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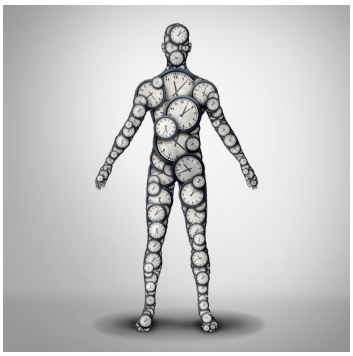
"Senescent Cell Burden," Lifestyle, and Senolytics



For cells, aging relates to changes in gene expression and cellular regeneration capacity caused by mitochondrial dysfunction, altered metabolic efficiency, clumping of cellular wastes, telomere/DNA/protein damage, and inflammation. Senescent cells are defined as having lost the ability to replicate, and because these cells are resistant to programmed cell death, they are seen to accumulate in tissues during biological aging. Senescent cells are more apt to secrete pro-inflammatory cytokines and related factors, a manifestation called the "senescence-related secretory phenotype" (SASP) to denote how cytokine production reflects cellular distress associated with biological aging. Heightened cell senescence is associated with reduced healthspan, fatty infiltration of the liver, and greater risk for cancer, cardiovascular and immunometabolic diseases, and neurodegenerative conditions, and for these reasons is increasingly considered a kind of cumulative metabolic burden.

The whole-body 'dose' of senescent cells has been termed the "senescent cell burden," and a recent study has found that in older mice, senescent cell numbers range from 2 to 10 percent of total cells in fat tissue. In this innovative experiment, researchers transplanted senescent pre-adipocytes into the abdomens of young animals, and discovered that transferring as little as around 7-14% of the equivalent 'old mouse body dose' of these aged cells produced a more aged functional phenotype (reduced strength and walking speed) in young animals and altered aspects of their immune balance in ways that replicate biological aging. These effects lasted beyond the lives of the transplanted cells, as the introduced senescent cells seemed to influence the host animals to develop more senescent cells; this effect was further augmented by providing

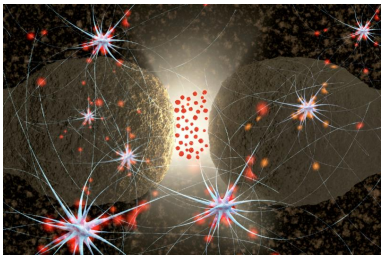
the animals a high-fat diet. (In related research, a fast food diet was shown to prematurely heighten levels of cellular senescence and the pro-inflammatory SASP in animals, but exercise partially mitigated these effects as well as fast food diet-related obesity, visceral adiposity, changes in fat cell morphology, and metabolic perturbations.) In other words, pro-aging influence appears to be transferrable to younger animals through fat cells or through diet, a result that is reminiscent of previous preclinical research finding adiposity apparently transferrable through microbiome transplantation; greater presence of senescent cells has also been noted in obesity.

This research team also investigated the reversibility of senescence-related dysfunction, and successfully employed the combination of quercetin with the cancer drug dasatinib as a "senolytic" agent to induce programmed death in senescent human cells, and analogously treated animals showed similar results as well as improved physical function. Finally, the researchers found that providing the senolytic combination to old mice extended their lifespans. A study published in March 2019 found that using dasatinib and quercetin as a senolytic agent "cleared" senescent cells (produced apoptotic death in them) in mice with diet-induced obesity, improving their glucose and insulin metabolism while also reducing the number of macrophages populating their fat tissue. This senolytic treatment, however, did not interfere with cells' progression into senescence.

This evidence, in turn, is reminiscent of research combining strategically-timed fasting or calorie-restricted ketogenic diet with cancer therapies in effective and well-tolerated approaches to treating cancer, and begs the question of whether phytonutrients with calorie restriction-mimicking properties (such as resveratrol and quercetin) might be used as "phyto-senolytics." Other recent research hints at this possibility, and the flavonoid fisetin (found in strawberries, persimmons, onions, and apples as well as in other fruits) shows promise. Greater senescent cell burden in older animals may reflect low or inefficient autophagic function with aging, and inability to proliferate is the main reason senescent cells remain in the minority within tissues. Because senescent cells cannot proliferate, they are actually considered desirable in active cancer and their creation (within tumors only, if possible) is a goal of some cancer therapies. Fasting-induced autophagy is thought to help distinguish between cells that can "switch gears" to conserve resources required for proliferation and active, transformed cells that cannot, which in turn provides a unique opportunity to target metabolically-inflexible cancer cells.

Research into senescence at the level of the cell provides new insight into what aging really means—and provides further clarity on what we can do about it at the human level.

GPCRs—Cell Membranes' Polyglot Consensus-Makers

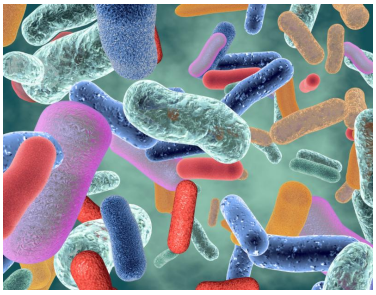


You may have heard of opioid, beta-adrenergic, and dopamine receptors, but did you know that many of them are classified as G protein-coupled receptors (GPCRs)? GPCRs are interesting because, like data in quantum computing, they aren't merely 'on'/'1' or 'off'/'0.' Instead, they exist in a complex equilibrium of intermediate states across the cell membrane, neither fully active nor inactive. Each can simultaneously accept a variety of signaling information and modify its conformation based on the 'consensus' of this input, resulting in the molecular shape and binding efficacy that faithfully transmits the summary of messages it receives. GPCRs recognize stimuli as varied as light, odorants, hormones, peptides, phytochemicals, eicosanoids, ions, and neurotransmitters; in fact, they can respond to multiple ligands at once while also interacting with GPCR-specific signal transducers that modulate their overall response. Epigenetic modification and polymorphisms additionally influence their activities, and GPCRs have the ability to interlink into oligomers, resulting in a broad range of potential responses.

Over 33% of drugs target GPCRs, and the wide scope of functions affected by GPCRs render them applicable in inflammatory, cardiovascular, psychological, cognitive, endocrine, and other conditions, and their networking nature coupled with differential responsivity to endogenous and environmental inputs makes them attractive therapeutic targets for lifestyle interventions. For example, GPCR signaling mediates the inhibitory effects of the omega-3 fatty acid metabolite resolvin E1 on central nervous perception of peripheral pain, as if to represent a group view that "help is on the way, we can safely dampen the message to discomfort instead of misery." In the digestive tract, metabolite-sensing GPCRs also help impart messages carried by food, and hormone- and nutrient-sensing GPCRs influence the stomach's secretion of ghrelin. GPCRs involved in cardiovascular function include angiotensin, endothelin, and opioid receptors that can bind with histamine as well as hormones and neurotransmitters; animals have even shown GPCRs for particular odorant molecules that are expressed solely in the heart. An intriguing finding from one study was that GPCRs may help carry a signal for vasoconstriction yet can also induce production of the metabolite diacylglycerol that, upon GPCR binding, attenuates the hypertensive effects of angiotensin.

Listen in as Professor of Pharmacology Richard Deth, PhD describes how a dopamine GPCR employs methionine to facilitate methylation in neurons, and he and Dr. Bland discuss the implications of methylation for attention, cognition, coordination of brain inputs, and autistic-spectrum conditions.

Protein and the Microbiome



Carbohydrates and other prebiotic substances can directly feed some gut microbes, while dietary plentifulness of fats may potentially limit the availability of fermentable nutrients. Dietary proteins can also affect gut microbiome composition in a somewhat specialized fashion, related to 1) metabolic protein sensing, 2) the unique profiles of other nutrients (minerals, prebiotics, immunoglobulins, etc.) provided by plant, animal, and insect sources of protein, and 3) the fact that plant protein sources tend to be digested lower in the human digestive tract (and thus later) than most animal proteins. Likewise, the microbiome can affect protein metabolism, as some bacteria (including potential pathogens like *Escherichia coli* and *Klebsiella*) possess enzymes for breaking down proteins and utilizing amino acids.

While mouse microbiome models do not fully predict dietary responses in humans, they are respected as a practical way of identifying meaningful food-microbiome relationships in a controlled fashion that is not easily replicated in humans. A 2017 mouse study compared soybean, casein, lactose-removed whey, pig plasma, wheat gluten, and mealworm proteins for their protein efficiency and effects on microbiome composition and on protein sensing (via activation of mTOR, the mammalian target of rapamycin).

Mealworm was discovered to be an especially efficient protein (maintaining weight despite a lower consumption level) while whey was associated with reduced body weights, consistent with previous research finding that it can increase levels of the satiety factor glucagon-like peptide-1 (GLP-1). In the microbiome, most of these protein sources cultivated Firmicutes phylum bacteria over Bacteroidetes, with mealworm clearly the strongest in this respect, and soybean alone encouraged the growth of Bacteroidetes over Firmicutes members. Whey protein was by far the most effective in increasing the growth of bifidobacteria, while whey, gluten, and soy (in descending order) were best at cultivating Proteobacteria and mealworm least encouraged them. It is perhaps not surprising that the animal and insect protein sources casein, whey, and mealworm were strongest activators of mTOR and that soybean was weakest (in effect downregulating it), but pig plasma was shown to be a weaker mTOR activator than wheat gluten. (This last finding might beg the question of whether proteins that downregulate mTOR may be particularly useful, in limited amounts, during fasting-

mimicking therapies.)

In this classic FMU, Dr. Bland and nutritional chemist Dr. T. Colin Campbell discuss what, within an increasingly toxic food supply, constitutes toxic food, and how certain proteins (including gluten and casein) contain exorphins that show neurotoxic potential in susceptible individuals.

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