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In this issue: The Gut is a Valuable Focal Point Immediately After Brain Trauma; Meet and Greet Kinases--Creatine Kinase & mTOR; Experience and Aging Stimulate a Lot of "Journaling" Within Cells

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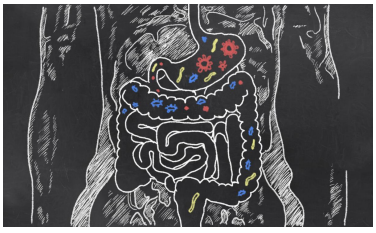
The Gut is a Valuable Focal Point Immediately After Brain Trauma



Each year, well over 1 million people in the US suffer brain trauma, which contributes significantly to early death and costs tens of billions of dollars annually, according to neurosurgical research.

The interplay between gut and brain affects blood-brain barrier integrity and inflammatory tone throughout the central nervous system, and considering the profound neurocognitive and behavioral effects of traumatic brain injury (TBI), it is perhaps not surprising that changes in gut microbiome composition, intestinal permeability, T cell subset balance, and function of the protective microglia are common in its aftermath. Scientists have even observed that gut microbiome and secondary neurological changes both generally occur within the same 24 to 72-hour period following TBI, and in order to limit its acute and chronic effects, the Institute of Medicine recognizes the importance of addressing nutrition immediately after TBI. While there is as yet limited clinical success in treating brain trauma, recent study has uncovered evidence that intestinal dysbiosis can worsen the course and outcome of TBI and that the use of probiotics may reduce time needed in intensive care. Early findings suggest that lactic acid bacteria and other probiotic species associated with increased production of the gut-nourishing short-chain fatty acid butyrate and of the immunomodulatory cytokine IL-10 (interleukin-10) may help support immune and gastrointestinal function in affected individuals, and researchers at Walter Reed (a military institute that treats many injured service members) note that microbiota transplants and use of diverse plant-based prebiotics are promising approaches.

Given the importance of maintaining immunometabolic equilibrium in the crucial hours after TBI, those at heightened risk for brain trauma (occupational or otherwise) may

benefit from diet and lifestyle strategies aimed at optimizing intestinal barrier function, increasing diversity in the gut microbiota, and minimizing whole-body inflammatory potential.

Meet & Greet Kinases--Creatine Kinase & mTOR

Kinases are perhaps *the* archetypal enzyme, comprising a dynasty of hundreds of hardworking proteins that accelerate processes enabling human metabolism. At the most basic level, they constitute a sort of energy transfer system in that their specialized molecular configuration allows them to convey highly reactive and unstable phosphate groups from high-energy molecules to substrates—and thus, they are considered phosphotransferases rather than phosphorylases. Most kinases act on proteins, and can activate, stabilize, deactivate, or tag them for further regulation, and their phosphorylation (typically at a protein's tyrosine, serine, or threonine residues) facilitates a broad range of metabolic events ranging from aiding mitochondrial energy production to influencing cell life and death. Other kinases act on lipids, carbohydrates, or other substrates. Here we introduce a few members of this stalwart family.

Creatine kinase (CK)

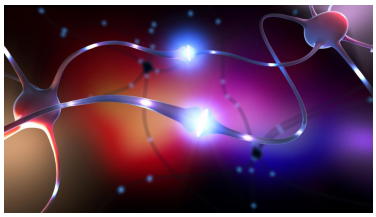
Juggling high-energy molecules takes skill, and creatine kinase (CK) catalyzes the creation and dismantling of the energy carrier phosphocreatine from magnesium-bound ATP (adenosine triphosphate) and creatine. This constitutes an acid/base- as well as energy-buffering system in areas with high aerobic energy needs, such as the heart, brain, retina, ear, sperm, smooth and skeletal muscles, and mitochondria—and takes advantage of the functional versatility of the tripeptide creatine in preserving homeodynamic balance. CK also helps regulate the cell cycle and cell division, and may therefore play a role in some cancers. Extracellular CK release is a marker of recent tissue damage (heart attack is a classic example), and different forms of this enzyme localize to different cell types. However, elevation in CK level is not necessarily proportional to the amount of damage, and gender, body composition, ethnicity, habitual muscular activity patterns, presence of fast twitch-type muscle fibers, use of branched-chain amino acids, certain drugs (like antipsychotics), certain disease states (renal, mitochondrial, or neuromuscular conditions and cancer), and several gene variants can also significantly impact CK levels.

mTOR—mammalian/mechanistic target of rapamycin

This serine/threonine protein kinase is part of the PI3K kinase family and its activity is central to skeletal muscle protein synthesis in response to exercise and to protein intake. It works in conjunction with mTOR complexes (mTORCs) that act as nutrient and energy sensors and activate or inhibit mTOR upon integrating signaling information regarding cellular energy status, amino acid availability (especially of leucine, glutamine, and arginine), and indicators of oxygen or energy stress or growth readiness. In nutrient insufficiency, mTORCs cooperate with the energy regulator AMP kinase and the peroxisome proliferator-activated receptor (PPAR) system to encourage autophagy and ketogenesis, and during times of plenty they collaborate with the insulin-sensitive PI3 kinase/Akt duo to 'approve' the synthesis of proteins, lipids, nucleotides, and, by extension, muscle tissue. Aging may interfere with mTOR signaling and protein synthesis, and mTOR is thus a key target in cancer-related wasting and age-related muscle loss (sarcopenia). Careful coordination of tissue growth and autophagy (with other pathways like NFκB, p53, and hypoxia-inducible factor) is crucial in long-term function of hard-working organs like the heart, and dysregulated mTOR signaling can contribute to pathology in cardiac hypertrophy, cancer, diabetes, and other conditions.

In this talk with resveratrol researcher Dr. David Sinclair, Dr. Bland explores the mechanisms underlying biological aging, how mTOR relates to sirtuins, and why Dr. Sinclair considers mTOR to be one of the "four horsemen of the aging field."

Experience and Aging Stimulate a Lot of "Journaling" Within Cells



Circadian rhythms in physical, cognitive, metabolic, and behavioral functions are guided by diurnal changes in the expression of "clock" genes, and research is discovering more about how the brain and organs and cells peripheral to the brain manage their daily scheduling and reprogramming.

Retinal information about daily light and dark patterns is transmitted to the central or "master" clock within the hypothalamic suprachiasmatic nucleus (SCN). This tiny node of around 20,000 neurons apparently establishes the baseline for other "peripheral" body clocks and determines, to some extent, how effectively various body functions are coordinated. Other body clocks are additionally influenced by temperature, timing of food intake, use of stimulants, sleep patterns, travel between time zones, behaviors, and other cues. Nightly production of melatonin is one such example of the responsivity of body clocks. In studies in athletes, night-time reading increased melatonin levels more than did solving puzzles, and those using multiple electronic devices before bed-time had more difficulty getting to sleep than those who did not, and night-time exercise appears to reduce night-time production of melatonin while increasing cortisol levels—both of which are the opposite of what normally occurs. A 2016 study found that circadian expression of clock genes in the blood was about 8½ hours ahead of that of brain clock genes, and the researchers hypothesized that increased exposure to artificial light with decreased exposure to sunlight may play some role in this time gap, and a May 2019 study reinforces the notion that, in addition to SCN input, light can also affect the rhythms of life in epidermal and other tissues, and may influence biological aging processes.

The work of gerontologist Steven Horvath, PhD, demonstrates that cells and tissues also have sophisticated epigenetic clocks that carefully note their genetic background and how they respond to healthful or stressful inputs. Through DNA methylation patterns, these epigenetic clocks keep track of cells' resultant biological age as well as that of whole organisms (including humans) especially in combination with clinical biomarkers and other signs of aging. This multilevel approach to organizing cellular circadian patterns (the experiences of a cell and its nucleus intermeshed with those of the SCN) is reminiscent of how adaptive immunity memorializes significant events while innate immunity remains prepared for novel happenings.

Why such painstaking regulation of body function in terms of time of day? At one level, it is because sympathetic and parasympathetic activities are distinct, and the body must parse incoming information about immediate and potential dangers, environmental circumstances, stressors, and behavioral inputs to determine what the most advantageous focus should be, from moment to moment. Healing takes place with sleep, but away from eating and digestion. Sleep takes place away from physical activity and exposure to light (whether sun or artificial) and electromagnetic fields. Cardiovascular events are more likely to take place in early morning hours, when coordination between sleeping and waking activities appears somewhat prone to dysregulation. Prime cognitive function in "morning" and "night" people can vary: while best focus, logic, and attention concord with preferred times of day, creativity and insight may be more apt to emerge at non-optimal times. Additionally, the burgeoning field of chronobiology is finding that circadian rhythms may influence individuals' response to therapies, and further research may guide optimization of scheduled treatments. This detailed journaling may therefore provide a great deal of valuable information that may be harvested in order to personalize optimal means of controlling diet, light exposure, physical activity, and the timing, quality, and quantity of food intake.

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