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SPORTS & RECOVERY

SEMINAR MAGAZINE



EDITOR’S LETTER

SPORTS & RECOVERY

Bloed- en speekselanalyses worden meer en meer ingezet om het herstel van een atleet op te volgen en te verbeteren, DNA-analyses worden aangewend om voeding en behandelingen te optimaliseren. Wat kunnen die nieuwe ontwikkelingen concreet betekenen voor een sporter en zijn herstel? Hoe kunnen de nieuwe inzichten in sportvoeding, nutrigenetica en cosmetogenetica gecombineerd worden met de “best practices” uit de medische en paramedische omkadering van een atleet?

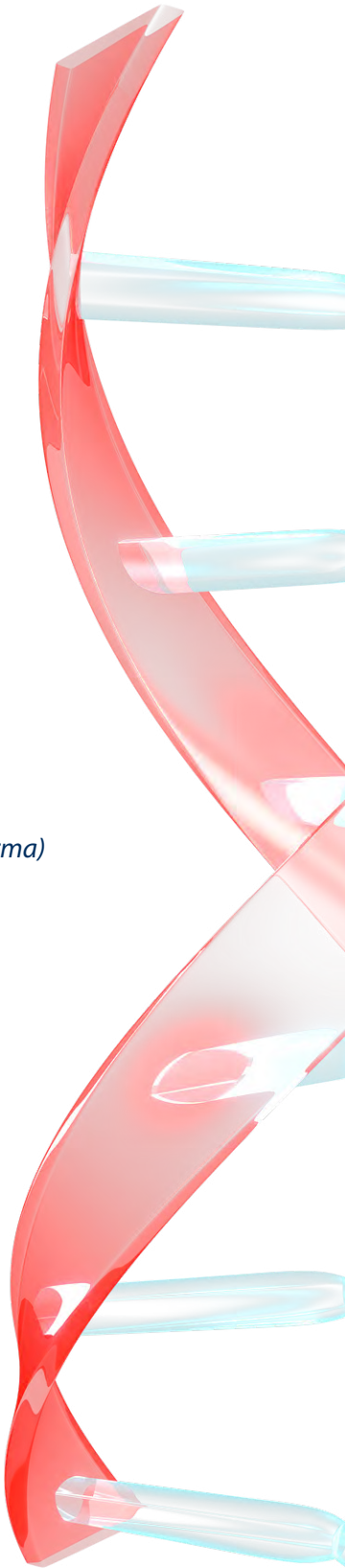
Edgard M.GEYSKENS
CEO NAQI nv

Brent Luyckx
CEO 4GOLD

PROGRAMMA

SEMINARIE RECOVERY BIJ ATLETEN

8u30	Ontvangst
9u00	Moderator , Dr. Servaas Bingé, Team Dokter Lotto-Soudal Cycling team & founder emma.health Introductie , Bert Celis, CEO Bike Valley
9u15	Recovery strategy in Elite Sports, where science meets practice Kinesist Vincent Callewaert (SQUADT)
9u40	Practical implementation of recovery strategies: the top of the iceberg Kinesist Thalia Kindt (GRIT Sports clinic)
10u05	Innovatie in sportvoeding Petra Van Gucht, Master of Biochemistry- Molecular Health Science (4gold/Cosmofarma)
10u30	DNA based nutrition: het geheime wapen voor herstel bij sporters Nikolaas Van Riet, MSC, Nutrigenetics & Nutrigenomics (Genopartner, AGR-Institute)
10u55	Demo DNA-analyse tools: Cosmetogenetica & Nutrigenetica Nikolaas Van Riet, MSC, Nutrigenetica & Nutrigenomics (Genopartner, AGR-Institute)
11u10	Pauze
11u30	Sportana neemt uw uitdaging bloedserieus , Thijs Wintein (Sportana)
11u55	Predictie en preventie van orthopedische letsels in triathlon Dr. Toon Claes, Orthopedisch Chirurg Herentals
12u20	Panel gesprek
12u40	Netwerkmoment





Recovery strategy in Elite Sports, where science meets practice

- Vincent Callewaert -

Zaakvoerder, Sportkinesitherapeut - SQUADT
- On Top of Physical Health (Waregem)



SQUADT staat in voor zowel de revalidatie, de performance-coaching als de preventie van zowel de recreatieve als de elite sporter.

In SQUADT werkt hij met vele individuele elite-atleten zoals: Koen Naert (Europees Kampioen Marathon), Fanny Lecluyse (Europees Kampioen zwemmen en WK Brons), Oshin Derieuw (tweevoudige wereldkampioene Boksen)...

Daarnaast werkt hij en zijn team voor heel verschillende teams en federaties: BOIC / Team Belgium, Vlaamse Atletiek Liga, Vlaamse Triatlon en Duatlon Liga, Vlaamse Zwemfederatie, Deceuninck Quick-Step Cycling, Voetbalclub KV Kortrijk, Voetbalclub SV Zulte-Waregem, No Limit Team Triathlon ...

In zijn presentatie zal Vincent het hebben over de laatste wetenschappelijke evidentie rond de verschillende recovery strategieën enerzijds en zijn ervaringen in de verschillende elite sporten anderzijds. Ligt de praktische implementatie dicht bij de wetenschappelijke evidentie of net niet?

Practical implementation of recovery strategies: the top of the iceberg

- Thalia Kindt -

Sportkinesitherapeute - GRIT Belgian Sports Clinic



Thalia Kindt is sportkinesitherapeute in GRIT Belgian Sports Clinic. Ze werkt er met topsporters voor revalidatie van blessures en in kader van blessurepreventie in binnen- en buitenland. Binnen GRIT is ze verantwoordelijk voor de begeleiding van de atleten en gymnasten. Dit mede door haar eigen ervaring binnen deze sporttakken. Gedurende tien jaar heeft Thalia ook een competitieploeg tumbling gecoacht zowel op gymnastiek specifiek vlak als voor de specifieke krachttraining.

Voor haar carrière in de klinische setting heeft Thalia werkervaring opgedaan aan de KU Leuven gewerkt als wetenschappelijk medewerker. De focus van het onderzoek lag voornamelijk op biomechanisch ganganalyse, hetgene dagelijks van pas komt ook nu in de klinische praktijk.

" We worden allemaal overspoeld door verschillende nieuwe hypes voor herstel na trainingen. Maar welke van deze technieken zijn nu echt evidence-based? En hoe passen we deze dan correct toe?

Herstel na training bestaat voor het grootste deel uit correcte voedinginname, voldoende slaap, voldoende hydratatie en een correct opgesteld trainingsschema. Op topsportniveau zijn we echter op zoek naar de kers op de taart. In deze presentatie gaan we verder in op het topje van de ijsberg en de praktische toepassing ervan. We belichten o.a. cryotherapie, myofasciale release, stretching en nog veel meer. "

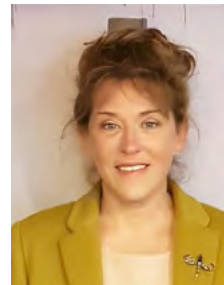
Thalia Kindt



Innovatie in sportvoeding

- Petra Van Gucht -

Master of Biochemistry, Spec. Biomedical Science –
Molecular Healthscience, Onderzoek en ontwikkeling
CosmoGroup, www.cosmogroup.eu



*Traceerbaarheid, personalisatie, flexibiliteit, efficiëntie, duurzaamheid ...
Het zijn slechts enkele van de vele uitdagingen waarmee producenten
momenteel geconfronteerd worden.*

*De laatste jaren is de maatschappelijke aandacht voor de relatie tussen voedingssupplementen
en preventieve gezondheid sterk toegenomen. Consumenten eisen ook meer transparantie
over de herkomst van de grondstoffen, de teelt- en verwerkingsmethode. Tegelijkertijd is
er een toenemende vraag naar het bewuster omgaan met grondstoffen en duurzaamheid
blijft een hot topic. Of het nu voor een groep van mensen is of op individueel niveau:
suppletie à la carte is de toekomst.*

Innovatie strategie in functionele voeding en supplementen...

Topics en trends anno 2019

*De integratie van blockchain technologie voor tracering en kwaliteitscontrole.
Geavanceerde technologie voor duurzame landbouw, verwerking van grondstoffen en
innovatie in verpakking.*

Trends in novel foods

De "proteïneshift" en het circulair inzetten van reststromen en co-producten.

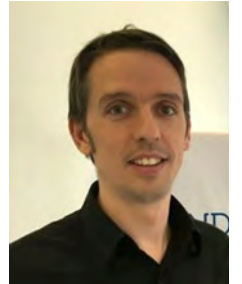
Wetgeving in Europa

*Uitdagingen en problematiek bij gepersonaliseerde 3D geprinte voedingssupplementen.
Systeem Biologie en omics: "Food4me".*

DNA based nutrition: het geheime wapen voor herstel bij sporters

- Nikolaas Van Riet -

MSC, Nutrigenetica & Nutrigenomics (Genopartner, AGR-Institute)



*N*ikolaas is een wetenschapper (fysicus) met onderzoekservaring (PhD.Cand.),
die een jarenlange achtergrond heeft opgebouwd in biochemie en epigenetica,
en een specialisatie heeft gevolgd in nutrigenomica.

*Nikolaas was de oprichter van Science In Health dat heel wat pro-atleten heeft
ondersteund met DNA gebaseerde voeding. Nu werkt hij samen met 4Gold in de ontwikkeling van
de nieuwste generatie DNA gebaseerde sportvoeding. Ook is hij als wetenschappelijk adviseur
betrokken bij NAQI in de ontwikkeling cosmetogenomische producten voor (fysio-)therapeutische
behandelingen. Zijn ervaring met DNA analyses wordt ook ingezet in de start-up Genopartner,
dat DNA analyse ontwikkelt voor bedrijven en het AGR-institute, dat een kenniscentrum is voor
ontwikkelingen in het domein van epigenetica...*

*" Nutritionele ondersteuning van herstel werd tot op heden alleen benaderd vanuit een
macronutriënten standpunt. Koolhydraten moeten spierglycogeen aanvullen, eiwitten
moeten de bouwstenen aanleveren om spier en ander zacht weefsel te herstellen en
versterken door microschade ten gevolge van de inspanning. Nutritionele ondersteuning
van herstel kan echter veel verder gaan. Het kan ondersteuning bieden bij het herstellen van
de pH in de spieren, alsook het bewaken en herstellen van de biochemische redox balans.
Deze laatste is cruciaal, want indien correct bewaakt zorgt deze voor een inperking van de
spierschade enerzijds, maar ook van de pro-inflammatoire respons anderzijds, daarnaast is
die ook betrokken bij de maximalisatie van de fysiologische adaptaties.*

*De reden dat de éne sporter veel sneller herstelt dan een ander zit grotendeels in de genen
van de sporter. Meer specifiek zijn er heel wat veel voorkomende genetische varianten die
een invloed hebben op al deze processen. Door deze genetische varianten te indentificeren
en het effect van die variant te bestuderen, is het mogelijk om doelgericht nutritioneel te
gaan ingrijpen en bijsturen in die onderliggende biochemische processen (met klassieke
nutriënten) om op die manier het herstel van een sporter te beïnvloeden = NUTRIGENTICA.
Deze manipulatie kan nog verder gaan door te werken met specifieke voedselbestanddelen
die in staat zijn de expressie van onze genen te beïnvloeden (aan-/uitzetten van genen) en
die dan selectief en specifiek te gaan inzetten in functie van aanwezige genetische varianten
= NUTRIGENOMICA "*





Sportana neemt uw uitdaging bloedserieus

- Thijs Wintein -

Master Lichamelijke Opvoeding, Business Developer Sportana



Sportana is de sport research groep van Anacura. Naast de referentie als sportmedisch labo met vergaande inzichten in sportspecifieke referentiewaarden, zette het een 2,5 jaar durende klinische studie op bij 300 duursporters. Hierbij werd gezocht naar vroegtijdige indicatoren van niet-functionele overreaching in biomerkers. Sinds midden 2018 kan via een eenvoudige klassieke bloedafname bij uw (sport)arts aangegeven worden hoe zwaar je jezelf als sporter belast. Een makkelijk te interpreteren kleurscore geeft je een inschatting van jouw fysieke en mentale fitheid. Een weerspiegeling van hoe jouw lichaam omgaat met de aangeboden load.

In de presentatie zal Thijs het hebben over de invloed van training, sociale en psychologische factoren op het lichaam en hoe dit kan gemeten worden in bloed. Aan de hand van een aantal cases wordt de Sportana manier van kijken naar biomerkers belicht. Het gebruik van algoritmes als innovatie bij een klassieke bloedafname zorgt voor inzichten die voor (duur)sporters zeer waardevol zijn in de voorbereiding op hun grote uitdaging. Een unieke en objectieve kijk in onze belastbaarheid.

Predictie en preventie van orthopedische letsels in triathlon

- Dr. Toon Claes -

Diensthooft van de dienst orthopedie AZ Herentals



Dr. Toon Claes is dienshoofd van de dienst orthopedie AZ Herentals en bouwde die dienst uit tot een nationaal en internationaal gerespecteerd orthopedisch centrum. Zelf is hij een gepassioneerd sporter, en de link naar sport- en topsportgeneeskunde is dan ook geen toeval.

Kritische klinische ervaringen leidden tot de oppuntstelling van verschillende nieuwe klinische entiteiten en de implementatie van nieuwe innovatieve behandelingen

Omdat voorkomen veel efficiënter is als behandelen, dient de aandacht van alle sportwerkers in de eerste plaats uit te gaan naar de preventie. Het is gekend dat triatlon één van de meest blessuregevoelige sporten is, en dat de lessen uit triatlon rechtstreeks kunnen doorgetrokken worden naar de andere duursporten. In de lezing wordt gerefereerd naar de vele studies rond de boeiende en soms verrassende relatie tussen letsels enerzijds en intrinsieke en extrinsieke risicofactoren anderzijds, waarbij een individuele risicoanalyse de way to go is. Het is evident dat ook voeding hierbij een belangrijke parameter stelt.



Only nutrigenomic anti-oxidant support beneficial for recovery in pro-athletes

– by **Nikolaas Van Riet**, Head of Nutrigenomics at the Advanced Genomic Research Institute and Co-founder and Chief Science Officer at Genopartner & **Brent Luyckx**, CEO and product development at 4Gold –

ABSTRACT

Redox cell and mitochondrial signaling can have both physiological (beneficial and important) and pathogenic role in our body. Intense exercise and environmental influences can create imbalances in the redox signaling leading to the expression of pathological pathways, and/or compromise important physiological pathways related to recovery. Intelligent nutrigenomic support can support and maintain proper redox balance. Standard anti-oxidant supplements, like vitamin C, can further imbalance the system. Contrary, correct nutrigenomic supplements upregulate the body's own mechanisms to balance free radicals, and thus yield important beneficial support for physiological signaling, which can boost our recovery and training adaptation systems, and even resulting in increased or enhanced super-compensation.

INDEX TERMS

Nutrigenomics, redox signaling, anti-oxidants, free radicals.

I. INTRODUCTION

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, oxidants are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process. These species play a dual role as both toxic and beneficial compounds. The delicate balance between their two antagonistic effects is an important aspect of our functioning and of even greater importance in pro-athletes and their ability to get stronger

after every workout or training session. Basically one can state that the role of the endogenous and exogenous antioxidant system is to keep the oxidants in check in order to keep them at moderate levels were to exert important and beneficial effects on cellular responses and immune function.

At high concentrations, ROS and RNS generate oxidative stress, a deleterious process that can damage all cell structures (1-10). Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The beneficial role of ROS and RNS on cell responses are the important signaling agents responsible for training adaptation and supercompensation in athletes.

II. THE ANTIOXIDANT CLASSIFICATION

Endogenous antioxidant compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants. The major antioxidant enzymes directly involved in the neutralization of ROS and RNS are: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GRx) (6-12). SOD, the first line of defense against free radicals, catalyzes the dismutation of superoxide anion radical ($O_2^{\cdot-}$) into hydrogen peroxide (H_2O_2) by reduction. The oxidant formed (H_2O_2) is transformed into water and oxygen (O_2) by catalase (CAT) or glutathione peroxidase (GPx). The selenoprotein GPx enzyme removes H_2O_2 by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG).

Intelligent nutrigenomic support can support and maintain proper redox balance...

Glutathione reductase, a flavoprotein enzyme, regenerates GSH from GSSG, with NADPH as a source of reducing power. Besides hydrogen peroxide, GPx also reduces lipid or nonlipid hydroperoxides while oxidizing glutathione (GSH) (2, 5-10). The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants, are produced by metabolism in the body, such as lipid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc (5, 6). While nutrient antioxidants belonging to exogenous antioxidants, are compounds which cannot be produced in the body and must be provided through foods or supplements. Some exert direct antioxidant abilities, like vitamin E, vitamin C. Other influence the expression of antioxidant pathways, like PUFA's,

carotenoids, alkaloids, isothiocyanates or polyphenols, or are cofactors for the endogenous enzymatic antioxidants like the trace metals selenium, manganese and zinc.

A. ANTI-OXIDANT PROCESS

When an antioxidant destroys a free radical, this antioxidant itself becomes oxidized. Therefore, the antioxidant resources must be constantly restored in the body. Thus, while in one particular system an antioxidant is effective against free radicals, in other systems the same antioxidant could become ineffective. Also, in certain circumstances, an antioxidant may even act as apro-oxidant e.g. it can generate toxic ROS/RNS (10). The antioxidant process can function in one of two ways: chain-breaking or prevention.

For the chain-breaking, when a radical releases or steals an electron, a second radical is formed. The last one exerts the same action on another molecule and continues until either the free radical formed is stabilized by a chain-breaking antioxidant (vitamin C, E, carotenoids, etc), or it simply disintegrates into an inoffensive product. The classic example of such a chain reaction is lipid peroxidation. For the preventive way, an antioxidant enzyme like superoxide dismutase, catalase and glutathione peroxidase can prevent oxidation by reducing the rate of chain initiation, e.g., either by scavenging initiating free radicals or by stabilizing transition metal radicals such as copper and iron (10).

III. THE IMPORTANCE OF PROPER PHYSIOLOGICAL REDOX SIGNALING FOR MAXIMUM RECOVERY AND SUPERCOMPENSATION IN ATHLETES

A. FREE RADICAL FORMATION

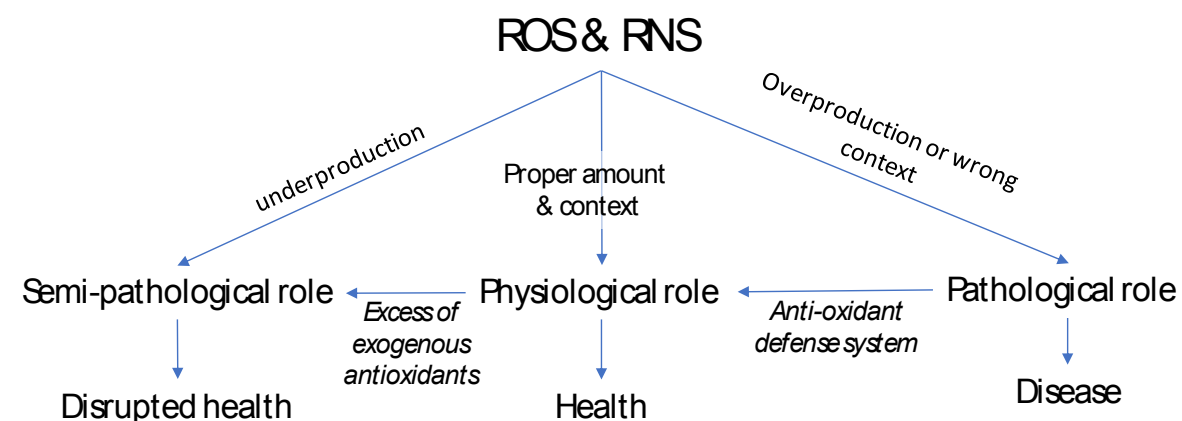
Formation of ROS and RNS can occur in the cells by two ways: enzymatic and non-enzymatic reactions. Enzymatic reactions generating free radicals include those involved in the respiratory chain, the phagocytosis, the prostaglandin synthesis and the cytochrome P450 system. from non-enzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing radiations. The non-enzymatic process can also occur during oxidative phosphorylation (i.e. aerobic respiration) in the mitochondria (4, 5, 8). ROS and RNS are generated from

either endogenous or exogenous sources. Endogenous free radicals are generated from immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer, aging. Exogenous ROS/RNS result from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs, industrial solvents, cooking (smoked meat, used oil, fat), radiation. (4-14). After penetration into the body by different routes, these exogenous compounds are decomposed or metabolized into free radicals. At low or moderate concentrations,

ROS and RNS are necessary for the maturation process of cellular structures and can act as weapons for the host defense system. Indeed, phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes as part of the body's defense mechanism against disease (5, 10). Other beneficial effects of ROS and RNS involve their physiological roles in the function of a number of cellular signaling systems (7-9). In brief, ROS/RNS at the correct levels are vital to human health.



B. REDOX SIGNALING AND EXERCISE



Physical stressors such as acute aerobic, anaerobic and intense exhaustive exercise can result in excessive reactive oxygen production.^{12–14} In this regard, the superoxide radical ($O_2^{\bullet-}$), resulting from monoelectronic reduction of oxygen, is considered to be the precursor of ROS including $OH^{\bullet}$, $RO^{\bullet}$, $ROO^{\bullet}$ and H_2O_2 . For instance, the superoxide radical ($O_2^{\bullet-}$) can react with nitric oxide ($-NO$), a nitrogen-centered radical, generating a highly reactive molecule, the peroxynitrite anion ($ONOO^-$), also termed a reactive oxygen and nitrogen species (RONS), able to cause DNA fragmentation and lipid oxidation.^(7-8,10) The effects of redox imbalances can have also a profound effect on energy production, such that an oxidative burden can impair energy production in the form of the energy storage molecule, ATP.

It must be clear that proper antioxidant activity is needed in the presence of strong physical stressors to ensure no excessive ROS are produced and redox balance is kept in check. At the same time, those physical stressors and following reactive oxygen production act as important signaling molecules, that promotes a large amount of physical adaptations in order for our bodies

to be able to cope with another similar burst of physical stressors. These oxidants acting as signaling molecules are the most important cellular communication mechanism and thus vital for any adaption of the body to these kind of stressors.

To achieve maximum physiological adaption through proper signaling, and to avoid any improper signaling and damage created by the ROS so that recuperation time minimized, and to avoid any disruption to the energy storage and productions systems, just the wright amount of antioxidant activity is needed. This is underlines the importance of redox balancing.

Antioxidant support by means of nutritional- or supplementation of exogenous antioxidants, is nearly impossible to dose correctly, in order to achieve the maximum physiological effect, as this kind of antioxidant support is disruptive by nature. Only when being consumed in their natural food matrices, doses are most likely to be in the beneficial range. On the contrary, intelligent nutrigenomic antioxidant support will provide a boost to the endogenous antioxidant system, which is more or less self-balancing and even aid in cell signaling, in

such a way that a homeostatic redox balance is attainable. Nutrigenomic antioxidant support can be seen as giving the proper those of certain redox signaling molecules with known and beneficial physiological adaptations.

IV. TRANSCRIPTION FACTORS AND REDOX BALANCE

Expression of antioxidant enzymes and pro-inflammatory cytokines, that produce free radicals, are regulated by transcription factors. Two important transcription factors involved in the delicate redox balance are NRF2 and NF- κ B.

C. NUCLEAR FACTOR (ERYTHROID-DERIVED 2)-LIKE 2

NRF2 or Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2, is a transcription factor that in humans is encoded by the NFE2L2 gene. Nrf2 is a basic leucine zipper (bZIP) protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation. Under normal or unstressed conditions, Nrf2 is kept

in the cytoplasm by a cluster of proteins that degrade it quickly. Under oxidative stress, Nrf2 is not degraded, but instead travels to the nucleus where it binds to a DNA promoter and initiates transcription of antioxidative genes and their proteins. Nrf2 is kept in the cytoplasm by Kelch like-ECH-associated protein 1 (KEAP1) and Cullin 3 which degrade Nrf2 by ubiquitination. Oxidative stress or electrophilic stress disrupts critical cysteine residues in Keap1, disrupting the Keap1-Cul3 ubiquitination system. When Nrf2 is not ubiquitinated, it builds up in the cytoplasm, and translocates into the nucleus. In the nucleus, it combines (forms a heterodimer) with one of small Maf proteins (MAFF, MAFK, MAFK) and binds to the antioxidant response element (ARE) in the upstream promoter region of many antioxidative genes, and initiates their transcription. metabolism in the body, such as lipid acid, glutathione, L-arginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc (5, 6). While nutrient antioxidants.

D. NUCLEAR FACTOR KAPPA-LIGHT-CHAIN-ENHANCER

Transcription factor NF- κ B or nuclear factor kappa-light-chain-enhancer

of activated B cells, is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF- κ B is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF- κ B plays a key role in regulating the immune response to infection. Incorrect regulation of NF- κ B has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF- κ B has also been implicated in processes of synaptic plasticity and memory.

NF- κ B is important in regulating cellular responses because it belongs to the category of "rapid-acting" primary transcription factors, i.e., transcription factors that are present in cells in an inactive state and do not require new protein synthesis in order to become activated (other members of this family include transcription factors such as c-Jun, STATs, and nuclear hormone receptors). This allows NF- κ B to be a first responder to harmful cellular stimuli. Known inducers of NF- κ B activity are highly variable and include reactive oxygen species (ROS), tumor necrosis factor alpha (TNF α), interleukin 1-beta (IL-1 β), bacterial lipopolysaccharides (LPS),

isoproterenol, cocaine, and ionizing radiation. The nuclear factor NF- κ B pathway has long been considered a prototypical proinflammatory signaling pathway, largely based on the role of NF- κ B in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules. Pharmacological and genetic studies suggest that there is functional cross-talk between these two important pathways. The absence of Nrf2 can exacerbate NF- κ B activity leading to increased cytokine production, whereas NF- κ B can modulate Nrf2 transcription and activity, having both positive and negative effects on the target gene expression. (15) These two pathways are expressed by oxidative stress and proposed to inhibit each other at their transcription level via protein-protein interactions or through secondary messenger effects. Nrf2 pathway inhibits the activation of NF- κ B pathway by increasing antioxidant defences and HO-1 expression, which efficiently neutralizes ROS and detoxify toxic chemicals and hence, reduces ROS mediated NF- κ B activation. Nrf2 pathway also inhibits NF- κ B mediated transcription by preventing the degradation of I κ B- α . Similarly, NF- κ B mediated transcription reduces the Nrf2 activation by reducing the ARE gene transcription, decreases free CREB binding protein (CBP) by competing with Nrf2 for CH1-KIX domain of CBP. NF- κ B also enhances the recruitment of histone deacetylase3 (HDAC3) to the ARE region by binding to Mafk and hence interferes with the transcriptional facilitation of Nrf2. Having the same initiator, but showing mutual inhibition, translates to a very delicate balance.

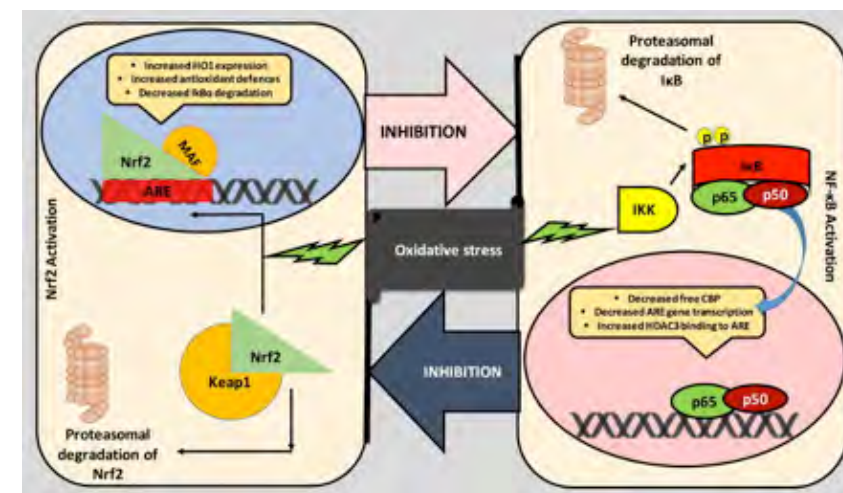


Figure 1 mutual inhibition - Yerra, Veera Ganesh & Negi, Geeta & Sharma, Shyam & Kumar, Ashutosh. (2013). Potential therapeutic effects of the simultaneous targeting of the Nrf2 and NF- κ B pathways in diabetic neuropathy. Redox biology. 1. 394-397. 10.1016/j.



Too much stressors on the body, as result of physical activity in combination with other external factors, can shift the balance towards NF- κ B and pro inflammatory pathways. Which lead to more production of free radicals and therefore disrupt the delicate balance in redox signaling, resulting in the improper physiological adaptations, often leading to inflammatory manifestation instead of supercompensation. In those unwanted inflammatory manifestations, providing support for the NRF2 pathway can shift the balance towards NRF2 or equilibrium and thus provide better physiological adaptation. Expression of the NRF2 pathway can be increased by specific nutrigenomic substances found in some plant matrices. This supports the global statement of this whitepaper, that nutrigenomic antioxidant support is beneficial for recovery and proper physiological adaptation in athletes.

V. CONCLUSION

The balance between oxidation and antioxidation (redox balance) is critical in maintaining a healthy biological system. In cellular redox state, the double-edged effect does not only concern ROS, but also antioxidants. Physiologic doses of exogenous antioxidants are required to maintain or re-establish redox homeostasis. However, high doses of exogenous antioxidants may disrupt redox balance. Considering epidemiological studies and trials on humans taking antioxidant compounds, it is evident that the health benefits of phytochemicals and nutrients were observed predominantly when being consumed within their natural food matrices (fruits, vegetables, grain, etc.). Compounds within plant foods may therefore be considered as being more safe and healthy compared to isolated, high doses, such as present in supplements. Two main factors seem to be predisposing

for the beneficial activities of plant foods: (1) the general low concentration of nutrients and non-nutrients in these natural food matrices and (2) the additive or synergistic actions of complex mixture profiles of phytochemicals and nutrients. Supplementation approaches do generally not take into account both aspects, which could explain the controversial results observed in supplementation studies. Intelligent nutrigenomic supplements upregulate the body's own mechanisms to balance free radicals, and thus yield important beneficial support for physiological signaling, which can boost our recovery and training adaptation systems, and even resulting in increased or enhanced super-compensation. NRF2 and NF- κ B are two important transcription factors involved in maintaining redox balance. Therefore they are excellent starting points in a nutrigenomic supplementation strategy for athletes.

References

- [1] Halliwell B, Gutteridge JMC. *Free radicals in biology and medicine*. 4th ed. Oxford, UK: Clarendon Press. 2007.
- [2] Bahorun T, Soobrattee MA, Luximon-Ramma V, Aruoma OI. *Free radicals and antioxidants in cardiovascular health and disease*. *Internet J. Med. Update*. 2006; 1: 1-17
- [3] Valko M, Izakovic M, Mazur M, Rhodes CJ, et al. *Role of oxygen radicals in DNA damage and cancer incidence*. *Mol. Cell Biochem*. 2004; 266: 37-56.
- [4] Valko M, Leibfritz D, Moncola J, Cronin MD, et al. *Free radicals and antioxidants in normal physiological functions and human disease*. *Review. Int. J. Biochem. Cell Biol*. 2007; 39: 44-84.
- [5] Droge W. *Free radicals in the physiological control of cell function*. *Review. Physiol. Rev*. 2002; 82: 47-95.
- [6] Willcox JK, Ash SL, Catignani GL. *Antioxidants and prevention of chronic disease*. *Review. Crit. Rev. Food. Sci. Nutr*. 2004; 44: 275-295.
- [7] Pacher P, Beckman JS, Liaudet L. *Nitric oxide and peroxynitrite in health and disease*. *Physiol. Rev*. 2007; 87: 315-424.
- [8] Genestra M. *Oxyl radicals, redox-sensitive signalling cascades and antioxidants*. *Review. Cell Signal*. 2007; 19: 1807-1819
- [9] Halliwell B. *Biochemistry of oxidative stress*. *Biochem. Soc. Trans*. 2007; 35: 1147-1150.
- [10] Young I, Woodside J. *Antioxidants in health and disease*. *J. Clin. Pathol*. 2001; 54: 176-186. 11. Valko M, Rhodes CJ, Moncol J,
- [11]
- [12] Bloomer RJ, Goldfarb AH. *Anaerobic exercise and oxidative stress: a review*. *Can J Appl Physiol*. 2004;29:245-263.
- [13] Rosa EF, Takahashi S, Aboulafia J, Nouailhetas VL, Oliveira MG. *Oxidative stress induced by intense and exhaustive exercise impairs murine cognitive function*. *J Neurophysiol*. 2007;98:1820-1826.
- [14] Volvaard NB, Shearman JP, Cooper CE. *Exercise-induced oxidative stress: myths, realities and physiological relevance*. *Sports Med*. 2005;35:1045-1062.
- [15] Yerra, Veera Ganesh & Negi, Geeta & Sharma, Shyam & Kumar, Ashutosh. (2013). *Potential therapeutic effects of the simultaneous targeting of the Nrf2 and NF- κ B pathways in diabetic neuropathy*. *Redox biology*. 1. 394-397. 10.1016/j.redox.2013.07.005.

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Novel way of promoting and maintaining tendon health in pro-athletes

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Abstract- A balance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs or nutrigenomic) is required to maintain tendon homeostasis. The extracellular matrix (ECM) of skeletal muscle and tendon is composed of different types of collagen molecules that play important roles in the transmission of forces throughout the body, and in the repair and regeneration of injured tissues. MMPs are required for baseline ECM homeostasis, but disruption of MMP regulation due to injury or disease can alter the normal ECM architecture and prevent proper force transmission. Chronic injuries and diseases of muscles and tendons can be severely debilitating, and current therapeutic modalities to enhance healing are quite limited. This hypothesis paper will discuss the mechanobiology of MMPs, and the potential use of MMP inhibitors, and redox modulators to improve the treatment of injured and diseased skeletal muscle and tendon tissue.





Key mechanisms for new era of personalised cosmetics

Voorwoord - De huid van elke sporter is voortdurend blootgesteld aan de omgeving. Deze omgevingsfactoren kunnen de huidveroudering versnellen: ultra-violette stralen, hitte, wind, luchtverontreiniging... De huid wordt dunner, droger en minder soepel waardoor ze gemakkelijker beschadigd raakt bij het schuren van sportkledij, door de inwerking van zweet op de huid, door repetitieve bewegingen, door frequent douchen... en extra huidverzorging schiet er vaak bij in. Bijgesloten artikel toont het potentieel dat lokaal inwerken op epigenetische mechanismen kan aanbieden om de vroegtijdige huidveroudering te vertragen.

- **Greet Claes**, Head of R&D at NAQI -



Abstract- Veroudering is een van de onvermijdelijke processen in het leven en kan worden gedefinieerd als veranderingen in structuren en weefselprocessen die met de tijd verwante organen en systemen beïnvloeden. We weten dat de omgeving en onze relatie ermee de celveroudering kunnen versnellen of vertragen. Epigenetica helpt om te begrijpen hoe sommige genen die betrokken zijn bij celveroudering, beschermingsmechanismen en celontgifting en zelfs de genen die deelnemen aan stamcelrenovatie, worden gereguleerd door processen op basis van DNA-methylatie, post-translationele histon-modificaties en niet-coderende RNA's (microRNA's) en lncRNA's. Verschillende studies hebben bevestigd dat celveroudering kan worden vertraagd en zelfs omgekeerd door epigenetische herprogrammering. Deze discipline biedt blijkbaar eindeloze mogelijkheden voor het ontwikkelen van nieuwe anti-verouderingsstrategieën.

In dit artikel worden enkele ouderdomsgerelateerde epigenetische mechanismen uitgelegd en hoe deze mechanismen belangrijk kunnen zijn bij huidverzorging en gezondheid. Ten slotte wordt het potentieel beschreven dat deze discipline heeft voor het ontwikkelen en typeren van nieuwe anti-verouderings cosmetische actieve principes.

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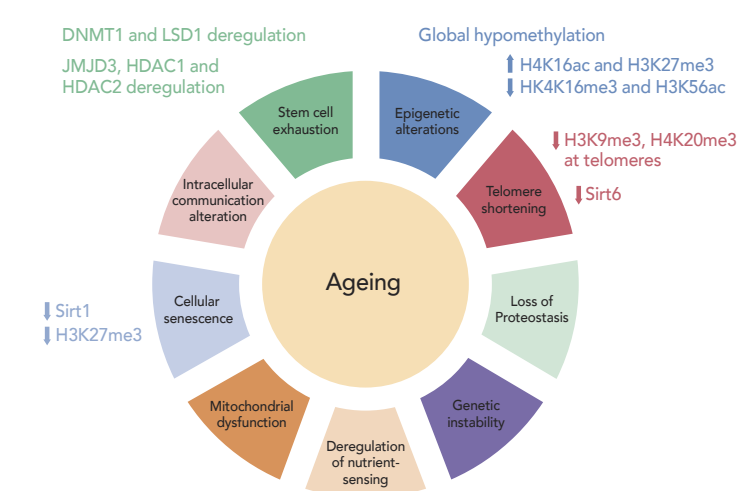


Figure 1: The nine hallmarks of ageing and main epigenetic mechanisms involved. Source: the Hallmarks of aging. Cell. 2013. Carlos López-Otín. 2013.4

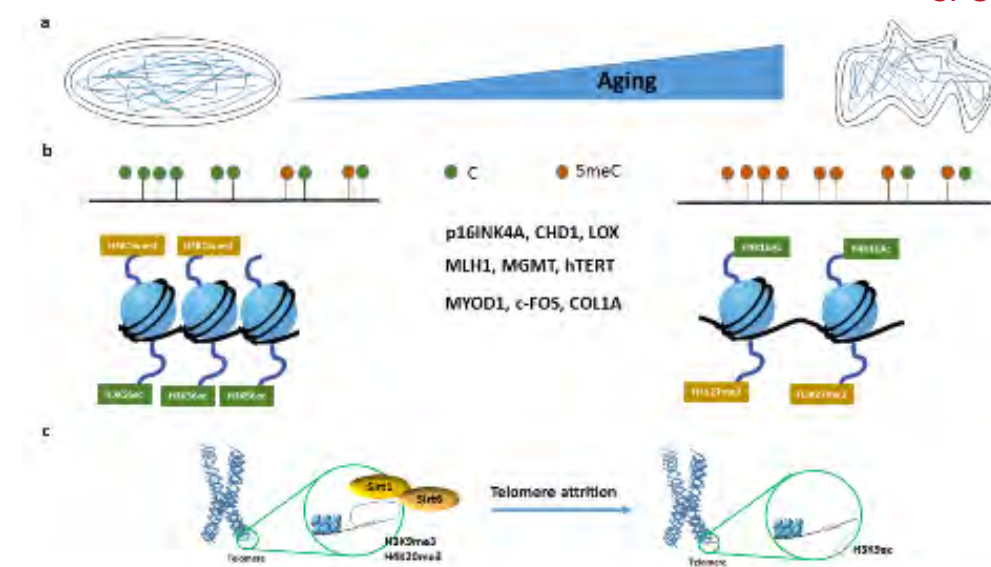


Figure 2: Epigenetic mechanisms that participate in the control of genetic regulation during ageing. a) Chromatin remodeling during cellular ageing; b) global epigenetic changes at DNA methylation and histone level during ageing; c) telomere attrition mediated by deregulation of epigenetic marks and epigenetic machinery.

tail modifications (proteins, which DNA is wrapped, forming nucleosomes), histone variants, non coding RNAs, including microRNAs (miRNAs) and long non coding RNAs (lncRNAs), and finally, spatial chromatin arrangement inside the nucleus.

DNA methylation is one of the most well-known mechanisms. It consists of introducing a methyl group (-CH₃) into the cytosine base of DNA that regulates chromatin compaction (Fig 2).

In 2001 researchers David Allis and Thomas Jenuwein coined the term "histone code" to refer to a whole series of post-translation modifications (methylation, acetylation, phosphorylation, etc.) capable of controlling chromatin packaging,² and capable of gene expression regulation (Fig 2).

Another epigenetic regulation component consists in non coding RNAs, of which the most widely studied are miRNAs. miRNAs are small nucleic acid molecules with 19-23 nucleotides that regulate the expression of the target gene by directly interacting with messenger RNA (Fig 2).

All these epigenetic mechanisms can be altered by external factors, like solar radiation and pollution,³ but also by our lifestyle.

Ageing is a biological process that is associated with intrinsic characteristics that have been established by researcher Carlos López-Otín as the nine ageing hallmarks.⁴

These nine ageing hallmarks are: 1) genetic instability; 2) epigenetic alterations; 3) mitochondrial dysfunction; 4) proteostasis loss; 5) telomeric shortening; 6) altered intercellular communication; 7) nutrient sensitivity deregulation; 8) stem cell exhaustion; and 9) cellular senescence (Fig 1).

Many of these alterations are the direct result of increased free radicals, normally reactive oxygen species (ROS), produced by mitochondrial dysfunction, alterations in antioxidant enzyme levels, and are even caused by alterations in the molecular pathways in which ROS participate as signalling molecules, among other reasons.⁵

This work centres on the hallmarks that can be regulated by epigenetic mechanisms, these being: epigenetic deregulation, telomeric shortening, stem cell exhaustion and cellular senescence. In fact, studies conducted into several systems have confirmed that the ageing clock can be delayed, or even turned back, by epigenetic reprogramming mechanisms.⁶

EPIGENETIC DEREGLATION

Changes in DNA methylation come with ageing⁷ and consist in the overall hypomethylation with local hypermethylation at specific genome sites.^{8,9} Overall hypomethylation is located in repetitive sequences, probably due to an increase in the genetic instability observed during the ageing process. With local hypermethylation, some genes acting as tumour suppressors, e.g. p16INK4A, CHD1 and LOX, others participating in genetic stability and DNA repair, e.g. genes MLH1, MGMT and hTERT, some genes like MYOD1 and c-FOS participating in cellular differentiation, something similar also happens in structural genes, such as COL1A1, when hypermethylating the coding gene. To obtain further information, we recommend reading the review by Zampieri et al¹⁰ and references therein. These changes in methylation patterns differ in each person due to the influence of lifestyle, and also to the natural environment that our cells are exposed to.¹⁰ Consequently, epigenetic reprogramming takes place in cells (Table 1).



Table 1: Global epigenetic changes associated to cellular ageing

DNA	
↓	DNMT1
↑	DNMT3b
↓	Global DNA hipomethylation ER, IGF2, p14ARF, p16ink4a, Rb, E-cadherina, c-fos, collagen a1, BRCA1, APC gene
↓	hypermethylation
Histone post-translational modification	
↓	SIRT1
↓	H3K9ac
↓	H3K56ac
↓	H4K16me3
↓	H3K36me3
↓	H3K9me3
↓	H4K20me
↑	H4K20me3
↑	H3K27me3
↑	H3K79me/me2
↑	H4K16ac
miRNA	
↑	miR-29a
↑	miR-203

ER: estrogen receptor; IGF2: insulin growth factor 2; p14ARF: tumour suppressor ARF; p16ink4a: Cyclin-dependent kinase inhibitor 2A (CDKN2A or p16); Rb: retinoblastoma protein; c-fos: proto-oncogen c-Fos, BRCA1: breast cancer 1; APC: activated protein C.

Post-translational changes also take place and it has been observed how cell ageing increases acetylation levels in lysine (K) at position 16 of histone H4 (H4K16ac) at the expense of methylation levels (H4K16me3: lysine 16 of trimethylate histone 4) which would increase chromosomal instability.¹¹H3K56ac reduces, while H3K27me3 increases, which slows down the histone exchange required for gene expression (Table 1).¹²

TELOMERE SHORTENING

Ageing has been related with telomere length. Telomeres are single-stranded structures that consist of some 2,000 repetitions of TTAGGG nucleotides bound to the proteins at the end of the chromosomes that protect chromosomes from degradation.¹³ DNA replication machinery cannot duplicate telomere tails, which means that each cell division of telomeres becomes shorter, which compromises their protective action and chromosomal stability. Epigenetic regulation is important for maintaining telomere stability.

Telomeric and subtelomeric regions are characterised by having a heterochromatin structure where methylations abound in histones like H3K9me3 or H4K20me3,¹⁴ along with low acetylation levels in histones H3 and H4.¹³ Changes in the methylation patterns of histones or DNA imply loss of control of telomere length (Fig 1).¹⁵ In turn, telomere shortening alters the epigenetic state of this chromosomal region.¹⁴ Sirtuins (SIRT) are NAD+-dependent deacetylases that play a fundamental role in many biological processes, e.g. regulating the energy status of cells, cellular differentiation and ageing, and telomere stability. Protein Sirt1 is responsible for the deacetylation of telomeric histones, which allows greater H3K9me3 or H4K20me3 methylation. An increase in the methylation of these histones contributes to telomeric heterochromatin compaction, which consequently improves telomere protection.¹⁶ Another sirtuin related with telomeric protection is Sirt6, an enzyme that participates in H3K9 deacetylation whose reduction has been observed in diseases that entail premature ageing.¹⁷

STEM CELL EXHAUSTION

The stem cell exhaustion theory postulates that the ageing process is the result of different stem cells not being able to continue generating the differentiated functional cells that allow tissue to maintain its original and physiological function.¹⁸ Stem cell exhaustion occurs with ageing, and epigenetic changes are also involved in this phenomenon. The dynamics of DNA methylation changes, and modifications in histones and chromatin structure, are required to conserve the self-renewal capacity of epithelial stem cells.¹⁹ In this context, proteins Ink4/Arf can detect aberrant structures in chromatin and can start cell senescence programmes, which sometimes results in epithelial stem cell exhaustion. Other proteins or protein complexes that participate in maintaining stem cell selfrenewal include DNA methyltransferase 1 (Dnmt1), which participates in maintaining DNA methylation, and also in histone demethylase LSD1 involved in the elimination of H3K4me3 transcriptional activation hallmarks.

Both DNMT1 and LSD1 are needed to maintain the identity and self-renewal programmes of epithelial stem cells.²⁰ Hence H3K4me is abundant in the key genes of epithelial stem cells, is required to maintain transcriptional programmes and is crucial for the epigenetic plasticity of pluripotent cells and for their self-renewal.²¹ Moreover, the histone demethylase of H3K27me3, Jmjd3, along with other deacetylase histones (Hdac1 and Hdac2), are essential for the transcriptional activation of the genes involved in epidermal stem cell differentiation.²⁰

CELL SENESCENCE

Cell senescence is the process by which cells limit their proliferation, which is initiated as a response to the stress and damage that take place in a cell. Cell senescence is an alternative response pathway to cell death programmed by apoptosis and is vitally important for preventing cancerous processes. In relation to cell senescence, both

reduced histone deacetylase SIRT1 activity and a drop in the levels of histone H3K9me3²² have been seen. Both lead to the so-called SAHF (senescence-associated heterochromatin foci), which give way to genetic and epigenetic deregulations, whose alterations create certain ageing characteristics like cell senescence.^{23,24} Furthermore, protein Jmjd3, which participates in the differentiation process of epithelial stem cells through H3K27me3 demethylation, contributes to induce cell senescence and ageing by activating gene locus Ink4/Arf.²⁵

MICRORNAS AS KEY MODULATORS OF CELL AGEING

miRNAs are small-sized non coding RNA molecules whose target is the messenger RNA molecules mainly in its 3'-UTR region, which has allowed them to be considered one of the most important post-transcriptional regulation mechanisms. The fact that the aberrant expression profiles of specific miRNAs of miRNAs





signatures are associated with ageing processes means that any intervention on these molecules is highly relevant for the design of anti-ageing treatments.²⁴

For non coding RNAs, several miRNAs have been described as being involved in the regulation of the nine ageing hallmarks (Table 2).

The miR-34 family expression is regulated by p53 in response to damaged DNA by activating DNA repair and cell cycle arrest processes to avoid genetic aberrations and genetic instability. Other miRNAs act as the modulators of the genes that participate in response to DNA damage by regulating gamma-H2AX (miR-24, miR-630), ATM (miR-630, miR-421, miR125b), P53 (miR-504, miR-34, miR-122) and MMR (let7 miR-16).²⁷

Other miRNAs, like miR-498, regulate catalytic telomerase activity. It has been recently found that miRNAs miR-140, miR-146a/b and miR-195 were over-expressed in old mesenchymal stem cells, and it has been reported how miR-195 inhibition achieves Tert re-expression (a catalytic telomerase component) that enables the restoration of stem cell proliferation which, in turn, favours telomere lengthening.²⁸

Among the miRNAs that control the mitochondrial function, miR-146 and miR-34 amend the messenger RNAs involved in mitochondrial transport and cell metabolism. Another form of cell metabolism regulation is the direct regulation of type I insulin growth factor (IGF-1). miR-223 represses this gene, which reduces its capacity to capture glucose. Loss of nutrient sensitivity is yet another of the ageing hallmarks. It has been described how let7 over-expression is involved in loss of sensitivity to glucos glucose and in insulin resistance, or how miR-122 participates in cholesterol regulation.²⁹ It has also been demonstrated that miRNAs miR-17, miR-19b, miR-20a and miR-106a can interact with the PTEN transcript, which codes an important AKT-mTOR

pathway silencer³⁰ and can, therefore, control cell metabolism. One of the most affected cell communication mechanisms is cell inflammation.³¹ A relatively small number of miRNAs exist, called 'inflamma-miRs', and are involved in this process. The 'inflammamiRs' group includes miR-155, miR-21 and miR-146a, which regulate some cytosines and NF-Scientists have identified nine ageing hallmarks. kB, among others.³² Regarding proteostasis regulation by microRNAs, miR-29b has been reported to play a key role by controlling the association of protein PA200 with the proteasomal complex and, in turn, by diminishing the peptidase activity of proteasomes and peptide degradation activity by aubiquitin-independent mechanism.³³ When studied cell senescence, it has been demonstrated that the over-expression of miR-152 and miR-181 suffices to induce cell senescence in fibroblasts.³⁴ Finally, it should be stressed that miR-29 and miR-21 are miRNAs that are involved in several of the processes of the nine ageing hallmarks,²⁶ including stem cell exhaustion, regulation, cell senescence and intercellular communication alteration.

That is why this miR-29 appears to be an interesting target to design anti-cell ageing interventions.

EPIGENETICS AND ITS POTENTIAL USE IN ANTI-AGEING COSMETIC TREATMENTS

Skin is directly exposed to many environmental factors, and also undergoes cell ageing, which is linked to the nine ageing hallmarks. Among the most relevant mechanisms we find renovation of progenitor cells, which are differentiated by being different cell types that comprise the epidermis, telomere control and cell senescence, which are all regulated by epigenetic mechanisms. Since epigenetic states are reversible and can be modified by environmental factors, epigenetics is a tool with enormous potential for the cosmetics sector. Indeed a series of active principles is appearing which are capable of regulating some epigenetic mechanisms through the expression of microRNAs, DNA methylation and post-translation histone modifications with a view to re-establishing the chromatin structure in skin cells.

The development of cosmetic products capable of modifying histones is still in its first stages. However given the rapid progress made in this area, they will no doubt allow different strategies to be adopted to intervene in post-translation histone modifications in the next few years.³⁵

Some active principles used in cosmetics can regulate some of the epigenetic mechanisms described in the previous section. Indeed some active principles that are currently employed have been shown to possess epigenetic activity. For instance, chamomile flower extracts (Matricaria recutita L.) or red grape pulp extracts are rich in apigenin (5,7-dihydroxy-2-(4-hydroxyphenyl)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4-benzopyrone), a flavonoid whose capacity for epigenetic modulation has been demonstrated by some studies,³⁶ achieved by regulating DNA methylation,³⁷ histone deacetylase activity³⁸ and anti-oxidant Nrf2 factor expression through the epigenetic regulation of this gene.³⁹ Moreover, apigenin has the capacity to rejuvenate skin by inducing collagen synthesis, which reduces wrinkling and offers skin a young appearance.⁴⁰

It would be interesting to demonstrate if this increase in collagen synthesis is related with the

expression of various miRNAs in the control of collagen synthesis, such as miR-29a, or to changes in DNA methylation in the COL1A gene promoter.

Other active principles have also shown their potential in the epigenetic regulation of ageing. The active principle based on the Calendula officinalis flower extract is able to regulate hsa-miR-29a expression. This miRNA inhibits the expression of collagen type I and type III genes.⁴¹ Zhang et al have shown that miR-29a is involved in elastin regulation.⁴² It is noteworthy that miR-29 has an anti-ageing effect thanks to the inhibition of histone deacetylase HDAC11 and histone methyltransferase EHMT2, both of which regulate the methylation levels of histone H3K9, which is essential in cell senescence processes.

Another interesting epigenetic active principle is the Plantago lanceolata leaf extract, based on the regulation of miRNAs. It is obtained from Plantago lanceolata stem cells, and acts by diminishing specific miRNAs, such as miR-29a, miR-196a, miR-25 and miR-150.⁴³ As described in the previous section, miR-29a regulates the expression of COL1A and COL3A. miR-196a also

contributes to the inhibition of the COL1A expression. Apart from this active principle, by diminishing the expression of senescence-related miRNA miR-21, the expression of the metalloproteinases of extracellular matrix MMP-1 and MMP-2 reduces via a mechanism that depends on inhibitors TIMP-1 and RECK.⁴⁴ This active principle also controls melanin overproduction and cell senescence and, although no information has been obtained out of this, some candidate miRNAs for this action should be miRNA-434-5p, which regulates tyrosinase expression, and miR-203, which regulates the transport of melanosomes and tyrosinase expression.

Nowadays, different types of active principles are appearing on the market, which demand epigenetic activity by acting on epigenetic mechanisms that affect some of the nine ageing molecular hallmarks.

The identification of new active epigenetic principles will allow a new generation of anti-cell-ageing cosmetics in the near future for personalised cosmetics, which will not only bear in mind an individual's genetic nature, but also one's interaction with the environment and lifestyle.

Table 2: miRNAs participating in the regulation of pathways associated to 9 hallmarks of ageing. miRNAs has been listed from works of LW Harries and XM Caravia. ^{24,25}		
	Hallmarks of aging	miRNAs
1	Genetic instability	miR-34a, miR-34b, miR-34c, miR-192, miR-194, miR-215, miR-421, miR-24, miR-504, miR-125b, miR-106b, miR-21, miR-210, miR-373.
2	Epigenetic alterations	miR-127, miR-124a, miR-34a, miR-34b, miR-34c, miR-200, miR-143, miR-148a, miR-152, miR-29, miR-193a-3p, miR-144, miR-98, miR-26a, miR-519, miR-137, miR-340
3	Mitochondrial dysfunction	miR-34a, miR-335, miR-146a, miR-145
4	Loss of Proteostasis	miR-320, miR-1, miR-26b, miR-106b, miR-301b
5	Telomere shortening	miR-155, miR-138, miR-34a, miR-34b, miR-34c, miR-498, miR-195
6	Intracellular communication alteration	miR-21, miR-29, miR-71, miR-80
7	Deregulation of nutrient-sensing	miR-17, miR-19b, miR-126, miR-190b, miR-122, miR-486, miR-20a, miR-106a, miR-1, miR-320, miR-206, miR-145, miR-223, let-7
8	Stem cell exhaustion	miR-371, miR-369-3p, miR-29a, miR-499, miR-290, miR-291*, miR-292*, miR-293, miR-294, miR-295
9	Cellular senescence	miR-499, miR-152, miR-373, miR-181, miR-372, miR-371, miR-369-3p, miR-29a, miR-20a, miR-17, miR-19b, miR-106a, miR-34a, miR-34b, miR-34c, miR-21





References

- 1.Tollefsbol TO. *Epigenetics of aging*, Springer; 2010
- 2.Jenuwein T, Allis CD. Translating the histone code, *Science* 2001 10;293(5532):1074-80
- 3.Kim M, Bae M, Na H, Yang M. Environmental toxicants—induced epigenetic alterations and their reversers, *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2012;30(4):323-67
- 4.Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging, *Cell.* 2013;6:153(6):1194-217
- 5.Vina J, Borras C, Abdelaziz KM, Garcia-Valles R, Gomez-Cabrera MC. The free radical theory of aging revisited: the cell signaling disruption theory of aging, *Antioxid Redox Signal.* 2013;19(8):779-87
- 6.Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock, *Cell.* 2012; 148(1-2):46-57
- 7.Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins, *Proceedings of the National Academy of Sciences of the United States of America.* 2005; 102(30):10604-9
- 8.Jung M, Pfeifer GP. Aging and DNA methylation. *BMC Biol.* 2015;13:7.
- 9.Heyn H, Li N, Ferreira HJ, et al. Distinct DNA methylomes of newborns and centenarians, *Proceedings of the National Academy of Sciences of the United States of America,* 2012;109(26):10522-7
- 10.Zampieri M, Ciccarone F, Calabrese R, Franceschi C, Burkle A, Caiapha P. Reconfiguration of DNA methylation in aging, *Mech Ageing Dev.* 2015;151:60-70.
- 11.Feser J, Tyler J. Chromatin structure as a mediator of aging. *FEBS Lett.* 2011; 585(13):2041-8
12. O'Sullivan RJ, Kubicek S, Schreiber SL, Karlseder J. Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres, *Nat Struct Mol Biol.* 2010; 17(10):12158-25
- 13.Blasco MA. The epigenetic regulation of mammalian telomeres, *Nat Rev Genet.* 2007; 8(4):299-309
- 14.Benetti R, Garcia-Cao M, Blasco MA. Telomere length regulates the epigenetic status of mammalian telomeres and subtelomeres, *Nat Genet.* 2007;39(2):243-50
- 15.Munoz-Najar U, Sedivy JM. Epigenetic control of aging, *Antioxid Redox Signal.* 2011; 15;14 (2):241-59
- 16.Palacios JA, Herranz D, De Bonis ML, et al. SIRT1 contributes to telomere maintenance and augments global homologous recombination, *J Cell Biol.* 2010; 27;191(7):1299-313
- 17.Michishita E, McCord RA, Berber E, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. *Nature.* 2008 27;452(7186):492-6
- 18.Smith JA, Daniel R. Stem cells and aging: a chicken-or-the-egg issue? *Aging Dis.* 2012 Jun;3(3):260-8
- 19.Iglesias-Bartolome R, Callejas-Valera JL, Gutkind JS. Control of the epithelial stem cell epigenome: the shaping of epithelial stem cell identity. *Curr Opin Cell Biol.* 2013;25(2):162-9
- 20.Mulder KW, Wang X, Escru C, Ito Y, Schwarz RF, Gillis J, et al. Diverse epigenetic strategies interact to control epidermal differentiation, *Nat Cell Biol.* 2012;14(7):753-63.
- 21.Gaspar-Maia A, Alajem A, Meshorer E, Ramalho-Santos M. Open chromatin in pluripotency and reprogramming. *Nat Rev Mol Cell Biol.* 2011 Jan;12(1):36-47
- 22.Mendelsohn AR, Larrick JW. Stem Cell Depletion by Global Disorganization of the H3K9me3 Epigenetic Marker in Aging, *Rejuvenation Res.* 2015;18(4):371-5
- 23.Fraga MF, Esteller M. Epigenetics and aging: the targets and the marks, *Trends in genetics : TIG.* 2007;23(8):413-8 24.Harries LW. MicroRNAs as Mediators of the Ageing Process, *Genes.* 2014;5(3):656-70
- 25.Barradas M, Anderton E, Acosta JC, Li S, Banito A, Rodriguez-Niedenfuhr M, et al. Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev.* 2009;23(10):1177-82
- 26.Caravia X, López-Otin C. Regulatory roles of miRNAs in aging. In: G S, editor. *microRNA: Basic Science: From Molecular Biology to Clinical Practice: Springer International Publishing; 2015,* 213-30.
- 27.Landau DA, Slack FJ. MicroRNAs in mutagenesis, genomic instability, and DNA repair. *Semin Oncol.* 2011;38(6):743-51
- 28.Okada M, Kim HW, Matsu-Ura K, Wang YG, Xu M, Ashraf M. Abrogation of Age-Induced MicroRNA-195 Rejuvenates the Senescent Mesenchymal Stem Cells by Reactivating Telomerase, *Stem Cells.* 2015; Sep 21.
- 29.Garcia-Segura L, Perez-Andrade M, Miranda-Rios J. The emerging role of Nutrigenomics. 2013;6(1):16-31.
- 30.Patel M, Gomez NC, McFadden AW, Moats-Staats BM, Wu S, Rojas A, et al. PTEN deficiency mediates a reciprocal response to IGF1 and mTOR inhibition, *Mol Cancer Res.* 2014;12(11):1610-20.
- 31.Zhang Z, Lowry SF, Guarente L, Haimovich B. Roles of SIRT1 in the acute and restorative phases following induction of inflammation, *J Biol Chem.* 2010; 285(53):41391-401
- 32.Quinn SR, O'Neill LA. A trio of microRNAs that control Toll-like receptor signalling, *Int Immunol.* 2011;23(7):421-5
- 33.Jagannathan S, Vad N, Vallabhapurapu S, Anderson KC, Driscoll JJ. MiR-29b replacement inhibits proteasomes and disrupts aggresome+autophagosome formation to enhance the antimyeloma benefit of bortezomib, *Leukemia.* 2015;29(3):727-38
- 34.Mancini M, Saintigny G, Mahe C, Annicchiarico-Petruzzelli M, Melino G, Candi E. MicroRNA-152 and -181a participate in human dermal fibroblasts senescence acting on cell adhesion and remodeling of the extra-cellular matrix. *Aging (Albany NY)* 2012;4(11):843-53
- 35.Konstantinov NK. *Epigenetics and Aging: A New Player in Skin Care, Cosmetics & Toiletries* 2015,
- 36.Shukla S, Gupta S. Apigenin: a promising molecule for cancer prevention, *Pharm Res.* 2010;27(6):962-78.
- 37.Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation, *J Nutr.* 2007;137(1 Suppl):223S-8S
- 38.Pandey M, Kaur P, Shukla S, Abbas A, Fu P, Gupta S. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: in vitro and in vivo study, *Mol Carcinog.* 2012;51(12):952-62.
- 39.Paredes-Gonzalez X, Fuentes F, Su ZY, Kong AN. Apigenin reactivates Nrf2 anti-oxidative stress signaling in mouse skin epidermal JB6 P+ cells through epigenetics modifications, *AAPS J.* 2014;16(4):727-35
- 40.Zhang Y, Wang J, Cheng X, Yi B, Zhang X, Li Q. Apigenin induces dermal collagen synthesis via smad2/3 signaling pathway, *Eur J Histochem.* 2015;59(2):2467
- 41.Maurer B, Stanczyk J, Jungel A, et al. MicroRNA-29, a key regulator of collagen expression in systemic sclerosis, *Arthritis Rheum.* 2010;62(6):1733-43
- 42.Zhang P, Huang A, Ferruzzi J, et al. Inhibition of microRNA-29 enhances elastin levels in cells haploinsufficient for elastin and in bioengineered vessels—brief report, *Arterioscler Thromb Vasc Biol.* 2012;32(3):756-9
- 43.Pressi G, Roberto T, Mondon P, Doridot E, Ringenbach M. Inventors Production method of meristematic cells of plantago lanceolata, composition comprising said cells or their cellular extract, and cosmetic, nutraceutical and dermatological uses, 2014.
- 44.Reis ST, Pontes-Junior J, Antunes AA, et al. miR-21 may acts as an oncomir by targeting RECK, a matrix metalloproteinase regulator, in prostate cancer, *BMC Urol.* 2012;12:14.



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RECOVERY GEL

- ✓ Reduces muscles stiffness and cramps
- ✓ Improves the circulation and reduces waste materials
- ✓ Lightens heavy legs
- ✓ Cooling and analgesic effect

NAQI® Recovery Gel helps reduce muscle fatigue and stiffness after physical activity.

NAQI® Recovery Gel relaxes the muscles and helps reduce muscle fatigue after physical activity. It contains essential oils of eucalyptus, peppermint, cypress, arnica and juniper, and vanillyl butyl ether to stimulate blood flow and increase the supply of nutrients and oxygen to tired muscles. By speeding up the removal of waste materials built up in the muscles, you will enjoy a quicker recovery after intense workouts. As a result, NAQI® Recovery Gel helps boost your performance.



Packaging
100ml • 500 ml



✓ apply after sports

Airless
Bottle
easy-to-use

USE: Rub into the skin immediately after sports and/or physical activity. For external use only. Keep out of the reach of children. Avoid contact with eyes and mucous membranes. Do not use on broken skin. NAQI® Recovery Gel is easily absorbed, non-greasy and has an intense and prolonged effect.



NAQI[®]

FOUNDATION

NAQI FOUNDATION
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