CONVERGENCE

News, Links, and Insights
by JEFFREY BLAND, PHD

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In this issue: Guarding the Windows of the Soul: Eye Health; Eternal Mitochondrial Quandary: Part 1 of 2 on Aging; Fasting Mimicking Diet (FMD) and Irritable Bowel Disease (IBD); The Seventh Annual Thought Leaders Consortium

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Guarding the Windows of the Soul

The eye's multilayered retina is tissue-thin, and the thinnest area of its central macular area, the pen tip-sized fovea, is one of the body's most specialized and metabolically demanding tissues, responsible for our most detailed vision. While many are aware of the importance of the blood-brain barrier in protecting the delicate environment of the central nervous system, the blood-retinal barrier deep within the vascular tissues of the eye constitutes another vulnerable entryway. The retina is poorly vascularized in service of vision, and relies on its supporting epithelium for protection and nourishment—but while the specialized photoreceptors that enable vision are frequently replaced, lifestyle and exposome factors can interfere with maintenance of this precious epithelium. The unique tissues of the eye are sensitive to nutrient and antioxidant insufficiency, oxidative stress, blood pressure and blood sugar levels, and blue light and other stressors—and if their nutrient demands are not met, vascular proliferation can occur in an attempt to aid survival, yet may instead impair vision.

The blood-retinal barrier (BRB) acts as a transport regulator, and consists of the retinal pigment epithelium (the outer BRB) and retinal vascular endothelium (the inner BRB), with tight junctions maintaining barriers between neighboring cells in both. At the inner endothelial BRB, the transport of some lipophilic molecules can occur passively, but most proteins, hormones, nutrients, and ions consume energy crossing the inner endothelial BRB, and some also require specific receptors. BRB tight junctions also influence cellular life cycles and gene expression. Of the two most common retinal diseases, diabetic retinopathy relates to altered function of the inner BRB while neovascular ("wet") age-related macular degeneration (AMD) results from altered function of the outer BRB; macular edema can be caused by either.

Globally, the prevalence of diabetic retinopathy is about 34.6%; around 25% of type 2 diabetics are affected, while risk among type 1 diabetics is considerably higher. Diabetic retinopathy is mainly caused by increased permeability of small blood vessels and of the BRB, which results in local edema, inflammation, increased oxidative stress, and eventually fibrosis and compensatory development of new blood vessels. The two major risk factors for diabetic retinopathy are hyperglycemia (especially HbA1c levels and duration of diabetes) and hypertension; others include hyperlipidemia, elevated BMI, puberty, and pregnancy, and chronic inflammation and particular genetic polymorphisms may also contribute. Global prevalence of AMD among adults over 30 is estimated at almost 9%, and it is the #1 cause of blindness among those over 55 in the developed world. While the etiopathology of AMD is not completely understood, heightened oxidative stress, inflammation, and angiogenesis are known to contribute to outer BRB deposition of inflammatory debris—which some consider functionally analogous to atherosclerotic plaques or diabetic aneurysms. Major risk factors for AMD include age, hypertension, cardiometabolic disease, high-fat diet; insufficient intakes of zinc, lutein, zeaxanthin, and other antioxidants and nutrients; smoking, family history, increased BMI, and hyperlipidemia, and genetic polymorphisms and vitamin D insufficiency may also heighten susceptibility.

Retinal surgeon Shalesh Kaushal, MD, PhD has found that eye tissues can manifest mitochondrial dysfunction, dysglycemia, inflammation, immune imbalance, and energy dysregulation—not infrequently related to the consumption of high-glycemic foods. In this FMU interview, Drs. Kaushal and Bland discuss underlying causes shared by retinal conditions, chronic systemic diseases, and biological aging. It would seem that our eyes, the windows to our souls, have several bodyguards: the inner (endothelial) BRB, the outer (epithelial) BRB, and everything we expose ourselves to, eat, and do.

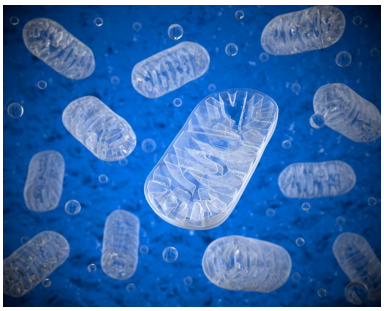
Shalesh Kaushal, MD, PhD

Live Educational Opportunity

Dr. Shalesh Kaushal will be a speaker at the 2019 Thought Leaders Consortium in Seattle this fall. This is an event that is organized by the Personalized Lifestyle Medicine Institute and hosted by Dr. Jeffrey Bland.

Early-bird registration expires **June 30th**. Register today to reserve your seat! Find useful informational links at the end of his email.

Eternal Mitochondrial Quandary: Accumulation or Spring Cleaning?



Part 1 of 2: Accumulation and Aging

Like the economies of countries, cells need energy for normal function and to withstand hard times, but while economies count on people to produce value, cells and bodies rely on mitochondria for energy. Like organisms, cells live and die, and can do so in ways that are either more or less organized, depending on circumstances. During cell life and even into cell death, mitochondria manage available resources to meet fluctuations in short- and long-term energy demand through several responses: splitting, fusing with another, lining up for sorting and recycling (mitophagy), limping along with increasing damage and dysfunction, or dying in controlled (apoptosis) or uncontrolled fashion—perhaps not so very different from human economies. Mitochondria face this decision

tree constantly and decide how to answer based upon their cell's needs, limitations, and priorities—which are in turn based on those of tissues, organs, and ultimately, the organism's.

A mitochondrion and its cell's nuclei communicate back and forth regarding oxygen consumption and capacity to produce energy. Quick increases in need (when starting exercise programs or heavy mental work, for example) may be met by heightened mitochondrial efficiency and by adjusting numbers of mitochondria through either fission (doubling 'daughter' mitochondria with each split) or fusion, wherein mitochondria bind together into longer structures containing electron transport complexes that create the energy currencies of NAD+ and ATP (reduced nicotine adenine dinucleotide and adenosine triphosphate). Neural plasticity is one interesting example of this: in response to novel mental tasks, neurons will 'order up' more mitochondria at prospective new synaptic connections to 'power up' new neural pathways and networks. Reactive oxygen and nitrogen species (ROS and RNS) are a necessary by-product of mitochondrial energy elaboration, and mitochondrial efficiency can roughly be considered the balance between 1) NAD+ and ATP produced and 2) ROS and RNS produced. Greater mitochondrial bioavailability of antioxidants possessing a wide range of redox potential limits the creation of ROS/RNS, and thereby aids mitochondrial efficiency. Ketones (and ketogenic diets) can also help mitochondria meet energy demands while producing fewer pro-oxidant substances.

Like bodies, cells, and genes, mitochondria age, and this can be accelerated by toxins. Examples of mitochondria-specific stressors include:

- pesticides, microbicides, herbicides, and persistent organic pollutants
- heavy metals, smoking, and radiation
- excessive oxidative stress, tissue injury, chronic inflammation
- accumulation of excess amyloid beta
- excess energy intake and unhealthy dietary choices
- insufficient rejuvenating sleep
- excessive or overly repetitive exertion of limited muscle groups
- chronic mental or physical stress
- drugs that deplete B vitamins, magnesium, coenzyme Q10, carnitine (especially as acetyl-L-carnitine), or other nutrients and antioxidants needed by mitochondria

These factors can damage mitochondrial membranes, mitochondrial DNA (mtDNA), or other structures. As mitochondria may have their origins in bacterial species that evolved independently before becoming an integral part of human cellular energetics, this injury to mtDNA (which is separate from the rest of a cell's DNA) may cause mitochondria to code for defective proteins that produce defective mitochondria. Mitochondria with structural or DNA damage, possessing particular mtDNA gene variants, or in a chronically inflamed environment may be prone to dysfunction, releasing high amounts of ROS/RNS in relation to energy produced. Impaired mitochondrial function has been implicated in many ailments including Parkinson's and Alzheimer's diseases, cancer, cardiovascular disease, diabetes, and mitochondriopathies. Even organized cell death takes some investment of energy, and in absolute energy lack, cells may die a disorganized necrotic death or can even transform into precancerous cells if there is critical DNA damage and/or the environment has been altered by genotoxins or carcinogens.

Mitochondrial aging can be lessened by regular aerobic work and exercise, ample intakes of substances that protect mitochondria, and two historically normal, natural activities that constitute mitochondria's primary beneficial challenges: periodic caloric restriction and limited episodes of intense physical activity, When balance among these influences is well maintained, cells and mitochondria alike are availed of all they need in order to carry out 'spring cleaning' programs—autophagy for clearing out overly-damaged cell organelles and mitophagy for recycling 'burnt out' mitochondria and replacing them through fission. An equilibrated lifestyle not only optimizes mitochondrial efficiency but also allows spring cleaning to occur in a coordinated manner wherein cell signaling of energy needs and mitochondrial aging are cunningly combined: during fission, mitochondria can sort well-functioning parts into one daughter mitochondrion—a kind of micro-recycling and rejuvenation—while the other receives damaged parts and is immediately readied for mitophagy—cellular 'composting' of parts that can no longer be used.

The ETA on FMD for IBD May be Soon

Research showing that the Fasting-Mimicking Diet can boost particular stem cell populations in animals and appears basically safe for humans has generated understandable excitement: imagine what that could mean in serious progressive illnesses like joint disease, neurodegenerative disease, autoimmune conditions, and inflammatory bowel disease. But FMD is still a very new therapy, and we as yet understand little about how it impacts people at different levels of wellness and disease, so safety concerns necessitate preliminary research to improve understanding for how FMD affects pathological as well as "normal" function.

In a recently published study on an animal model of inflammatory bowel disease, application of two cycles of the Fasting-Mimicking Diet (FMD) was compared with other treatments: 1) FMD with fecal microbial transplantation, 2) water fasting, and 3) supplementation with *Lactobacillus casei* ssp. *rhamnosus* GG. Results showed that, in affected animals, FMD treatment alone reversed intestinal pathology, improved intestinal morphology, reduced inflammation, improved abundance of certain lactobacilli and bifidobacteria in the gut, and boosted intestinal stem cell numbers. In contrast, water fasting was found to reduce intestinal inflammation and increase intestinal stem cell numbers without reversing essential intestinal pathology. In this IBD model, FMD also made a greater overall impact on gut microbiome composition than either supplementation with *Lactobacillus casei* ssp. *rhamnosus* GG or the combination of FMD with fecal microbial transplantation.

Though FMD has not yet been clinically tested in ulcerative colitis or Crohn's disease, the results of this preclinical study are promising, and they realistically boost hope.

THE SEVENTH ANNUAL THOUGHT LEADERS CONSORTIUM

Registration is open and seats are filling quickly! Dr. Jeff Bland is the conference host and facilitator. Join more than 300 attendees from around the world in Seattle this fall.

Click HERE to view the current program schedule.

Click HERE for a conference overview.

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