



Reactive Oxygen Species and the Regulation of Gene Expression, Part Two

How the Yin and the Yang of Free Radicals (ROS) May Impact the Naturopathic *Vis Medicatrix Naturae*

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Editor's Note: Part one of "Reactive Oxygen Species and the Regulation of Gene Expression" appeared in the July issue (www.naturopathydigest.com/archives/2006/jul/bishop.php).

Modern medicine does not entirely answer all of our questions with regard to disease. With the increase in chronic degenerative diseases, the conditions of a superior principle of order overriding the cell must be extensively explored. This principle we are looking for might exist in the extracellular matrix (ECM) and the regulatory mechanisms that exist therein. The regulatory capacity of the ECM has major significance in disease processes (both acute and chronic disease). This is what a prominent English cell biologist, Pischinger, wrote about when he explored the "ground substance" (aka, extracellular matrix) in his classic book, *Matrix Physiology*, published in the 1960s. Here in the ECM, you have a vast humoral intermeshed system whose historical scientific predecessors show up again and again in the classical "vital juice theory." We now know that phylogenetically, the ECM is older, in fact, than the nerve and hormone systems.

The ECM is the turnpike of the cell; it permeates the extracellular spaces of the entire organism, reaching every cell. It is the vital transit route into the nucleus. The ECM is far from an obstacle course since it forms an intricate, well-designed meshwork of high-polymer sugar protein complexes with proteoglycans predominating, followed by structural proteoglycans, glycosaminoglycans (GAGs) and structural glycoproteins (collagen, elastin, fibronectin, laminin, etc). It's a molecular sieve through which the entire metabolism of the capillaries has to penetrate. You will read more on the **biofilm theory**, and the importance of how sugars might be involved in most of the enzymatic reactions in the ECM and cells, in my next article.

What goes on at the cell membrane and consequently inside the cell on a microscopic level impacts the entire organism. The ECM ultimately is connected to the endocrine gland system via the capillaries and to the CNS via the peripheral nerve endings; both systems are connected to each other in the brain stem.

In many respects, the ECM is like a right of passage for cell materials to transverse before the expression of the DNA can be fully realized. Molecules of a certain size are selectively excluded. Others of the right size and charge will pass through. Much of this sieve process is controlled by deviations in the action potential, and with each and every change in the ECM (polarization and depolarization) the key that is determinant is information. Information encoded via the ECM can inform (or dis-inform) the cell membrane (as a potential deviation of the glycocalyx) and lead to:

1. cell membrane depolarization;
2. second messengers on the membrane via cyclic adenosine monophosphate, etc., transmitting info to the cell nucleus and finally coming into contact with the genetic material of the cell nucleus, followed by;
3. transcription of the appropriate DNA gene in the various types of RNA.

You have the messengers/carriers of information: macrophages, leukocytes, and mast cells constantly in motion being informative through released cell products (prostaglandins, lymphokines, cytokines, proteases, protease inhibitors, etc.).

Let's go one step further. The sugar polymers of the ECM are storing and transmitting info. These polymers are taking up and giving off electrons via a **redox** system. Due to this redox system, every situation that alters the electrical potential of the ECM can be encoded, and reciprocally spread and processed throughout the organism. Simultaneously, excess

extracellular electrons and protons in the form of oxygen and hydroxyl radicals can be intercepted by the water/sugar polymers.

Energy is taken into the physiological redox potential of the organism via the ECM. Under ideal circumstances (perfect health), the body can eliminate most toxins by performing the ongoing task of detoxification in the cell. However, if the enzymatic stages responsible for electron and proton transfer are disturbed in any way (inadequate blood supply, metabolic waste deposits [slag], etc.), the result is an accumulation of free radicals and thus the stage is set for disease to occur. If unchecked over time, you have chronic inflammatory DZ and, eventually, the development of more serious lesions in these pathways in the form of tumors. This is where naturopathic physicians play a significant role. **As naturopathic physicians, we approach medicine from this vantage point; this is called preventative disease.** A classic naturopathic fundamental, such as fasting, becomes ultimately important when we design protocols to enable the patient to release the buildup of slag out of the cell matrix. How we open up the transit system (ECM) of the cell ultimately is what determines health or disease success or failure.

An example is protein storage diseases. In familial hypercholesterolemia, we subscribe to a linear thought pattern, using medicines to block the very pathways of cholesterol formation when we should be looking at the transport medium for LDL molecules, which is dependent on receptor-guided info. There are other protein storage diseases in which we might want to rethink our approach, such as Alzheimer's (amyloid deposits in brain), Down's syndrome (trisomy 21 = amyloid deposits in brain), etc.

As Pishinger stated in *Matrix Physiology*, "[T]he entire system of cellular activity and information exchange occurs in the extracellular fluid matrix."¹ Recent research shows that flavonoids are in some way actually enhancing extracellular and intracellular communication by principally being involved in cell signaling through kinases at very low levels.¹² An underlying theme also was presented by three scientists at the International Berry Symposium from *in vitro* research: it is believed flavonoids might be preserving the mitochondrial membrane.

Recent research might be showing us the yin and yang of free radicals in a more delineated way. We know that an increase in ROS levels above a certain threshold (i.e., oxidative stress = lipid peroxidation, oxidative modification of proteins and nucleic acids) correspondingly causes certain processes that are deleterious to cell survival. However, at low level concentrations, ROS act as secondary messengers. They do this by responding to extracellular signaling, triggered by membrane receptors and via signal transduction, to trigger intracellular regulatory systems which control gene

expression. Certain studies demonstrate that cellular transcriptional response to ROS is mediated mainly by activation of MAP protein kinases and transcription factors AP-1, ATF and NF-kappaB. Other studies seem to show that nitrous oxide, together with ROS, becomes a mobile and highly reactive signaling molecule. Yet, under conditions opposite to oxidative stress such as hypoxia, a number of specific genes are induced. The cellular transcription response is mediated by such factors as HF-1 and AP-1. Depending on the appropriate ratios of intracellular concentrations of NO and ROS, the highly reactive intermediates of NO with the superoxide anions might be enhanced or attenuated.¹⁶

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In summary, there is a growing body of evidence from recent research showing free radicals, previously considered to be dangerous pathogens, actually serving vital functions in normal cell physiology. Harmon's proposed process of aging (1956) is now understood to be due in part to radically mediated oxidative damage. ROS also are indispensable for multiple functions of living cells, both pathological and physiological. Understanding the yin and yang changes in free radical populations and other free radical-mediated processes might result in a better understanding of gene expression impacting overall cellular health. 🌿

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