CAN LIFESTYLE REVERSE YOUR BIOLOGICAL AGE?

COGNITIVE ENHANCEMENT, HEALTHFUL NUTRITION, MOVEMENT & EXERCISE, RESTORATIVE SLEEP, SOCIAL ENGAGEMENT, STRESS MANAGEMENT

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We all know that eating right, sleeping well, and minimizing stress are good for our health, but what if they could turn back the clock on biological aging? A small but groundbreaking 2020 study found that an 8-week prescription of a healthful diet, stress reduction breathing practices, and exercise decreased participants' epigenetic age by a little over three years relative to a control group. Sounds too good to be true, doesn't it? And what do we mean by epigenetic age? We'll answer those questions and more, but first, a primer in epigenetics. Epigenetics describes reversible molecular modifications made to DNA. At the cutting edge of our modern understanding of medicine and cellular biology, epigenetics facilitates variation between genetically identical cells like your neurons and muscle cells. In the case of twins, for example, you can think of the DNA as the blueprint shared by twins, while epigenetics is the footnotes — instructions that dictate how the blueprint is interpreted and applied. Think of it as the mechanism that bridges nurture and nature, fine-tuning your genetics in response to your environment and lifestyle. At the molecular level, that tuning involves the addition or removal of small molecules like methyl groups to DNA and its packaging. Some molecules make the genes to which they are attached more accessible to the machinery that will translate them, essentially turning those genes on, while others do just the opposite. Evolutionarily, these changes facilitate rapid adaptation to an ever-changing environment. An individual's experience of famine, for example, can epigenetically tune their metabolism and growth for energy conservation. These epigenetic changes may also be seen in their descendants for several generations to come. The exciting news is that tuning isn't permanent, which is where lifestyle medicine comes in. Many of the epigenetic phenomena that we understand are related to metabolism and stress responses. Though evolutionarily conserved, these epigenetic changes can be maladaptive in the modern context. A traumatic childhood experience, for example, can trigger epigenetic modifications that not only alter an individual's stress response to cause chronic stress, but are also heritable to their offspring. This enhanced stress response may have protected an early human in the savannah from repeating risky behaviors, but in our more predictable modern world, chronic stress more often contributes to poor mental health and diseases like cardiovascular disease and high blood pressure. Thinking back to epigenetic age, it seems rational then that if we know the patterns of epigenetic modifications associated with failing health and the diseases of aging, we can use them as a surrogate measure of healthfulness. Though we don't yet fully understand its nuances, molecularly determined epigenetic age is a better predictor of an individual's health and longevity than chronological age, presenting an exciting frontier for understanding and modifying health and longevity through lifestyle medicine and targeted therapeutics. For example, a team led by scientists here at Stanford and at the Buck Institute for Research on Aging used deep learning to identify key molecules of systemic inflammation such as CXCL9 that correlate closely with morbidity, cardiovascular degradation, frailty, and other signs of biological aging. As we age, this increasing chronic, systemic inflammation is likely driven by epigenetic changes, raising the tantalizing possibility that it could also be reversed.

How can we use lifestyle medicine to modify our epigenetic fate?

So far, the main clinical epigenetic therapies that have seen success are small molecules that reduce DNA methylation to treat cancer. These molecules function by pushing the reset button on many of the accumulated epigenetic changes that allow the cancer cells' runaway growth. What if we could do the same to the changes that predict ageing, chronic inflammation, and disease? For now, it seems that our therapeutic tools are too blunt, lacking the precision to target the maladaptive and disease-associated epigenetic changes. So, for now, our best tool for harnessing our epigenetic destiny is our lifestyle. Let's take a deeper dive into what that looks like at the cutting edge of each of our Stanford Lifestyle Medicine Pillars.

Epigenetics & Physical Activity

Daily exercise has long been associated with health benefits from reduced incidence of cardiovascular disease and improved cancer prognosis to slower cognitive decline. The CDC recommends getting at least 150 minutes of moderate-intensity aerobic activity and 2 strengthening workouts a week for optimal health benefits. There is now evidence that exercise also broadly improves the capacity of your cells to alter their methylation patterns. **Exercise leads to higher levels of the protein superoxide dismutase, which works through a series of receptors and pathways in the liver to alter the methylation of key metabolism genes and enhance metabolic function.** These pathways affect health in a myriad of ways including improving glucose tolerance to reduce the risk of diabetes. Though some of those epigenetic changes are maintained from parents to children, many are re-programmed during critical developmental periods in-utero, allowing maternal exercise during pregnancy to have profound impacts on offspring health later in life. Lifestyle, it seems, is preventive care that begins even before we're born. The systemic epigenetic changes induced by physical activity were seen in a recent study by Washington State University that analyzed differences between physical activity and epigenetics in identical twins. Researchers found that twins who exercised for 150 minutes a week or more had more epigenetic markers related to lower risk of metabolic syndrome than twins who exercised less.

Epigenetics & Nutrition

According to recent research, what you eat, and perhaps more unexpectedly, what your parents ate, seems to affect our health through epigenetics in two interesting ways. First, by the availability of small molecules that participate in and modulate the biochemical reactions that add and remove epigenetic tags. For example, plant-forward diets tend to be high in epigenetic substrates like folate, a precursor of the methyl groups added to DNA; cofactors that facilitate that reaction like vitamins A and C; and polyphenolic compounds like curcumin (found in turmeric) that modulate DNA Methyltransferase, the protein that initiates the reaction. Leading theories suggest that by maintaining abundant nutrients involved in epigenetic processes, the body's response to stress and ever-changing metabolic supply and demand can be efficiently fine-tuned. Diseases like diabetes arise in part because of maladaptive or improper metabolic tuning. A second way that nutrition impacts epigenetics seems to be mediated by metabolic stressors and nutrient sensing. Our cells work along the spectrum between two main modes; when nutrients are limited, pathways turn on that favor maintenance, and clearing and recycling debris, to enhance cellular function and efficiency. Abundant nutrients, on the other hand, downregulate the efficiency pathways and promote storage and more reckless use of resources. With time, famine or feast can become encoded as heritable epigenetic changes, contributing to the increased risk of obesity, diabetes, and several other health conditions in the offspring of parents with poor diet and nutritional profile.

Epigenetics & Sleep

Sleep, namely the lack thereof, has been associated with everything from heart disease and stroke to metabolic disruption. Its greatest impact, though, is on the brain. Interestingly, susceptibility to sleep deprivation is a highly genetic phenomenon. Some people can barely function without 8 hours of sleep, while for others, 6 is more than enough. This suggests a significant role for epigenetics. Cognitive functions like learning and memory rely on neural plasticity, which requires fine-tuned epigenetic adjustments to the gene expression patterns of individual neurons. This process requires sleep, and even single sleep disruption events can impair them, especially in the hippocampus, one of our primary memory and learning centers. More chronic sleep deprivation can alter mood, exacerbate psychiatric disorders, and increase the risk of neurodegeneration as in Alzheimer's. **Most of the epigenetic changes seen with sleep deprivation modify genes involved in metabolism, circadian rhythm, and synaptic plasticity and signaling.** For example, night shift workers have altered expression of the genes CLOCK and Dlg4, a master regulator of our body's internal clock, and a protein implicated in autism that scaffolds synaptic signaling respectively.

Epigenetics & Stress

Technically, stress is any stimulus that disrupts our body's homeostasis, whether running from a predator in our evolutionary past, experiencing a traumatic life event, or persistent psychological distress. The hypothalamus-pituitary-adrenal (HPA) axis, then, is the stress response control center, a system that connects our brain to our hormone-secreting glands that release systemic stress signals like cortisol, adrenaline, and pro-inflammatory molecules. These signals go on to modulate all our body's systems, from metabolism and neuronal activity to immune function, and are themselves epigenetically tuned. Typically, our bodies overcome the stressor and return to homeostasis, but traumatic and chronic stress can lead to compounding epigenetic changes that dysregulate our immune, metabolic, neuronal, cardiovascular, and other systems. For example, traumatic childhood experiences trigger epigenetic changes in immune cells like macrophage, increasing pro-inflammatory reactivity and hormonal dysregulation, which may underlie the plethora of adverse health outcomes associated with childhood trauma. Much like the epigenetics of nutrition and exercise, parental stress can be passed on to children both through inherited epigenetic patterns, and through stress hormones circulated from the mother to the developing fetus. **On the bright side, positive life experiences, social relationships, and mindfulness practices like meditation and breathing exercises all work to short-circuit these maladaptive stress responses and associated epigenetic changes.** For example, one mindfulness-based intervention in breast cancer patients resulted in a reduction of greater than 50% in the epigenetically controlled levels of 91 pro-inflammatory hormones and molecules compared to control patients, an effect that persisted 12 months later.

Epigenetics & Social Engagement

Our capacity to form complex social bonds is evolutionarily foundational to survival, so it's no wonder that relationships, too, are intimately tied to epigenetics. On one hand, the epigenetic changes associated with chronic and traumatic stress are implicated in impaired capacity for developing and maintaining social bonds. On the other hand, **Strong social relationships are important for mitigating stress and its deleterious epigenetic effects, and are one of the strongest predictors of health, happiness, and longevity**. Though this is one of the more complex and least understood areas of epigenetics, it's hard to overstate its role. For instance, mutations in MeCP2, a gene that helps interpret epigenetic methylation patterns, results in the profound cognitive and social dysfunction known as Rhett syndrome.

Epigenetics & Cognitive Enhancement

As it turns out, synaptic plasticity, the phenomenon underlying higher cognitive functions like memory and learning, is largely governed by epigenetic mechanisms. In a highly simplified sense, the strength of patterns and combinations of synaptic firing are enhanced by repeated stimulation, and conversely tuned down in the absence of activity. This is accomplished by epigenetic changes that modulate the sensitivity of neurons to subsequent stimulation. Carrying that principle one step farther, research indicates that enhanced synaptic activity is also essential in synaptic and axonal regeneration after damage such as in the brain of a stroke patient. In animal models, for example, exposure to stimulatory physical and social environments after a brain injury or in disease states such as Parkinson's leads to increased synaptic activity, which triggers epigenetic changes that promote regenerative healing. Given this observation, it is speculated that similar mechanisms underlie the positive effects of exposure to nature and socially stimulating environments on cognitive and neurological recovery after a brain injury or in diseases like Alzheimer's. Further, it is plausible that the epigenetic benefits of physical fitness, a varied, plant-based diet, sleep, and relationships translate to beneficial effects on cognitive performance in both health and recovery. For example, the Mediterranean Diet is associated with slowed brain aging and improved cognitive functioning, whereas the Western Diet has been implicated in accelerating natural brain aging processes.

APRIL 26, 2023 / BY DOM-WP-ADMIN