NAOS

Updates on dermatology

Proteome Science

NAOS AGING SCIENCE

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Edito

Stéphane FAUVERGHE
NAOS International Medical Director

Dear All,

I am very pleased to present you the fifth edition of the BIODERMA/NAOS Updates on Dermatology.

BIODERMA/NAOS has been regularly organizing international events dedicated to Dermatology. These events, for dermatologists and all healthcare professionals interested in Dermatology, are always presented by renowned experts in their field. In our approach to promote the development of knowledge in Dermatology, we have the pleasure to offer you this new publication. You will find hereafter the summary of the NAOS Symposium held during the IMCAS World Congress in Paris in January 2023 - *A fundamental discovery on aging: beyond the genome, the proteome*. The speakers were Marco ROCHA from Brazil, Miroslav RADMAN from Croatia, and Isabelle BENOIT from France (NAOS).

During this symposium, Miroslav RADMAN presented a proteome-centric view of aging and age-related diseases. Isabelle BENOIT delivered a lecture on the proteome alteration as the root-cause of skin aging. And Marco ROCHA presented the protection of the proteome as a new therapeutical path for healthy aging.

I wish you all an enjoyable, enriching, and interesting reading.

Summary

Miroslav RADMAN
Croatia

Prof. RADMAN is an internationally renowned geneticist and molecular biologist.

He is known for his discovery of the SOS response to DNA damage, and for highlighting the importance of proteome protection in cellular resistance to extreme conditions (radiation, temperature, desiccation...). His work has resulted in more than 200 publications in the most prestigious international scientific journals and the filing of numerous patents.

His research on the implication of proteome damage as a cause of age-related diseases such as Parkinson's, Alzheimer's, Charcot... has opened up the most promising research strategies in aging therapies.

Isabelle BENOIT
France (NAOS)

Chemical engineer by training (CPE & EM Lyon). After more than 15 years in the B2B sector of cosmetic active ingredients, in France and abroad, she joined the NAOS group as Institut Esthederm Scientific Director, then BIODERMA.

Today member of the NAOS Scientific Committee, she ensures compliance with the principles of Ecobiology at all stages of the company's Research and Innovation processes.

Speakers' biographies

Marco ROCHA
Brazil

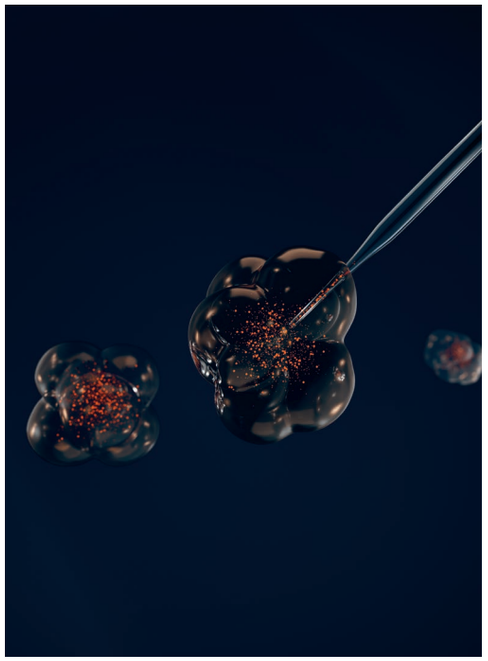
Marco Alexandre Dias da Rocha, MD, PhD is a Brazilian Dermatologist. He has graduated the Federal University of São Paulo. Since 2013, he is Volunteer Professor and Researcher at the Federal University of São Paulo. From 2010 to 2019, he worked as dermatologist of the Plastic Surgery group – Sírio-Libanês Hospital.

In 2004, he created his own private medical clinic: Marco Rocha Dermatologia. He is member of the American Academy of Dermatology and Brazilian Society of Dermatology. He actively assists and participates as speaker at International Conferences. His work has been awarded in 2014 and 2016, respectively "Best scientific-Fleury São Paulo / Brazil" and "Scientific excellence – International Acne Congress - Shanghai / China".

Author of international publications in peer-reviewed journals, he currently dedicates himself to researching and teaching dermatology focused on acne, adult female acne, rosacea, skin barrier and microbiome.

Fundamental common mechanism of aging and age-related diseases

Miroslav RADMAN
MedILS, Split Croatia - INSERM unit 1001, University R. Descartes, Paris, *France*



What do the following three questions have in common?

1. What does time do to cells and organisms to cause morbidity and mortality?

2. What determines species-specific longevity?

3. What determines the predispositions to different age-related diseases (ARD)?

The answer is: oxidative damage to the proteome.

Aging and age-related diseases (ARD) share a common biological clock that appears to be their root cause: protein damage. Two variables appear common in the studies of the aging process of all living organisms: Reactive Oxygen Species (ROS) and disturbed tissue homeostasis. Figure 1 shows the shared variables from the studies of aging in invertebrate model organisms, mammals and human progerias.[1]

Currently, it is recognized that virtually every diseased state involves some degree of inflammation and oxidative stress. In normal, healthy tissue, redox chemistry and ROS are kept under control to maintain homeostasis at the cellular level.[2] Cellular generation of ROS occurs from both enzymatic and non-enzymatic processes.[3, 4] However, ROS can also be the outcome of acute cell stress and may cause cell death *via* apoptosis or necrosis.

Proteins are major biological targets of ROS and oxidative stress when these are formed *in vivo,* either in intra- or extracellular compartments. Proteins are able to scavenge 50 to 75% of free ROS such as -OH within a cell by g-radiolysis.[5, 6] Figure 2 shows how ROS inflicts protein damage in cells and organisms.

Some ROS-induced protein modifications have a preference to occur in misfolded proteins and then provoke further unfolding of the protein structure, while some are essentially harmless events.[7]

Irreversible protein modifications and aggregates lead to the inactivation of both protein functions and interactions with other proteins or molecules, resulting in harmful cellular effects and diseases.[8] Among the consequences of oxidative damage to proteins are cell dysfunction, aging and diseases as shown in Figure 3.

However, this process can be reversible. In embryonic stem cells and in *Deinococcus radiodurans*, the ratio of carbonylated and intact proteins is in favour of the latter.

In young, healthy organisms, the concentration of ROS and misfolded proteins is balanced, and both are present in small quantities. Oxidative damage targets misfolded proteins, resulting in an increased level of irreversibly misfolded proteins. Once oxidatively damaged proteins reach a certain level, premature death - mainly by ARD - occurs by the catastrophic loss of protein quality control.[9]

Cellular life is maintained by protein activities; therefore protein damage ruins the functions of life, including the prevention of molecular damage and repair of damaged DNA, proteins and other damaged cellular components. Hence, cellular fitness decreases due to persisting protein damage, leading to the progressive degeneration of cellular functions and even direct cell death, due to the cytotoxic structures of damaged proteins (Figure 4).

The ultimate liability to protein function is an irreversible oxidative protein modification called protein carbonylation (PC).[10-12] Since cellular aging can be defined as a progressive degeneration of vital cellular functions, and an increase in mutation rates, oxidative proteome damage appears as the most likely cause of aging and ARD, including cancer.[10]

In conclusion, oxidative damage to the proteome can be considered as the root cause of aging and all, or nearly all, ARD.

Figure 1 _

Pathways shared between aging in invertebrate model organisms, mammals and human progerias

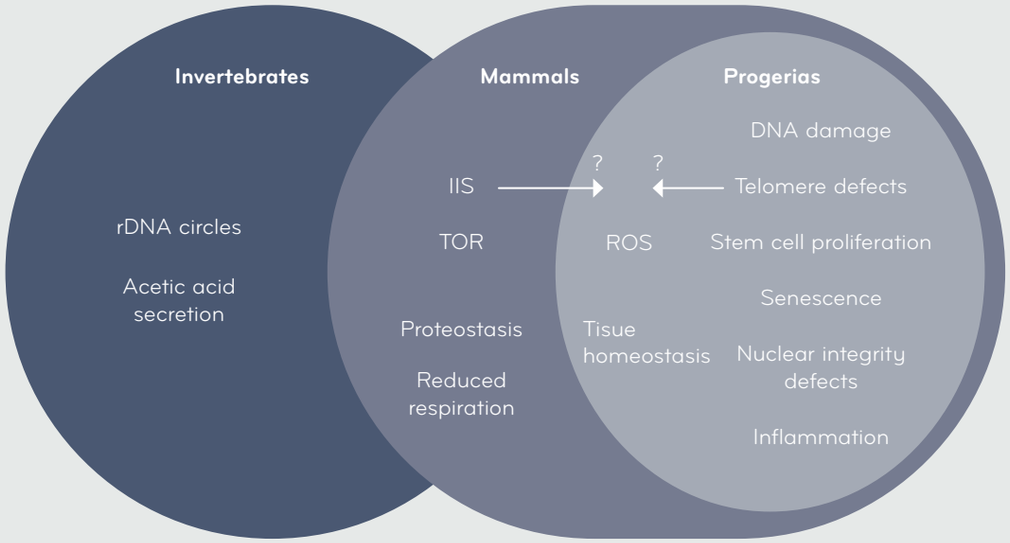
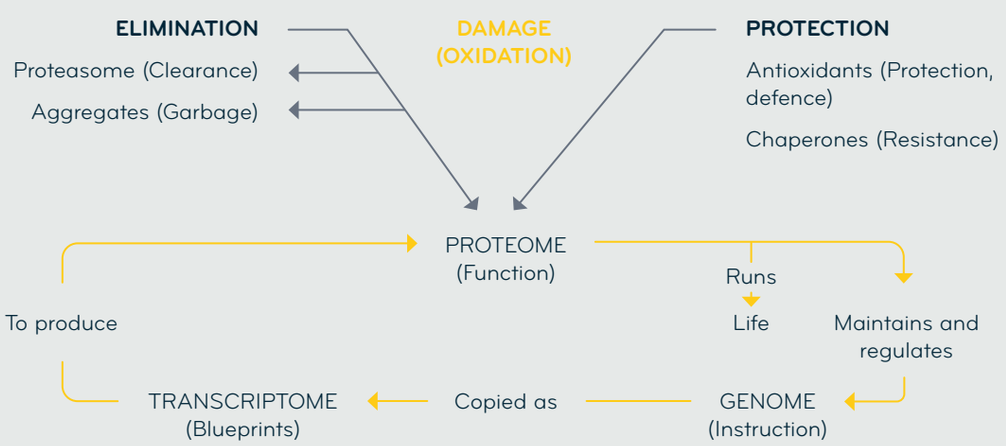


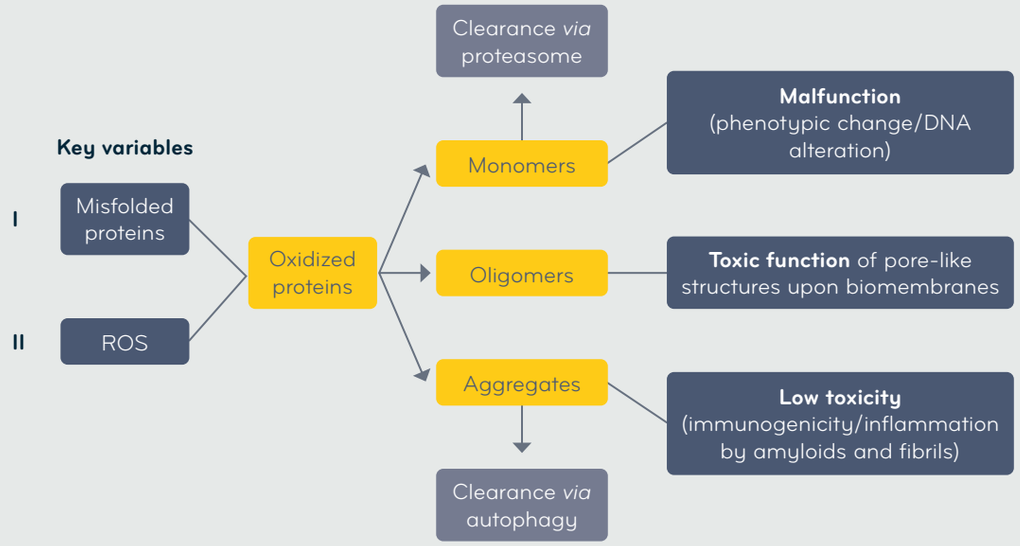
Figure 2 _

Impact of reactive oxygen species on the organism



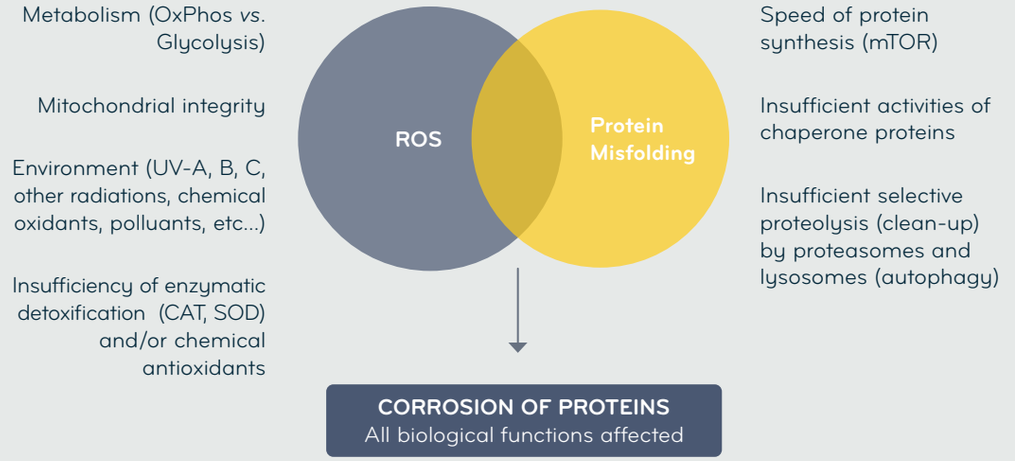
_ Figure 3

Oxidation process resulting in cell dysfunction, aging and diseases



_ Figure 4

Essentials of aging and diseases



Conclusion

In conclusion, oxidative damage to the proteome can be considered as the root cause of aging and all, or nearly all, age-related diseases.

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A change of paradigm for a new scientific era

Isabelle BENOIT
NAOS-ILS, Aix-en-Provence, *France*

Extremophilic organisms are considered as models of biological robustness to aging.

Research conducted by KRISKO and RADMAN showed that the **extremophilic bacterium Deinococcus radiodurans is able to fix DNA damage using non-oxidable repairing proteins,** thus being almost eternal.[1] Results also confirmed that longevity is not exclusively linked to the genetic code, but mainly to the capacity of the organism to repair this code rapidly; the authors concluded that protecting the tool that repairs and protects the DNA, *i.e.* the proteome, which comprises all proteins of the body, may be key for cellular longevity. **Thus, a damaged proteome or the loss of proteostasis may be considered as the first step, the root cause, of cellular dysfunction, leading to diseases and aging.**

With 15 to 27.5% of its total composition, proteins are the second main component of the skin after water.[2] Proteins such as collagen, elastin, keratin, and many more elements that constitute it play a structural role in the skin. Functionally, proteins are involved in cellular metabolism and tissue homeostasis through enzymes, cytokines, hormones and growth factors, as well as other functional elements. **Damaging the skin proteome may impair cellular and tissular functioning, thereby causing skin alteration and skin aging. Thus, protecting the proteome may be essential for skin longevity and may be considered as the meta theory beyond most currently accepted theories of aging.**

López-Otín *et al.* proposed the Biological Geriatric Assessment (BGA) concept.[3] This concept describes nine hallmarks that are currently considered as the denominators of body aging. BGA includes genomic instability, telomere attrition, epigenetic alterations, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, chronic inflammation, stem cell exhaustion, altered intercellular communication and loss of proteostasis (protein homeostasis).[4] Today, telomer attrition and chronic inflammation are the most frequently discussed mechanisms in aging[5, 6] and can be related to proteome damage. Thus protecting the proteome encompasses preventing telomers attrition and chronic inflammation.

Several alterations of numerous proteins have been reported in tissue aging. Such proteins are highly sensitive and impacted by Reactive Oxygen Species (ROS).[7, 8] During aging, senescent cells accumulate in all tissues and contribute to their functional decline *via* the Senescence-Associated Secretory Phenotype (SASP).[9] SASP is thought to trigger several pathological aging features, among them chronic inflammation, which is the principal biomarker of aging.[10] Sirtuins are protein deacetylases associated with aging. They are involved in chronic inflammation through the inactivation of NLRP3, which inhibits aging.[7, 11] Cell Senescence (CS) is associated with telomere shortening, which leads to permanent cell cycle arrest.[12] Consequently, preventing telomere attrition by protecting their protein coat may thus also prevent CS and related chronic inflammation in tissues.[13]

The accumulation of carbonylated proteins has been associated with skin aging.[14, 15] Protein Carbonylation (PC) is irreversible oxidative damage, frequently resulting in the loss of protein function and aggregation.[16] In the skin, PC results in distinguishable clinical changes. Transepidermal water loss is increased in the *stratum corneum*.[17] In the supra-basal epidermis, the accumulation of carbonylated keratins disrupts light transmission, which, in turn, alters the subjectively-perceived skin radiance and homogeneity of skin complexion.[18, 19] Carbonylated proteins alter the dermis by damaging collagen and elastin, and by altering fibroblasts and causing changes in the expression of metalloproteases, such as MMP-1, resulting in chronic inflammation involving IL-8.[20, 21] Therefore, preventing PC and maintaining the balance between protein synthesis and degradation is essential in maintaining a youthful appearance of the skin, reflecting a harmonious cellular biochemistry.

Protein Quality Control (PQC), involving multiple chaperones and degradative pathways, identifies and eliminates abnormal and misfolded proteins that are deleterious to cells and tissues.[22] If PQC fails, then protein aggregation may occur. While many of these aggregations are eliminated *via* autophagy, others accumulate in the cells and tissues, leading to cell damage and apoptosis and may be considered markers for aging and age-related diseases.[23-25]

Until recently, much research about aging has focused on the protection and repair of DNA, as well as genes that control and prevent cell and tissue aging. However, since proteins repair DNA and synthesize antioxidant protecting molecules, it is not surprising that, for instance, extreme radiation resistance is achieved by the protection of the proteome, rather than the genome.[26] **Therefore, protecting the proteome may prevent the body from signs of aging through chaperone systems that stabilize the conformation of proteins and antioxidant molecules that neutralize carbonylation triggers.**

Recent research has shown that antioxidant chaperones constitute a major breakthrough compared to current antioxidant approaches in this deleterious process.

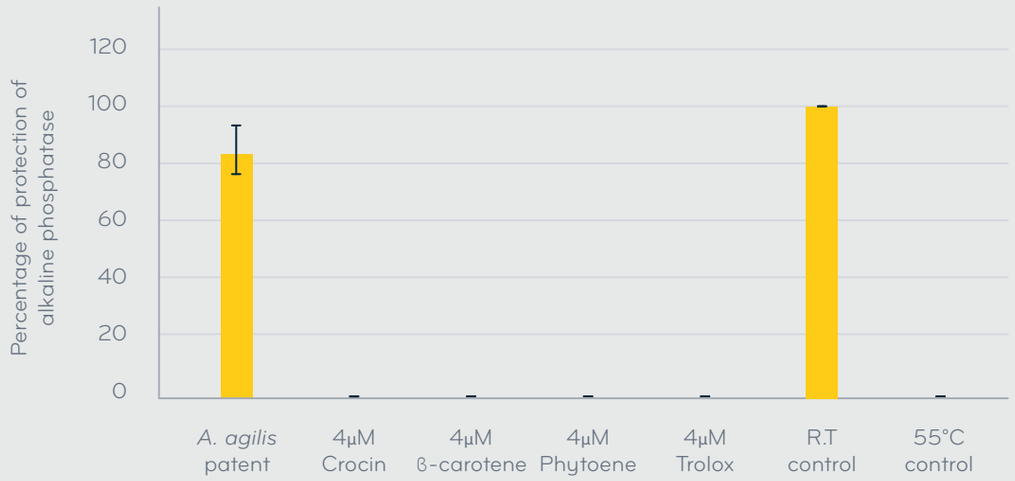
Arthrobacter agilis (A. agilis), an extremophilic bacterium isolated from snow crystals is ultra-resistant to UV radiation, very low temperatures and oxidative stress. It is able to self-repair and survive in extreme conditions.[27]

The NAOS-patented extract of *A. agilis* is a synergistic combination of 6 anti-oxidant chaperone-like molecules, also called bacterioruberins. They are unique in nature and have a distinctive affinity for proteins, providing a protective, chaperone-like activity, as well as a powerful antioxidant effect.

An *in vitro* heat test, which uses heat to destabilize protein alkaline phosphatase, showed that *A. agilis* extract provides protection of more than 80% of the activity of the 3-D protein structure compared to currently available anti-oxidants. This highly protective capacity is due to its specific chaperone-like activity (Figure 1). Other work has confirmed the high antioxidant potential of *A. agilis* extract compared to different reference molecules (Figure 2). Moreover, *in vitro* investigations have demonstrated that the *A. agilis* extract protects elastin from oxidative stress (Figure 3) induced by UVA radiation and pollution (Figure 4), and that it physically protects DNA repair enzymes (T4 endonuclease) and their functionality against UVA irradiation (Figure 5). Moreover, it significantly shields cultured keratinocytes against carbonylation induced by UV and blue light radiation, as well as pollution (Figure 6).

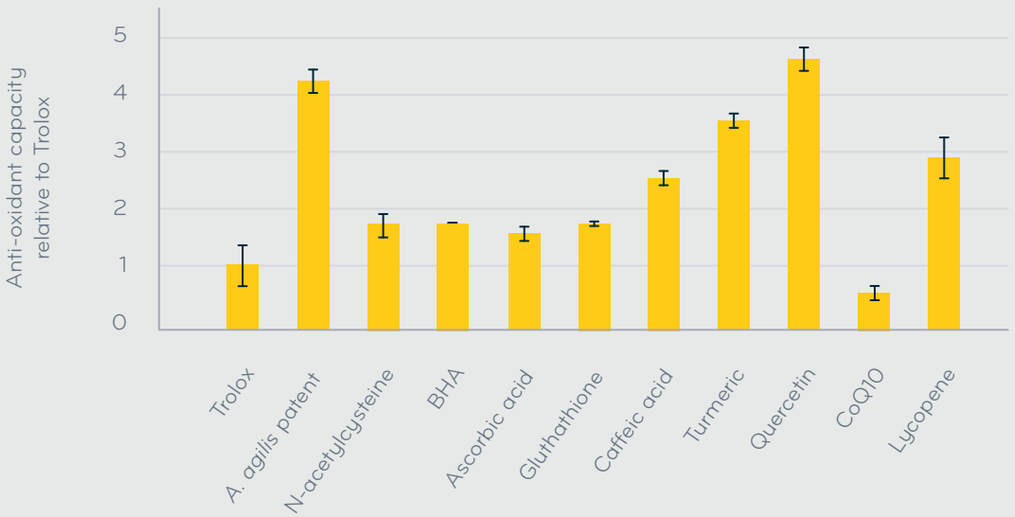
_ Figure 1

Heat test confirming *in vitro* the high protective potential of *Arthrobacter agilis* extract of the 3-D protein structure compared to reference molecules



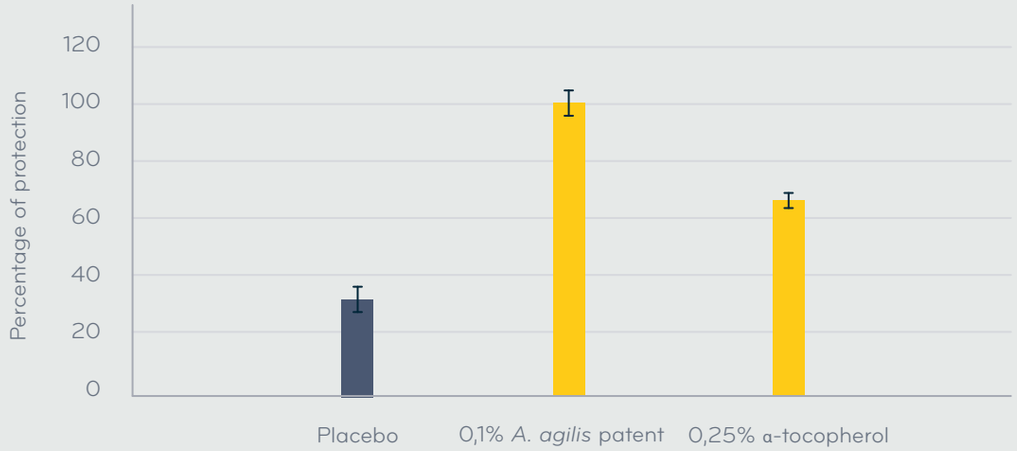
_ Figure 2

In vitro antioxidant potential of *Arthrobacter agilis* extract compared to reference antioxidants



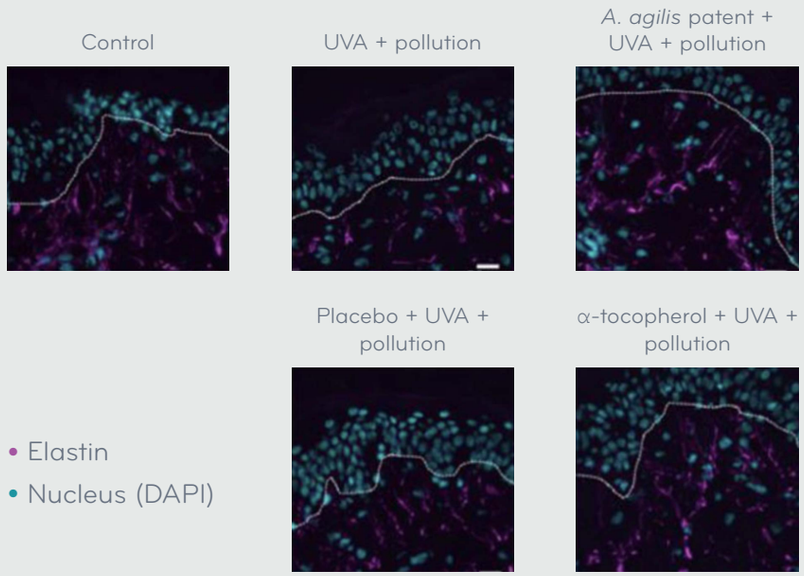
_ Figure 3

Protective potential of *Arthrobacter agilis* extract against oxidative stress of elastin compared to α-tocopherol



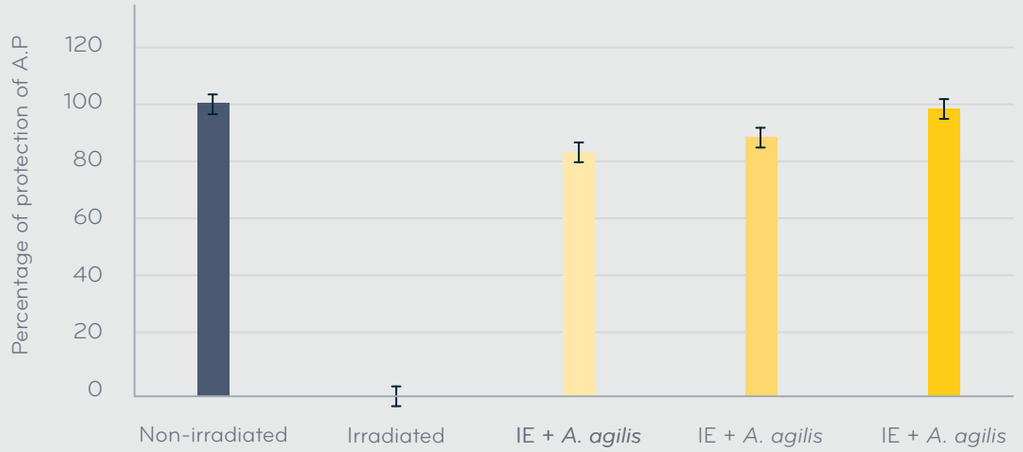
_ Figure 4

Protective potential in skin explants of *Arthrobacter agilis* extract against UV radiation and pollution compared to *α-tocopherol*



_ Figure 5

In vitro testing of the functional protective potential of *Arthrobacter agilis* extract of T4 endonuclease against UVA irradiation



Conclusion

In conclusion, a proteomics-centered R&D strategy consisting in protecting the proteome rather than the genome opens the perspective of major breakthroughs in age management. Protecting the proteome is the meta theory beyond most other theories about aging. Using antioxidant molecules with a chaperone-like activity, such as bacterioruberins instead of "classical" antioxidants, is a novel and promising approach to protect the proteome and to impact aging, including that of the skin.

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Protection of the proteome: a new therapeutic way for healthy aging

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The human body is composed of about 60% water, 16% proteins, as well as fats and other components.[1] The human genome is made of about 20,000 to 25,000 genes and alternative promoters, splicing and mRNA. Editing processes lead to the transcriptome of about 100,000 transcripts which, through post-translational modifications processes, produce more than 1,000,000 different proteins.[2]

The proteome comprises the ensemble of proteins in any organism.[3] Proteins are the most diverse and structurally complex macromolecules in the cell. They participate in nearly every known aspect of life, either directly or by synthesizing other active biomolecules. Their function is determined by specific native three-dimensional structures. These structures ensure that new polypeptide chains adopt, and native proteins keep, their properly folded conformation, even during stressful situations.[4, 5]

A healthy proteome is achieved and maintained by proteostasis, an optimal turn-over process of proteins, with a high ribosomal fidelity in translation and a high accuracy of protein folding assisted by Chaperone Proteins (CP). This process is also called Protein Quality Control (PQC) *via* the proteostasis network.[6, 7] Failing of PQC results in a low quality proteome that misfunctions or leads to detrimental accumulation of misfolded proteins that form toxic small aggregates and large amyloids or fibrils.[8] It has been shown that protein oxidation precedes aggregation, to the extent that over 90% of carbonylated proteins are found in aggregates.[9] This is explained by a high sensitivity to the oxidation of misfolded proteins.[10]

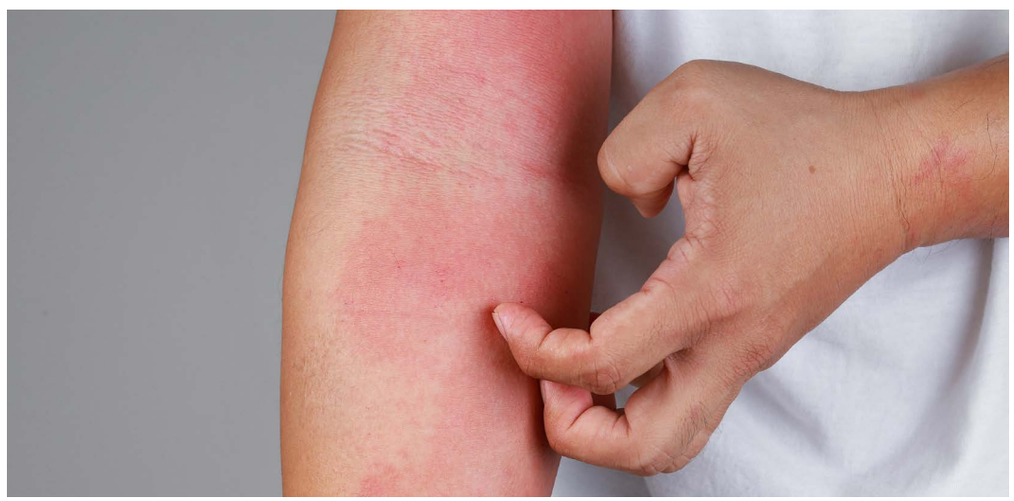
In the skin, protein damage mostly results from external stimuli, including exposure to oxidants present in air pollution, ozone, chemical agents and radiation, such as UV light.[11-16] Moreover, protein damage can be caused through internally generated oxidants and reactive oxygen and nitrogen species, which are produced during metabolism or immune responses.[17, 18] Finally, they can be produced because of transcriptional or translational errors, since misfolded proteins become sensitive to carbonylation.[19, 20] The resulting modified cornified envelope leads to an altered anti-oxidative capacity and the reduced barrier function of the epidermis.[21]

Oxidative stress plays a major role in skin disease and the aging process. It is the imbalance between pro- and antioxidants in favor of the former, causing proteotoxicity.[22] Proteotoxicity is cellular dysfunction, caused by protein misfolding, damage and aggregation. It is used as a biomarker for a number of Age-Related Degeneration and Diseases (ARDD), including psoriasis, Atopic Dermatitis (AD) and cancers, as well as aging.[23, 24]

In psoriasis, the multifunctional cytokine Tumor Necrosis Factor-alpha (TNF-alpha) plays an important role in the inflammatory and immunological response of the skin. Reactive ROS are involved in the TNF-alpha-induced signaling pathways, leading to the production of primary human keratinocytes inducing the release of cytokines, inflammation and Protein Carbonylation (PC).[25]

In AD, PC may play a significant role. The etiopathogenesis of AD is complex and multifactorial, with a mix of genetic, immunological and environmental aspects, and its physiopathology is still not completely elucidated. However, as in other chronic inflammatory diseases, oxidative stress may play an important pathogenetic role.[26]

In skin cancer, growing evidence suggests that the efficiency of DNA repair after exposure to UV radiation is highly dependent on the levels of oxidative protein damage, including, but not limited to, DNA repair proteins. Besides DNA lesions, UV-induced oxidative stress can indeed result in the carbonylation of proteins, a major form of irreversible protein damage that inactivates their biological function.[27]



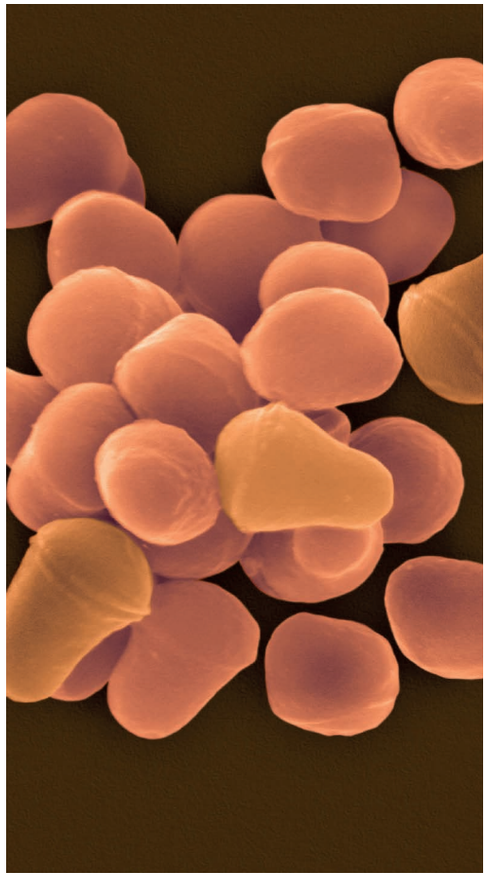
Nine hallmarks are currently considered as the denominators of aging, including that of the skin.[28] They include genomic instability, telomere attrition, epigenetic alterations, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, chronic inflammation, stem cell exhaustion, altered intercellular communication and loss of proteostasis or protein homeostasis.

Skin and tissue aging *via* protein damage is mainly caused by protein glycation, carbonylation and, to a lesser extent, through carbamylation. The accumulation of Advanced Glycation End products (AGEs), protein carbamylation and PC have been causally associated with skin aging.[29-31] PC forms reactive ketones or aldehydes.[32]

In the skin, PC results in three distinguishable clinical changes, as presented by Isabelle Benoît. Transepidermal water loss is increased in the *stratum corneum*.[33-35] In the supra-basal epidermis, the accumulation of carbonylated keratins disrupts light transmission that alters the subjectively perceived skin radiance and homogeneity of skin complexion.[36, 37] Carbonylated proteins alter the dermis by degrading collagen and elastin. PC is associated with an alteration of fibroblasts, as well as changes in the expression of metalloproteases such as MMP-1, the development of a chronic inflammation involving IL-8.[38-42]

In the skin, as in any other tissue, a damaged proteome may be considered as the first step, the root cause, of cellular dysfunction, leading to diseases and aging.

There is growing evidence that protecting the proteome will help to build and maintain healthy tissues and thus allow to slow down the process of aging, in particular skin aging.



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