a versatile nutrient, and is partitioned among needs such as neurotransmitter synthesis, building fluid yet protective cell membranes, and aiding fat metabolism. It cooperates closely with nutrients involved in methylation (folate, betaine, etc.), to regulate proper cell division and growth of new tissues—especially the fetal central nervous system. Liver synthesis of choline is low, and most people do not receive enough from their diets to make up the shortfall. (The adult Reference Daily Intake for choline is 550 mg). In both men and women, insufficiency can alter how the liver processes fats and increase the propensity to fatty liver disease, but during pregnancy and lactation, it makes it especially challenging for the body to serve
high-level functions, and can relate to birth defects as well as risk for cancer and other long-term health issues.

Though research into the genetics of choline is relatively new, several single-nucleotide polymorphisms (SNPs) in genes coding for choline and folate have been found to influence choline metabolism, among them:

- Pregnancy boosts choline synthesis, but in about half of women, a G-to-C substitution at the rs12325817 locus of the PEMT gene virtually **negates this estrogenic effect**, greatly increasing dietary need for choline among these women and their fetuses.
- Individuals with a G-to-A switch at the rs2236225 locus of the MTHFD1 gene were 7-15 times more likely to show **elevated liver or muscle enzyme levels**; however, an A-to-C SNP at the rs9001 locus of the CHDH gene reduced this risk.
- Lactating mothers with this same MTHFD1 rs2236225 SNP given 480 mg choline daily showed sub-optimal **sharing of it between** synthesis of betaine (which helps detoxify homocysteine) and of cell membrane components, which normalized when they received 930 mg choline daily.
- Non-pregnant women with a major (“wild-type”) A allele (not the A-to-G SNP) at the rs1805087 of the MTR gene also displayed the choline-partitioning difficulty of the previous example, which also normalized at the higher 930 mg daily intake level.
- Non-pregnant women with the well-known C-to-T SNP at the rs1801133 locus of the MTHFR gene also showed the same pattern of partitioning (as the last two examples) at the lower choline intake, with normalization at the higher intake.
- Mexican men with this same MTHFR rs1801133 SNP experienced **increasing blood levels of homocysteine** (evidence of decompensated choline/folate function) when their daily choline intakes were 300 or 550 mg but not at 1100 or 2200 mg.

Individuals with any of these genetic variants may wish to discuss nutritional strategies for optimizing their intakes of all methylation-related nutrients, and may benefit from choline intakes above levels recommended for the general population.

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