October 2018

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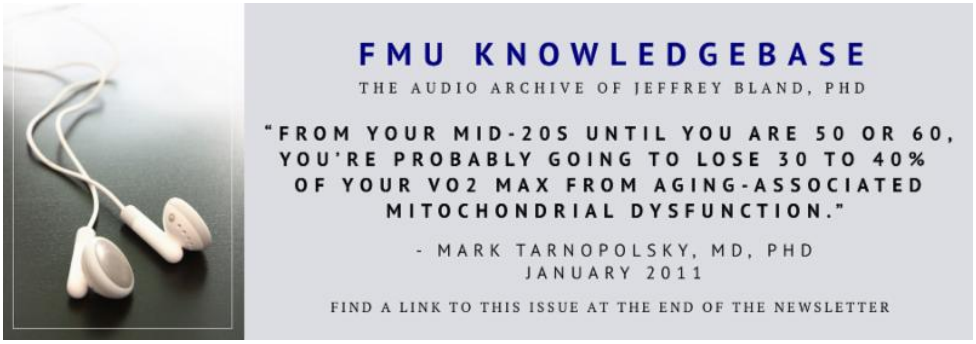
In this issue: Cardiovascular Injury and Inflammation; What Does it Take to Change an Industry? (video blog); The Impressive Bandwidth of Stem Cells; SNiPpets: Pancreatitis; Atorvastatin and Resolvins; Classic FMU: Mark Tarnopolsky, MD, PhD



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At Heart, Would You Choose Rescue or Prevention?

Research into lipid mediators (like the metabolites of omega-3 fats) introduced the concept that, both in health and disease, tissue conditions contribute extensively to the programming of immune cells, and subsequently, their relative balance. For example, injury calls for skewing towards a T-helper cell type 1 (Th1) orientation during the acute crisis followed by a Th2-oriented follow-up to restore normal tissue tone, whereas in chronic inflammation, the Th1-directed activity remains uppermost, and autoimmune conditions involve Th17 and T-regulatory cell population imbalances. Chronic inflammation disallows the Th2-directed "housekeeping" functions like clearing away cellular debris, reducing oxidative stress, and remodeling cells, mitochondria, and tissues for more efficient function.

In conditions like obesity and atherosclerosis, tissue macrophages are characterized by Th1 dominance (and directly contribute to plaque formation and instability), reflecting the chronic inflammation that accompanies these conditions. Biological aging can further complicate this picture through accumulation of genetic mutations that order single immune cell clones to proliferate, greatly distorting balance among cell populations. This recent Nature article discusses impressive pharmacological approaches for resetting balance among immune cells at the hematopoietic level, but also points out that lifestyle intervention addresses every modifiable major risk factor for cardiovascular disease, including:

- diet, hyperlipidemia, and hypertension
- obesity and diabetes
- smoking and psychosocial stress

There will undoubtedly be many new (and costly) immunotherapies and stem cell treatments for addressing cardiovascular injury and inflammation. But lifestyle medicine presents a way of improving the very "soil" in which cardiovascular pathology "grows," thereby preventing inflammation and cardiovascular aging at their very source and instead establishing long-term wellness and vitality.

Dr. Bland's Latest Video Blog

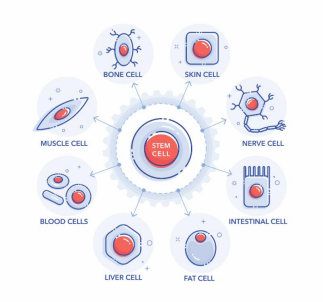
What Does it Take to Change an Industry?

Dr. Jeff Bland has long been acknowledged as a pioneer in the natural products industry. His work in this field has taken many forms over the past four decades and led him down many paths. In this modern era our food choices plentiful—visit just about any grocery store and you are likely to see options that are advertised as "natural," or "organic," or "ethically raised." Did you ever stop to consider how we got to where we are today? In this video, Dr. Bland shares a bit of history and pays a tribute to Mel and Polly Coleman—Colorado cattle ranchers, champions for change, fellow pioneers, good friends.

Video Link: https://www.youtube.com/watch?v=J4j8ZHJkxAk

Video is one of Dr. Bland's favorite communication tools. Subscribe to his YouTube channel to never miss an update, and also find many additional videos on the Personalized Lifestyle Medicine Institute Vimeo page.

Stem Cells' Impressive Bandwidth—From Fetus to Cancer



Stem cells have a ticket to ride: they can go almost anywhere in the body and become almost any kind of cell. Embryonic stem cells contain every genetic necessity for becoming a spleen, hair follicle, lung, or any other kind of cell in a growing fetus, and adult stem cells harbor considerable rejuvenative and therapeutic potential. Recent studies are investigating another avenue of this pluripotentiality displayed by stem cells, whose broad versatility could make them a master of disguises in cancer—especially if unintentionally aided by immune cells.

As a result of their capacity to be reprogrammed for cellular defense, offense, housekeeping, or tissue rebuilding according to current need, macrophages (one type of immune cell) also employ a spectrum of functions. They migrate, transform, develop and diversify their immunologic capabilities, and secrete factors that enable the breakdown of cellular and tissue barriers. Some evidence indicates that these hematopoietic cells may, under conditions of injury and/or inflammation, fuse with adult stem cells such as those in the intestinal epithelium. Though this may take place to promote healing or otherwise enable a return to normal function, in chronic inflammation, it may encourage the development of an environment conducive to cell proliferation and thereby predispose to a higher risk for local or remote cancer.

It is ironic that stem cells bear some resemblance to tumor cells, and tissues with greater stem cell capacity appear to be more susceptible to cancer via this inflammation-induced mechanism, including the liver, intestines, skin, brain, and bone marrow. Other new research clarifies that stem cells themselves may accumulate mutations associated with biological aging, providing yet another avenue for cancerous transformation in these cell populations. In this article published in Critical Reviews in Oncology, cancer researchers Thomas Seyfried and Leanne Huysentruyt describe the difficulty in determining whether such cells have transformed: "It is not easy to distinguish neoplastic from non-neoplastic macrophages in the inflamed tumor microenvironment, as both cells are similar in gene expression, morphology, and function."

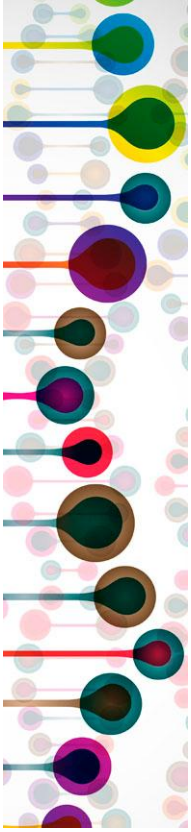
Surprisingly, the theory that ability to metastasize is the result of fusion between white blood cells and somatic germ cells was first proposed over 100 years ago, yet realistic mechanisms behind such transformation are increasingly recognized through modern research methods, though the theory yet to be conclusively proven. This putative fusion could create eminently reprogrammable cells with an oddly broad genetic identity and increased tissue evasion potential. In this 2013 edition of the FMU, Dr. Bland discusses stem cells in relation to the BRCA oncogene, while in this earlier talk, he describes their therapeutic potential.

SNiPpets

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

Gene Variants Linked to Pancreatitis—With and Without Alcohol

Pancreatitis has been related to dysregulated activation of digestive



enzymes, especially trypsin. This mechanism may be heightened by abuse of alcohol, and recent research suggests that it may in turn increase intestinal inflammation and bacterial translocation, encouraging a self-perpetuating, chronic inflammatory condition. A large genome-wide association study (GWAS) has identified several variants associated with increased pancreatitis risk in non-alcoholics as well as alcoholics. In non-alcoholics, this condition is linked to variants in genes coding for proteins involved in trypsin metabolism, including *PRSS1*, *SPINK1*, and *CTRC*, but this GWAS also found variants at closely-related loci that increase risk in alcoholics:

- the *PRSS1-PRSS2* locus rs2855983 (presence of G allele)
- the *SPINK1* locus rs146437551 (presence of G allele multiplied risk almost 4-fold)
- the *CTRC* locus rs545634 (presence of A allele)
- an additional variant at rs12688091 locus of the *CLDN2-MORC2* gene (presence of G allele multiplied risk over 2.5-fold) which codes for a claudin, a type of protein that affects digestive organ barrier function

The study also noticed differences in an area containing two chymotrypsin genes that, interestingly, are read in opposite directions during gene transcription, and found that the presence of a C allele at *CTRB1-CTRB2* locus rs8055167 increased pancreatitis risk for non-alcoholics as well as alcoholics.

This GWAS demonstrated that similar mechanisms may underlie both non-alcohol- and alcohol-related pancreatitis. For this reason, while alcoholic carriers of these gene variants may wish to re-evaluate aspects of life and lifestyle influencing alcohol-related behaviors, any carriers of these or related variants that alter digestive enzyme metabolism might consider receiving functional medical assessment of their metabolic detoxification capacity, intestinal barrier function, and body burden of inflammation as well as contributing factors such as pro-inflammatory diet, chronic stress, exposure to certain toxins and medications, and alcohol and tobacco use.

A Statin Joins Aspirin's Unique Club

It's been fascinating, in the last few years, to learn various ways in which intermediate and end metabolites of eicosapentaenoic and docosahexaenoic acids (EPA and DHA) are more active than these essential fats themselves. However, a few jaws dropped upon hearing that taking aspirin could greatly hike production of these metabolites—though in a way that Emily Dickinson might term "slant," because aspirin specifically induces formation of molecules configured in the mirror image of what the body produces.

History sometimes rapidly repeats itself, and noted lipid mediator researchers Charles Serhan, Nan Chiang, and Jesmond Dalli have further discovered that a particular statin drug (atorvastatin) is capable of encouraging the formation of resolvins from another omega-3, docosapentaenoic acid (DPA). These resolvins contain 13 carbons (in contrast to the 10-, 14-, 17-, and 18-carbon resolvins formed from EPA and DHA), and are thus named the "13-series resolvins." In early research, these 13-series resolvins appear to aid the resolution of inflammation related to infection, and are additionally formed in humans as a result of exercise—apparently part of the immune-stimulating effect of physical activity. Researchers are now looking into whether or not administering preformed 13-series resolvins can help prevent increased disease risk and adverse events associated with long-term statin use.

Where in the World is Dr. Bland?

Every year, Dr. Jeff Bland speaks in front of audiences around the world. **His next stop is the 2018 Thought Leaders Consortium in Tucson, Arizona.** Dr. Bland is hosting this event and registration will close October 5, 2018. Don't delay your registration any longer! >> www.plminstitute.org

View Appearances Calendar

FMU KNOWLEDGEBASE

For more than three decades, Dr. Jeff Bland recorded and self-published a monthly audio journal called Functional Medicine Update (FMU). Although he is no longer recording new issues, an archive of content spanning 1997-2016 is free to explore on Dr. Bland's website, and this extraordinary collection is now known as the FMU Knowledgebase.

To access the **January 2011** issue, which is featured at the start of this newsletter, click here. That issue features an interview with Mark Tarnopolsky, MD, PhD.

Which single behavioral change best improves mitochondrial function? Are there ways to encourage "clean" energy production at a cellular level? What are the cardinal signs of mitochondrial aging and dysfunction, and what can blood, urine, and muscle biopsy show? In this classic FMU discussion with mitochondria expert Mark Tarnopolsky, MD, PhD, we learn that early in our cellular evolution (probably around 1.5 billion years ago, at a proto-eukaryotic stage), we made the single greatest deal in human history, "merging" with what was probably a photosynthetic bacterium, which allowed much more efficient conversion of oxygen into energy in an environment of increasing oxygen concentration—a modification that later on enabled mental as well as muscular feats not otherwise possible. Though mitochondrial DNA is quite distinct from human DNA, genes coding for around 1500 mitochondrial proteins now reside in human DNA, so mutations in human as well as mitochondrial DNA can impact their function. Through appreciating the primary and backup metabolic pathways through which these adopted organelles produce energy as well as pro-oxidants, we gain knowledge of how to formulate individualized nutrient "cocktails" to optimize the dynamic balance between them.

Classic FMU Top Ten Clinical Pearls From This Issue:

1. #1 mitochondrial tonic: regular gentle strength and aerobic endurance challenge, which exercises creation of clean cellular energy and boosts antioxidant enzyme capacity to counter oxidative stress.
2. Mitochondria establish cellular energy and redox potential and influence insulin sensitivity; mitochondrial redox status relies on Nrf2, a master regulator of antioxidant enzyme expression.
3. Some reactive species are hormetic signaling molecules for physiological adaptation but can harm if production exceeds antioxidant capacity.
4. Hard-working tissues are most vulnerable to mitochondrial aging/dysfunction: neurons, heart and skeletal muscle, and lungs; signs can include forgetfulness, cognitive decline, depression, less muscle mass/strength, lower peak aerobic capacity, muscle pain, and fibromyalgia.

5. Mitochondrial DNA is circular and, unlike human DNA, contains few regulatory regions, making it more susceptible to damage; mitochondrial poisons include excitotoxins, endotoxins, ionizing radiation, mutagens, some drugs (especially antibiotics), and pesticides.
6. Nutrients that improve mitochondrial energy/pro-oxidant production balance include lipoic acid, N-acetylcysteine, coQ10, vitamin E, creatine, acetylcarnitine, resveratrol, succinate, and omega-3 fatty acids.
7. Food "reducing equivalents" (a measure of redox potential) drive energy production through complexes I through V, but how antioxidants interact in the body is more relevant than ORAC scores.
8. Up to 10 percent of autistic kids may have mitochondrial disorders—but among kids with mitochondrial disorders, many will have autistic features.
9. Muscular activity exerts systemic effects through its influence on PGC1α (PPARγ coactivator 1α)—the focal point in generating new mitochondria.
10. Health conditions recognized as having mitochondrial origins will increase; lactate is #1 indicator, others include increased alanine, creatine kinase, and urinary 3-methylglutaconic acid levels.

Interview Link:
http://jeffreybland.com/knowledgebase/january-2011-issue-mark-tarnopolsky-md-phd-mcmaster-university/

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