USANA Health Sciences White Paper on InCelligence Technology™

Introduction: The Next Evolution in Cellular Nutrition

Dr. Myron Wentz' experience using proper nutrition to optimize cellular health has influenced USANA—the company he founded in 1992—for more than two decades. His pioneering approach to antioxidants and cellular nutrition has been the catalyst for numerous innovations in nutritional supplements and personal-care products.

The foundational understanding of nutrition's role in cellular health remains, but an evolution of this understanding has taken place at USANA. Under the guidance of Dr. Wentz, scientists and researchers continued to study cellular processes and the role nutrients, bioflavonoids, and phytochemicals play in supporting good cellular health, specifically through optimal cell-to-cell communication.

This work has led to breakthroughs in USANA's ability to utilize cell signaling and targeted nutrients to activate positive cellular responses that promote protection, renewal, and adaptation. The company's cell-signaling knowledge has crystalized into a new product-formulation platform based on innate cellular intelligence—USANA InCelligence Technology™.

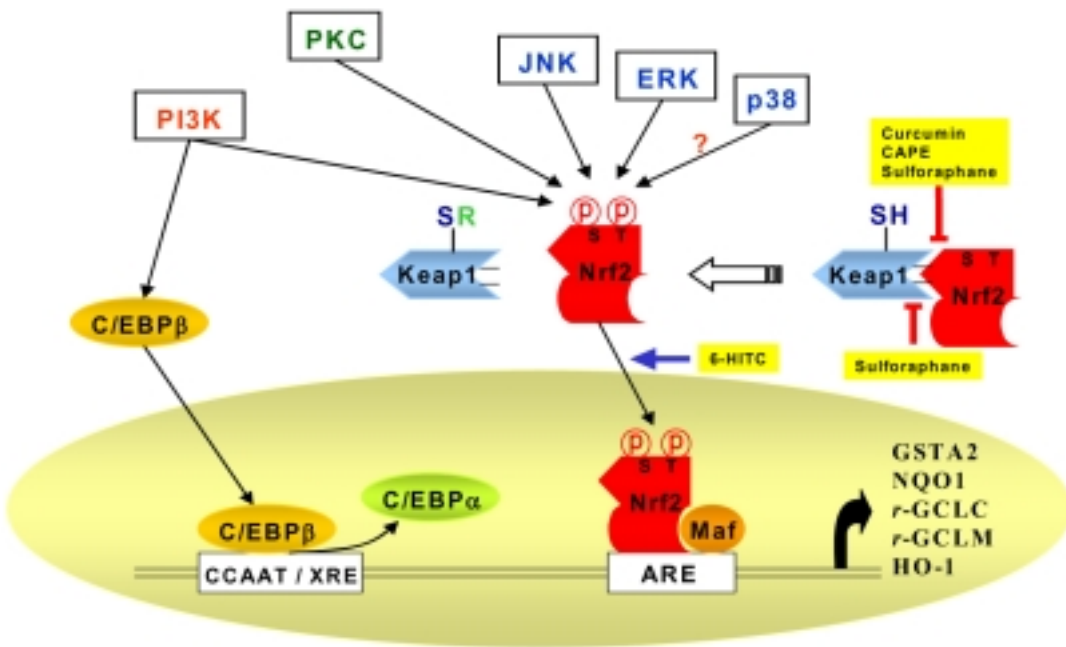
What is molecular or cell signaling?

Our body contains within it an incredibly elaborate and complex communication network that is reliant on a variety of molecules that act as informational messengers. Proteins, enzymes, hormones, cell receptors, binding sites, genes, and their transcription factors are all part of this system. They are responsible for the transmission of information that initiates and controls some of the most basic and yet life-essential functions in the human body. The activation of our immune system, the transfer of electrical impulses from one neuron to another throughout our nervous system and brain, the maintenance of growth, metabolism and repair, as well as the influence of gene expression are all accomplished through the various chemicals and molecular messengers produced in our body. These communications can occur within the cell itself, from cell to cell, from cell to tissue, or from tissue to organ, through a countless array of messenger chemicals, pathways, cross talk and conversational channels.

Scientists and researchers have now discovered that our food can also act as informational messengers; messengers that deliver vital and dynamic information that can have, depending on the quality and type of food, either a positive or negative consequence. Plant-based phytonutrients especially, can act as powerful signaling molecules which interact with our intrinsic cell-signaling pathways, initiating the activation of and influencing a variety of systems and bodily functions that include the immune system, healthy inflammatory response associated with exercise, and interior antioxidant defenses. It can also positively impact cellular performance through a process called mitophagy.

Genes, for instance, which are made up of DNA, are instructions for the creation of proteins. These proteins are responsible for the function, regulation and maintenance of an infinite number of essential and vital body processes. As mentioned above, our food can influence the expression of genes that are favorable to our health. For example, in figure 1 below, extracts of broccoli and specifically the broccoli-derived phytonutrient, sulforaphane, has been shown to increase gene expression for healthy cellular function.

Figure 1. The Antioxidant-Signaling Effect of Sulforaphane



Signaling pathways involved in the Antioxidant Responsive Element (ARE)-mediated transcriptional response through the activation of Nrf2. A protein designated as Kelch-like-ECH-associated protein 1 (Keap1) has been shown to be a cytoplasmic repressor of Nrf2 and thus inhibits its ability to translocate to nucleus and transactivate the ARE. These two proteins interact with each other through the double glycine-rich domains of Keap1 and a hydrophilic region in the Neh2 domain of Nrf2. Keap1 contains many cysteine residues. Oxidants or phase II enzyme inducers can cause oxidation or covalent modification of these cysteine residues. As a result, Nrf2 is released from the repressor (Keap1). Dissociation of the Keap1-Nrf2 complex is also assumed to be facilitated through the phosphorylation of Nrf2 by upstream kinase(s) such as MAPK, PKC, or PI3-K. PI3-K is also considered to phosphorylate CCAAT/enhancer binding protein-β (C/EBP-β), inducing its translocation to the nucleus and binding to the CCAAT sequence of C/EBP-β response element within the xenobiotic response element (XRE), in conjunction with Nrf2 binding to ARE. Active C/EBPβ may compete with C/EBP-α for the C/EBP binding site. After nuclear translocation, Nrf2 associates with a small Maf protein, forming a heterodimer that binds to ARE, stimulating the ARE-driven expression of gene that encode phase-II detoxifying or antioxidant enzymes, such as glutathione S-transferase alpha2 (GSTA2), NAD(P)H:quinone oxidoreductase (NQO1), γ-glutamate cysteine ligase (γ -GCLC and γ -GCLM), and heme oxygenase-1 (HO-1). Nrf2 can also dimerize with c-Jun, ATF-4, PMF and PPAR-gamma, but the physiologic significance of Nrf2 dimerization with such different bZIP proteins remains to be clarified. Curcumin and caffeic acid phenethyl ester (CAPE) disrupt the Nrf2-Keap1 complex, leading to increased Nrf2 binding to ARE. Sulforaphane directly interacts with Keap1 by covalent binding to its thiol groups. 6-(Methylsulfinyl)hexyl isothiocyanate (6-HITC) - a sulforaphane analog derived from Japanese horseradish (wasabi)-stimulates nuclear translocation of Nrf2 (Surh, 2004).

Food as Information: The History and Importance of Phytochemical Diversity

A discussion of the scientific inspiration for InCelligence cell-signaling technology must begin with an understanding of the way human cells interact with compounds that enter our bodies—specifically, food.

In a lifetime, humans consume 60–100 tons of food—about one ton per year (USDA). Every molecule of food is a messenger capable of carrying information across the gut barrier and into our cells, where it can impact our DNA. So, if a person's DNA were itself a culinary dish, it would be an egg poached in a broth of his or her collective dietary choices. That illustrates the tremendous impact diet has on our DNA, our cells, and, as a result, our overall health.

And this is not a modern phenomenon. Over the last seven million years, *Homo sapiens* have co-evolved with their environment. A constant flow of chemical information—via molecular messaging—has shaped the relationship between humans and plants. This process is driven by the ability of secondary plant metabolites to influence their consumers on a physical level (attraction or repulsion), as well as a molecular level. One of the myriad examples is the ability of many flavonoids to influence gene transcription and utilize mammalian steroid receptors to modulate the endocrine system.

The impact of phytochemicals was amplified by the sheer diversity of plants consumed by past generations. For the vast majority of human evolution, our species regularly consumed 88 to 220 different plants as part of its diet, exposing cells to upwards of 200,000 phytochemicals. Even hunter-gatherer societies with greater access to meat were consuming roots, leaves and fruits, as well as leaner, omega-3-rich meat containing a variety of secondary plant metabolites.

The availability of such nutrient and phytonutrient diversity generation after generation limited humans' ability to synthesize important molecules, like polyphenols. But we maintained processes that respond to plant-based messenger molecules, which suggest the response mechanisms hold significant evolutionary importance. The retention of this trait may be tied to a molecular early warning system for environmental change set off by phytochemicals that trigger an adaptive response in humans.

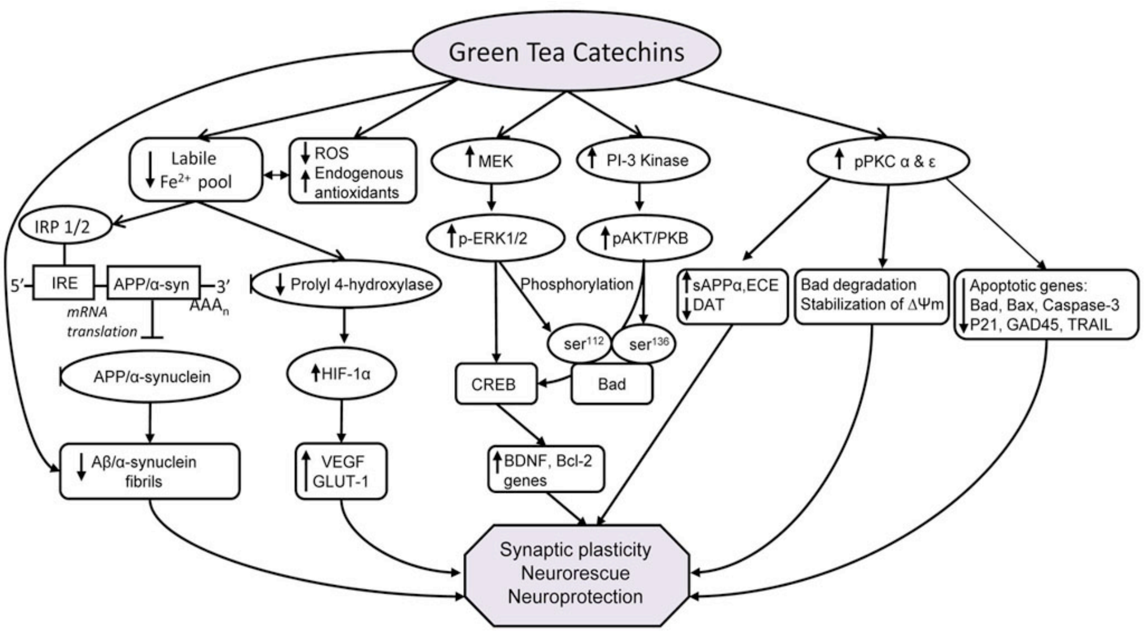
It's no surprise a growing body of research suggests phytonutrients are favorable and necessary to human health. Multiple studies (Liu, 2003; McCarty, 2004; Norris et al., 2003) showed a diet rich in phytochemicals—as part of a healthy lifestyle—is associated with efficient longevity. And low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Broccoli is high in vitamins A and C, and it is a good source of dietary fiber.

A key point is that the body's response to these phytonutrients, provokes an innate cellular action that results in positive biological activity at the molecular level. We consider this a form of intelligence: Human cells demonstrate an innate cellular intelligence, or InCelligence, to act on the information from phyto-nutrients, found in our foods. At USANA Health Sciences, we are building this InCelligence Technology™ into our supplements.

Other examples of phytonutrients acting as cell-signaling molecules include the flavonoid curcumin from the Indian culinary root spice turmeric. Curcumin acts on the NFκB immune response molecular signaling pathway where it can help modulate healthy immune reaction.

Another example is the green tea polyphenol EGCG. As shown in the graphic below, EGCG exerts its influence on a variety of cell-signaling pathways that ultimately result, in this case, in healthy neurological tone.

Figure 2. Cell Signaling of the Catechins



Schematic illustration of the proposed mechanism of neuroprotective/neurorescue action by green tea catechins. Catechins are phenolic compounds and as such, they act as powerful hydrogen-donating radical scavengers of oxygen and nitrogen species and possess the ability to complex transition divalent metal ions (Cu^{2+}, Zn^{2+}, Fe^{2+}), thereby reducing the iron pool and preventing the formation of iron-induced free radicals by Fenton chemistry. Abnormal serum iron transport to the neurons may result from a disruption in the blood-brain barrier or from release from its storage protein ferritin, thereby increasing the free-labile iron pool (ionic iron). Chelation of iron by green tea catechins can also interfere with the iron-induced degradation/inactivation of iron regulatory proteins (IRP1/2) resulting in reduced translation of amyloid precursor protein (APP) and alpha-synuclein mRNA from their 5'-UTR. Catechins may directly inhibit formation of nascent Ab and alpha-synuclein fibrils, elongation of the fibrils, and destabilization of the formed assemblies. The net result would be a decrease in the generation and load of amyloid-beta (Aβ) peptide and alpha-synuclein fibrils. An additional target of green tea polyphenols involving iron-chelation is the inhibition of the iron and oxygen-activated prolyl-4-hydroxylases that regulate hypoxia-inducible factor (HIF)-1 stability, resulting in selective induction of cell survival genes (e.g., vascular endothelial growth factor, VEGF; glucose transporter-1, GLUT-1). The neuroprotective effect of green tea polyphenols may also involve the regulation of antioxidant protective enzymes and modulation of survival protein kinases. The latter maybe related in part to the ability of EGCG to interact with the head group region of the phospholipids within lipid bilayers and alter membrane fluidity. Indeed, EGCG induces a PKC-dependent a) fast degradation of pro-apoptotic Bad protein by the proteasome and b) prevention of mitochondrial potential collapse upon oxidative stress and reduction of apoptotic gene expression. Other PKC-accredited beneficial effects may be related to activation of α-secretase to promote generation of the non-amyloidogenic neurotrophic, soluble amyloid precursor protein-alpha (sAPPα) and activation of endothelin-converting enzyme (ECE) that degrades Aβ. Other membrane-associated signaling pathways affected by EGCG include the MEK/ERK1/2 and PI3K/AKT cascades, promoting the phosphorylative inactivation of Bad and activation of their downstream substrate, cAMP responsive element binding protein (CREB), which in turn binds to promoters of genes crucial for memory consolidation and synaptic plasticity (Silvia et al., 2012).

As depicted above in multiple examples, food-based cell-signaling molecules like phytonutrients have the ability to interact and converse with our internal communication network. And with the information they carry as messengers of health, plant-based phytonutrients have arguably become as indispensable to human health as vitamins and minerals.

On the other hand, poor food choices in addition to unhealthy chemicals and toxins can have the opposite effect, affecting genes in a deleterious way, influencing cell-signaling pathways that will set off a chain of events that can lead to poor health.

What is meant by pleiotropic?

When scientists and researchers turn to the topic of mechanism of action, they are referring to the way a molecule such as a drug or biomolecule affects a cell-signaling pathway and subsequently how it exerts its effect on a particular function or health condition. In drug development, the goal is to have a strong effect on a particular biochemical pathway, a specificity to a particular molecular target, and little effect in the way of adverse events. This goal of potency, selectivity and acceptable toxicity is considered the holy grail of drug discovery. This selectivity does make pharmaceuticals strong but at a cost of a very high rate of adverse effects.

In understanding the mechanisms of action of biomolecules such as phytonutrients, it is important to note that these compounds rarely behave in the same way that synthetic molecules do in regard to potency, selectivity and toxicity. As plant-based compounds generally have numerous health benefits, unlike drugs, they influence a wide array of cell-signaling pathways. This concept of one molecule possessing numerous properties while exerting its influence over a wide range of signaling pathways, resulting in multiple effects, is called pleiotropism.

Green tea polyphenol EGCG possesses quite an impressive array of health benefits. These many health benefits result from EGCG's pleiotropic activity, that is, numerous cell-signaling pathways are positively influenced. This multi-pathway approach makes for a dramatically less invasive and less harmful approach, thus significantly reducing any potential prospect of adverse reaction.

USANA's InCelligence Technology™

The concept of pleiotropism and the ability of plant-based phytonutrients to beneficially influence, engage and participate in cellular and molecular communication pathways is the primary advantage of using these compounds in the service of human health. By studying and thoroughly understanding these principles including mechanisms of action, USANA can accurately identify which plant compounds more significantly influence a certain set of cell-signaling pathways and thereby design products that can focus on a particular condition, system or function that is broad, providing multiple health advantages.

In summary, phytonutrients can interact and communicate with cell-signaling pathways that influence additional key pathways such as the inflammatory and immune response related to exercise and muscle exertion, neurological activity, and healthy insulin and glucose levels. These biomolecules can help modulate and improve our internal antioxidant defense system and cellular performance and subsequently the cell's ability to generate energy.

InCelligence Technology is a revolution from the old paradigm of nutritional supplements. While the old approach is to provide support (such as substrates or co-factors) for functional proteins (such as enzymes, receptors, and transporters), InCelligence directly engages these targets. Traditional multivitamin supplements supply the building materials, while the InCelligence paradigm puts the builders into action.

Through this approach, USANA has developed its new InCelligence Technology, a technology that understands the intimate partnership between beneficial plant-based compounds and nutrients and their dynamic interplay with our cellular and molecular communication system. We think of it as pleiotropic molecular nutrition. The outcome for the consumer of USANA products is added resilience and adaptation to the stressors that a consumer faces in their day-to-day life.

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