White Paper on Real Chemistry's MTHV Complex and Its Impact on Skin Care

The molecular aspects of skin and skin structure aging have been a focus of cosmetics and skin care research for some time. Aging results when the body's natural defenses against structural damage are unable to keep up with that rate at which damage occurs. Thus skin aging research looks to both reduce the rate of damage and increase the rate at which repair occurs.

The processes that contribute to damage can be broken down into intrinsic and extrinsic components. Intrinsic components are those that result from normal metabolic processes within the body while external components arise outside the body. They are both referred to collectively as "oxidative stress." Combating oxidative stress by boosting the body's own defenses is the most natural and effective mechanism available. It is also the most difficult mechanism to exploit. This white paper discusses a dual therapy, topical approach to exploiting the body's natural defense against aging by both improving blood flow and by directly supplementing the systems responsible for limiting and repairing oxidative stress at the molecular level.

Reactive Oxygen Species

The skin is subject to oxidative stress from reactive oxygen species (ROS or free radicals) on two levels. First, internal biologic processes create ROS that can damage proteins, fats, DNA, and other cellular components. Second, the skin, more than any other tissue, is exposed to the external environment and the toxins that it contains. These toxins can be free radicals themselves or they can drive the production of free radicals by internal biologic processes. No matter which way the problem is sliced, the skin is subject to a number of threats to its structure and function constantly.

Natural antioxidants, under normal conditions, attenuate the damage caused by ROS. They repair DNA, discard and replace damaged proteins, and scavenge (remove through chemical reaction) ROS before they have a chance to do any damage. Unfortunately, natural antioxidants are limited in supply and can be overwhelmed by prolonged free radical action. (Trouba, Hamadeh, Amin, & Germolec, 2002).

Prolonged free radical action results from a combination of environmental insults, normal metabolic byproducts, and genetic factors. While natural antioxidants can deal with most ROS insults individually, they are not capable of dealing with the combined effects of both. The result is pathogenic action against collagen, elastin, keratin, and other skin proteins. A second result is damage to DNA and the release of pro-inflammatory molecules. This is the foundation of skin aging, in the form of wrinkles, lost elasticity, and damaged vascular structures, but it can also be the underlying impetus for inflammatory diseases and even cancer.

As if the above where not enough, research also suggests that certain combinations of genetic makeup and lifestyle can lead to a decline of normal physiology of the skin by as much as 50% by middle age. In other words, skin can lose half of its normal free radical fighting capabilities by roughly forty years of age in some people(Tabor & Blair, 2009),(Fenske & Lober, 1986).

Some people, it would seem, have a genetic composition that makes their natural defenses even easier to overwhelm than normal.

UV Radiation

Ultraviolet (UV) radiation is the single most important extrinsic factor in skin aging. The process by which UV radiation damages skin is called photoaging. The damage, a form of oxidative damage, causes both structural and physiological changes in the skin. In particular, research has shown that UV radiation is responsible for the development of matrix metalloproteinases, which are enzymes that degrade collagen(Taihao et al., 2009). Collagen is the major support structure for the skin, allowing it to resist tears, wrinkles, blemishes, and other physical damage. Without collagen, skin because brittle and fragile.

UV radiation directly depletes antioxidants like vitamin E and ascorbic acid, which normally protect collagen from damage. UV radiation doesn't just target the antioxidants though; it also targets the systems that replenish those antioxidants. UV radiation damages the superoxide dismutase (SOD) and glutathione-S-tranferase systems. SOD is directly responsible for free radical scavenging whereas glutathione is responsible for replenishing the supply of SOD and other antioxidants. This is a perfect example of the kind of damage that UV radiation can cause.

The solution to UV damage is to avoid UV radiation either by avoiding the sun or by wearing sunscreen. The first position is completely untenable for most people and, more importantly, not a recommended practice. Despite the damage caused by UV radiation, there is a great deal of benefit to be had from time in the sun and the active lifestyle that spending times outdoors encourages. The second position is no less tenable because sunscreen is not full proof. The better solution would be to replensih the systems that address UV damage naturally and thus let he body take care of itself.

Environmental Toxins

Tobacco smoke is the largest environmental toxin implicated in skin damage. That said, tobacco smoking is declining. More important, in the future, is the effect of air pollution on premature skin aging. Epidemiological studies have demonstrated that particulate pollution, of the type found in many urban areas, is directly related to accellerated skin aging. The aging effects of particulate pollution are generally seen as hyperpigmentation (darkening of the skin) and as slowed skin renewal (skin does not replenish itself as often)(Vierkotter et al., 2010).

Like UV radiation, the solution to environmental toxins is to avoid them. Once again, this solution is untenable. Many people don't even know they are being exposed to toxins at the time the exposure happens. What is more, there is no effective barrier method for minimizing exposure to toxins that could play the same role sunblock does in reducing UV radiation exposure. While reducing environmental toxins is an important political and social goal, addressing the damage they cause by boosting the body's own defense mechanisms would be the most direct and effective means of reducing skin damage due to these and other toxins.

Vascular System

Antioxidants are not the only defense the skin has against free radical damage, toxins, and other insults. The vascular system plays a dual role in protecting the skin. First, it allows for immune system cells to reach the dermal and epidermal layers of the skin where they can neutralize toxins and pathogens. Second, the vascular system provides a means for removing ROS and toxins to the liver where they can be more adequately dealt with.

Langerhans cells, a special type of immune system cell, recognize foreign substances and induce antibodies to eliminate those substances. Aging skin has a reduced number of Langerhans cells, which makes it more difficult for for the skin to ward off damage from oxidation, infection, and malignancy(Ogden, Dearman, & Griffiths, 2011).

Immune cells, like Langerhans cells, must be delivered to the skin through the blood-lymph system. This same system also helps to remove toxins and free radicals from the skin. As the body ages, blood vessels atrophy and become smaller, resulting in a decreased blood flow, but only in certain regions. Studies have shown that even though overall supply of blood to the skin does not change with age, areas with normally high blood flow do experience a decrease. These regions include the lips, fingers, forehead, around the eyes, and nasal tip(Waller & Maibach, 2005). This decrease in blood flow to and from previously high-flow regions of the skin explains why the effects of aging are more prevalent in the hands and face than the trunk and proximal limbs.

Summary of the Problem

The essential problem of aging skin comes down to a decreased ability of the body to limit damage and repair damage. The factors that lead to this decrease in function are multiple. While genetic factors cannot yet be reversed, problems related to oxidative damage and decreased vascular function can be addressed. In particular, external agents can be applied to the skin or consumed orally to boost antioxidant responses and to improve blood flow to the skin.

Scope of the Problem

The world's population is aging. By 2020, the United Nations (UN) estimates that there will be more than 650 million people over the age of 65+("World Population Aging: Clocks Illustrate Growth in Population Under Age 5 and Over Age 65," n.d.). This "baby boomer" population will also drive revenue in the skin care industry to more than $114 billion (USD) in the next few years("Boomers Will Be Pumping Billions Into Anti-Aging Industry," n.d.). Facial care alone is expected to gain roughly $16 billion per year. The market, in short, is massive and the skin care sub-market, which has been the cornerstone of beauty and personal care for nearly two decades, is expected to continue to be the bedrock of the industry. The skin care category has shown growth year upon year, even during the height of the global recession, because people care about their health and about their appearance.

The market for anti-aging therapies is growing faster than any other cosmetic market, spurred by new technologies, new biologic breakthroughs, new ingredients, and new pharmaceuticals. The

premium anti-aging therapy category grew 7.7% in 2011 and is expected to grow at roughly 7% per year through 2016("Skin Care Market Radiant for Foreseeable Future | GCIMagazine.com," n.d.). The growth of the premium category has been fueled, in part, by the introduction of specialized products that rely on sophisticated technology for their production. Examples of such products include rose stem cells, glucose-based polymers, and glycobiology derivatives.

The growth of technology and the advent of premium products has only served to increase the demand for unique ingredients. A unique ingredient is now essential to developing a solid and differentiated selling point. Natural components are a must, which means these new ingredients need to be backed by solid science. High purity, improved efficacy, and products targeted at specific skin conditions are now expected by the majority of consumers. As the skin care market becomes increasingly saturated, the need for a unique product with unique, demonstrable properties becomes essential.

The Real Chemistry Solution

Real Chemistry has spent the last twenty years searching for natural ingredients for skin care and developing products that are aimed at treating specific skin conditions. Real Chemistry now has a line of skin care products that range from peels to an environmental rescue mask, each designed to address one or more of the problems that lead to premature skin aging. The company has recently turned its attention to anti-aging research that deals with biologic agents. The result of that research is Real Chemistry's Daily Serum with MTHV Complex.

The Daily Serum is a kind of invisible armor against oxidative damage as well as a restorative elixir. It protects against hyperpigmentation, wrinkles, fine lines, and other types of age-related skin damage. It is applied twice per day, before other skin products, and can be worn under foundation, moisturizers, and sun blocks. That's what Daily Serum with MTHV Complex is, but what it contains and what those ingredients do are the real story behind this breakthrough product. MTHV Complex is a combination of two proteins: metallothionein and recombinant hirudin. The two molecules are quite different in structure and function, but both promote healthy skin by improving blood flow and boosting natural antioxidant systems. Here is how.

Hirudin

Hirudin is a naturally occurring enzyme found in the saliva of leeches. It allows them to keep blood flowing, when they attach to a host, by preventing clots. The anticoagulant effects of leeches have been understood for centuries, though the discovery of hirudin is relatively recent. More recent still has been the development of molecular tools and techniques that allow for the production of hirudin through recombinant DNA technology. The result is the hirudin is now affordable enough that its myriad health benefits are available to the general population.

The Role of Thinner Blood

Blood coagulation results from a biological cascade that starts with platelet activation and ends only after a number of different proteins have come together to activate a final protein called fibrinogen. The fibrinogen, in turn, is converted to fibrin, which produces a clot. Interfering with

the coagulation cascade, at any step, causes "blood thinning," which is the colloquial term for impaired blood clotting. As it turns out, interference with different proteins within the cascade will result in different levels of "thinning." In other words, it is possible, with the right ingredients in the right doses, to control just how thin the blood gets.

If the blood is too thin, then even normal trauma, like walking, can lead to serious bleeding. If the blood is too thick, it clots and can cause problems like deep vein thromboses (DVTs), pulmonary embolisms, stroke, and heart attack. The body strikes a balance between blood that is too thin and blood that is too thick by modulating the activity of the proteins in the coagulation cascade.

As was pointed out in previous sections, one of the primary causes of skin aging is decreased blood supply to the cutaneous surface. Decreased blood flow to the skin prevents cells of the immune system from reaching the locations they need to be and also restricts the removal of toxins. One of the effects of thinner blood, however, is to increase perfusion (blood flow) to restricted areas. Thus, thinner blood can be used to counteract the normal effects of aging that lead to reduced blood flow.

Hirudin thins the blood by directly inhibiting thrombin, one of the last proteins in the coagulation cascade and the one that directly converts fibrinogen to fibrin to form clots(Greinacher & Warkentin, 2008). The effect of hirudin is unique among blood thinners (heparin, aspirin, etc.) because it takes place without the need for cofactors (additional biologic molecules like vitamin B12 or other proteins) and more than 80% of hirudin remains in the extravascular space.

The fact that hirudin does not requires cofactors means that it is better able to inhibit thrombin. This is important for improving blood flow through small vessels in the skin, which are prone to transient blockage due to injury or wear and tear. By preventing the formation of clots secondary to normal daily activities, hirudin, at low levels, is able to improve microvascular circulation in the skin and thus maintain the delivery of immune cells (e.g. Langerhans cells) as well as the efficient removal of toxins (both metabolic byproducts and environmental toxins)(Zhao, Shi, Sun, Yin, & Yang, 2012).

The fact that hirudin remains in the extravascular space is also of importance because it ensures that hiurdin is effectively absorbed when the molecule is applied topically. More importantly, this means that hirudin is released into the vasculature slowly and so continues to work long after having been applied. The slow release into the vascular space also means that topical applications of hirudin are less prone to systemic absorption and thus cause fewer systemic side effects (e.g. bleeding, bruising, etc.).

Studies show that hirudin is highly effective in maintaining blood flow to less perfused areas of the skin. In fact, surgical models have shown that hirudin can substantially improve the success rates of skin graft procedures by improving microvascular circulation(Zhao et al., 2012),(Guo-Quin, Gang, & Zhi-Yong, 2012). This research can easily be extrapolated to explain how hirudin, in cosmetics, could benefit healthy skin. Improvement in circulation, however, is not the only benefit that hirudin offers.

Hirudin as Antioxidant

Studies have shown that hirudin has anti-inflammatory and anti-oxidative qualities in addition to its anti-coagulant activities(Ying-Xin, Guo-Quin, Jia-Quan, & Han, 2012). Hirudin lowers levels of free radicals (ROS) and also appears to increase or boost levels of the antioxidant molecules that eliminate free radicals. In particular, hirudin has been found to significantly raise levels of superoxide dismutase (SOD), one of the most important antioxidant defenses in nearly every cell in the body. It also reduces levels of malondialdehyde and endothelin.

Malondialdehyde is a natural byproduct of cellular metabolism and is produced when reactive oxygen species attack fats in the body. It is thus an excellent marker for the level of oxidative stress in a cell or tissue. Malondialdehyde is also a free radical in its own right, causing stress in cells and producing advanced glycation end products when it reacts with fats. The molecule is also known to interact with DNA, causing damage and mutation. In short, malondialdehyde is a potent free radical that causes cell damage. (Del Rio, Stewart, & Pellegrini, 2005),(Marnett, 1999). Studies show dramatically lower levels of malondialdehyde in groups treated with hirudin, which translates into less oxidative damage to cell structure and DNA.

Endothelin is a molecule produced by the cells that line blood vessels. Its primary purpose is to cause the blood vessels to constrict (narrow) to control the flow of blood. When found at high levels, however, it can substantially increase blood pressure. Over-expression of endothelin is a significant factor in diseases such as type 2 diabetes, cancer, and heart disease. By counteracting the vasoconstricting effects of endothelin, hirudin not only improves blood flow with all of its concomitant benefits, it also lowers blood pressure. It is interesting to think that, long term, a cosmetic may actually provide major health benefits.

Recombinant Hirudin

Having leeches attached to the skin is an untenable therapy. For one, people would find it revolting. Additionally, it would hard to isolate any meaningful quantity. Most importantly, however, is the fact that leeches secrete a number of different substances that can all elicit allergic reactions. A better solution is recombinant hirudin.

Recombinant hirudin is made by taking the portion of the hirudin DNA sequence that codes for the active part of the enzyme and expressing it in yeast. The result is a pure fragment of hirudin that can be made virtually on demand and in any quantity without concerns regarding contamination, raising and harvesting leeches, allergic reactions other proteins, etc. Recombinant hirudin is also less expensive to produce, thus keeping final cost in the products affordable("Hirudin | ProSpec," n.d.).

Real Chemistry products containing MTHV Complex® are made only with Recombinant Hirudin.

Is Hirudin Safe?

Hirudin is a blood thinner, which means it is has the potential to cause life-threatening bleeding. The question is whether or not it is safe to use in topical preparations? A double-blind, placebo-controlled trial (the gold standard of clinical research) has demonstrated that topical hirudin (administered in a cream in the study) is safe.

The study included sixty men and women, aged eighteen to sixty-five, who used a hirudin cream that contained 280 UI/100g of hiurdin to treat bruises. They used the product 3-4 times daily for five days. The group that used hirudin experienced significant improvement in bruising compared to the placebo group without any significant differences in pain, redness, burning sensation, or bleeding(Stamenova, Marchetti, & Simeonov, 2001). In other words, the hirudin effectively eliminated bruises without causing any side effects that were not also seen with placebo.

The Benefits of Metallothioneins

Metallothinoneins are a group of proteins, found within cells, that bind heavy metals (e.g. mercury, arsenic, etc.). Research has indicated that the cysteine residues (amino acids) on metallothioneins are capable of capturing ROS like super oxide and hydroxyl radicals(Kumari, Hiramatsu, & Ebadi, 1998). In particular metallothinoneins have been investigated for their role in protecting against radiation damage such as that caused by UV radiation. UV radiation produces high levels of hydroxyl free radicals which metallothinoneins are particularly adept at scavenging. Research also indicates that the way metallothinoneins scavenge free radicals may allow them to make use of other cellular antioxidants like glutathione and isoflavonoids(Thornalley & Vasak, 1985), (Widyarini et al., 2006).

The effect of metallothinoneins in response to radiation has been confirmed in studies on keratinocyte proliferation and skin aging. Keratinocytes are the cells responsible for producing the upper layer of skin that protects the underlying layers from dehydration, chemicals, etc. Research shows that metallothinoneins, while protecting against UV damage, are also depleted by exposure to UV radiation. Skin with depleted metallothinoneins shows decreased keratinocyte proliferation and thus faster aging in terms of the development of fine lines, wrinkles, discoloration, and so forth(Ma, Li, & Chen, March2011). This research suggests that supplementation of lost metallothinoneins could inhibit skin aging, particularly photo-aging.

UV radiation can lead to skin cancer, so it stands to reason that metallothinoneins, by repairing the damage caused by UV radiation may protect against skin carcinogenesis. That is to say, metallothinoneins may protect against the formation of skin cancer. While it is not yet firmly established if supplementation with metallothinoneins is protective, it is clear that a deficiency of metallothinoneins increases skin carcinogenesis(Suzuki et al., 2003). It isn't hard to reason that replenishing metallothioneins, which becomes deficient due to natural aging and sun exposure, can help to protect against skin cancer.

Summary

Oxidative stress is the primary cause of cellular damage, a process that is accelerated by the presence of free radical molecules. The effects of oxidative stress are enhanced by exposure to environmental toxins and by a lack of blood flow to the skin. Inadequate blood flow decreases delivery of essential nutrients and immune cells to the skin while simultaneously restricting the removal of toxins. The solution to this problem is a two-fold approach that increases blood flow and replenishes the body's natural antioxidants.

Real Chemistry's MTHV Complex, containing hirudin and metallothinoneins, meets both requirements. Hirudin, the "HV" in the MTHV Complex, fulfills the first goal of dual-therapy by enhancing blood flow in the microvasculature of the skin, thus improving the ability of immune cells to reach the skin to combat the presence of foreign compounds (e.g. viruses, bacteria, toxins) as well as increasing removal of toxins. Hirudin can also replenish antioxidants and decrease levels of free radicals, thus fulfilling the second goal stated above.

Metallothinoneins, the "MT" in the MTHV Complex, are natural antioxidants found in the human body. They are particularly important in protection against UV radiation damage in the skin and play critical roles in activating cellular repair pathways. The very stresses that metallothinoneins protect against also lead to their degradation and reduction over time, a process referred to as photo-aging. By additing metallothinoneins to its serum, Real Chemistry's has created a product that replenishes one of the body's most important anti-aging compounds, protecting not just against the visible signs of aging, but skin cancer as well.

Real Chemistry's MTHV Complex is a daily therapy created to actively fight against the aging effects of free radical damage, sun damage, and normal metabolic byproducts. As a daily therapy, MTHV Complex has been designed to be used with other skin care products, including foundations, sunscreens, and other cosmetics. It is, in short, a critical addition to any anti-aging skin care regimen.

Resources

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