Sunscreens, suntan and anti-sun-burn preparations today

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Summary

Until recently, the only strategy affording the protection of the skin against the harmful solar radiation was to reduce the number of impinging photons with fabrics, umbrellas, hats, sunglasses or sunscreens.

Diverting impinging photons is the first step in sun protection. It is not the only one. Non-diverted photons enter the skin and provoke molecular damages to DNA, RNA, proteins, lipids, vitamins etc. often by indirect oxidative reactions.

It is important to perform a second step and scavenge the reactive species, which provoke these residual reactions, by using antioxidants against different reactive oxygen species such as superoxide, hydroxyl radicals and singlet oxygen.

The third step in sun protection is to stimulate the endogenous self-defense responses. As of today it is possible to stimulate DNA repair, energetic metabolism, heat shock proteins, immune response, etc.

Riassunto

Oggi come oggi, la sola strategia che permetta di proteggere la pelle contro i danni del sole è quella di ridurre il numero dei fotoni incidenti. Questo può essere ottenuto usando parasole, cappelli, vestiti, occhiali da sole ed anche mediante l'applicazione di preparati che assorbono o riflettono la radiazione solare, i cosiddetti schermi o filtri solari.

Contrariamente a quanto comunemente si crede, è stato recentemente portato all'attenzione dei ricercatori come un'abbronzatura naturale fornisca solo un piccolo fattore di protezione. In termini di Sun-Protection-Factor (SPF), l'abbronzatura è equivalente a un filtro solare con un SPF = 3 o 4. È quindi imperativo tener presente, quando ci si espone agli ultravioletti, non solo che il processo di abbronzatura si accompagna comunque alla produzione di danni molecolari, ma anche che l'abbronzatura stessa non offre protezioni particolari e che, quindi, l'uso dei filtri solari non deve essere abbandonato mai, neanche ad abbronzatura ottenuta.

Deviare o assorbire i fotoni incidenti è solo il primo passo di una moderna strategia per la protezione solare. Non è l'unico! I fotoni che non sono riflessi o assorbiti penetra nel pelle e provocano danni agli acidi nucleici (DNA e RNA), alle proteine ed ai lipidi. È necessario rimuovere questi danni perché essi provocano la morte cellulare e la conseguente reazione infiammatoria, che, come è noto, accelera il processo di invecchiamento cutaneo, inducendo mutazioni anche troppo spesso
sottovalutate.
È da poco tempo possibile fornire preparati in cui il rilascio di anti-ossidanti è ritardato nel tempo, e che contengono enzimi di riparazione del DNA. È anche possibile fornire prodotti che provocano un'abbronzatura artificiale con piccola ma misurabile capacità di protezione. Permettendo di mantenere il livello di danni molecolari al minimo, tali preparati riducono l'intensità dell'eritema solare ed i danni secondari associati alla risposta infiammatoria.
I risultati scientifici degli ultimi anni lasciano ben sperare su un progresso tecnologico che permetterà l'aumento del numero delle armi di difesa anti-solare per usufruire di un'abbronzatura senza danni. Gli induttori della sintesi della melanina e delle proteine da choc termico, gli stimolatori del metabolismo energetico e della risposta immunitaria (che è parzialmente ridotta dall'esposizione agli UV) sono in corso di studio approfondito. È la possibilità di ottenere la protezione mediante somministrazione di farmaci per via orale è anch'essa allo studio.
Abstract

Until recently, the only strategy affording the protection of the skin against the harmful solar radiation was to reduce the number of impinging photons with fabrics, umbrellas, hats, sunglasses or sunscreens.

Diverting impinging photons is the first step in sun protection. It is not the only one. Non-diverted photons enter the skin and provoke molecular damages to DNA, RNA, proteins, lipids, vitamins etc. often by indirect oxidative reactions. It is important to perform a second step and scavenge the reactive species, which provoke these residual reactions, by using antioxidants against different reactive oxygen species such as superoxide, hydroxyl radicals and singlet oxygen.

The third step in sun protection is to stimulate the endogenous self-defense responses. As of today it is possible to stimulate DNA repair, energetic metabolism, heat shock proteins, immune response, etc.

INTRODUCTION

It is a truism that solar radiation is one of the major environmental factors on earth. Another major environmental factor is oxygen. Oxygen and light are essential for several life forms, and specifically for vertebrates and higher plants. Until the middle of the twentieth century, solar radiation was known to be the cause of erythema, but was substantially believed to be harmless. The discovery of the biological role of DNA in 1944 and the use of UV-C to generate mutations attracted the attention of the scientists on the importance of avoiding radiations which might be absorbed by DNA. It turned out that sunscreens produced to avoid the erythema in summertime sunbathers were able to filter off the UV-B part of solar radiation, which is both erythemogenic and absorbed by DNA.

In the second half of the twentieth century it was observed that skin cancers in humans, such as squamous and basal cell carcinomas, occurred much more frequently in the skin of zones exposed to UV (hands, face, neck) than in non-exposed regions. Work with laboratory rodents pointed out that UV-B is a complete carcinogen, and UV-A was found out to be a cancer promoter. Humans exposing themselves to solar radiation with UV-B protection experienced sagging of the skin and this led to the understanding that UVA can be harmful.

In the last decade of the twentieth century it was observed that, in the presence of oxygen, UVA damages biological macromolecules, such as DNA, lipid and proteins (1, 2, 3, 4). It was realized that UV from solar radiation can be directly absorbed by biological molecules and provoke direct damages, or generate reactive species, such as singlet oxygen or other oxygen-containing free radicals, which can provoke oxidative damages to these same macromolecules. It was therefore proposed to associate antioxidants to sunscreens, in order to avoid the oxidative damages generated by those photons, which happen to reach the skin notwithstanding the presence of sunscreens.

STRATEGIES TO ACHIEVE SUN PROTECTION

The biochemical analysis of organisms exposed to UV radiation led to the understanding of the mechanisms of DNA repair (5). Other repair and/or defense systems were uncovered in the skin of vertebrates. The induction of heat shock proteins, was originally thought to be elicited only by a sudden increase of the temperature. Later it was observed that cells under a variety of stresses were also induced to synthesize heat shock proteins. In recent years it was observed that the accumulation of mRNA of a major heat shock protein was associated to exposure to UVB (6) and UVA has been shown to provoke the synthesis of heat shock proteins in human skin (7). It was also observed that UV radiation from a solar simulator (UVA + UVB) provokes the degradation of NAD, the arrest of glycolysis.
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and cell death (8). All these and other observation led to the conclusion that the capability to simulate the responses of skin to solar radiation might be helpful in the overall protection against sun exposure.

A reasonable strategy to protect against solar radiation can therefore rest on the following actions:

1- aver impinging photons
2- scavenge reactive species
3- stimulate the endogenous mechanisms of repair

1- Avert impinging photons

Impinging photons can be averted by several artificial devices such as umbrellas, hats, clothes, sunglasses etc. It has to be pointed out that umbrellas and fabrics have a limited capability to filter off impinging photons. In some instances, wearing a shirt will still allow 10% of the impinging photons to reach the skin (9) and it is well known that, because of the reverberation of sand, being at the beach under an umbrella might well be insufficient to avoid an erythema (10).

It has been long time believed that natural tan constitutes, per se, a great protection against solar radiation, and that, once a tan is achieved, the skin is fully protected against UV. This is not true. It has been recently shown in a cohort of several dozen individuals, by comparing the amount of DNA damage elicited by a same UVB dose in tanned and non-tanned skin of the same individual (11), that a natural tan reduces the damages by only about 50%-60%.

For people desiring or needing to be undressed under the sun, sunscreens in creams for topical application are at hand. Great progress has been made in the conception and in the cosmetic formulation of sunscreens and there are now a dozen or so which offer broad spectrum protection (UV-B and/or UV-A), are photo-stable and do not generate photo-irritations or photosensitizations (12).

To offer protection against UV-B or UV-A, a molecule has to scatter or to absorb the radiation at these wavelengths. Because of the limited molar extinction coefficient of any molecule, the fraction of absorbed photons by a sunscreen topically applied in a cream with limited thickness will always be less than 100%. Moreover, when a photon is absorbed, an electron goes in an excited state and the chances are that the excitation energy be transferred to molecular Oxygen to generate a very reactive species called singlet oxygen (see 3, 4 and 12). This is true also for the so-called "physical filters" such as TiO2 and ZnO which do indeed not only scatter, but also absorb UV-A and UV-B.

It appears therefore not only that a fraction of the impinging photons does reach the skin even in the presence of sunscreens, but also that the energy of a fraction of the photons absorbed by sunscreens is used to generate singlet oxygen.

2- Scavenge reactive species

Non-absorbed photons can be directly absorbed by macromolecules such as DNA and proteins and can also strip hydrogen atoms from lipids and trigger the peroxidative cascade. Singlet oxygen can be generated ubiquitously and react everywhere within the cell or in the extra-cellular matrix. It is therefore mandatory to supplement sunscreens with ingredients able to interrupt the peroxidative cascade and to scavenge reactive oxygen species such as superoxide, hydroxyl radical and singlet oxygen. Vitamin E and Vitamin C together with Butylated Hydroxy-Toluene and Nor-Dihydro-Guaiaretic Acid and histidine are known to efficiently counteract those reactive species. Hydrogen peroxide is generated during the oxidative burst associated to the inflammatory reaction following cell damage, and catalase-like molecule will be welcome to join the pano-
ply of the anti-oxidants.
There has been a considerable amount of research conducted about the possibility to induce protection by oral administration of specific anti-oxidants such as β-carotene or vitamin E, or by specific diets. The oral administration of vitamin E and vitamin C for several weeks doubles the value of the minimal erythema dose (MED) (13). Other anti-oxidants gave deceiving results. On the other hand it is very interesting to note that the oral administration of ω-3 fatty acids seems to have a very positive effect against UV-induced skin cancer (14).

3-Stimulate the endogenous mechanisms of repair

DNA repair
It has been observed that the same dose of UV-A + UV-B originating from a solar simulator elicits different damage-repair patterns in individuals with the same MED (15). These results can be interpreted either as a consequence of the fact that the MED is not linked to DNA damage in a bi-univocal manner (15) or that individuals with the same MED have DNA repair mechanisms of different efficacy (11). It is conceivable to try and increase the efficacy of the mechanisms of the endogenous DNA repair system. The DNA repair systems are crucial: it is indeed known that when these mechanisms are impaired, genetic diseases such as Xeroderma pigmentosum (XP) or Thio Tricho Distrophy (TTD) can follow.

In humans, the expression of DNA repair genes is constitutive, not inducible. The DNA repair enzymes, however, can be protected against UV-linked oxidative damage and therefore their activity can be increased. DNA repair activity can be increased in human cells, by the topical application of liposomes containing exogenous DNA repair enzymes. Liposomes are instrumental in helping the repair enzymes to enter the epidermal cells.

One of these enzymes can be the T4endo V nuclease, which nicks DNA in the close vicinity of a pyrimidine dimer (16). Other DNA repair enzymes can be used, such as DNA photolyase. DNA photolyase binds to pyrimidine dimers in nuclear DNA and utilizes the energy of UVA radiation to undo the dimers and restore the DNA in the undamaged form. It has been shown on human skin that the application post-UVB of Photolyase under UV-A irradiation for a half an hour removes 50% of the UV-B generated pyrimidine dimers (17). It also restores the inducibility by IFN-γ of the synthesis of ICAM-1, which is inhibited by UV-B (17). This is to say that repairing DNA restores the immune response depressed by exposure to UV-B, which is known to provoke the migration of Langerhans cells and to practically suppress Contact Hypersensitivity (CHS) and Delayed-Type Hypersensitivity (DTH) (18). Interestingly enough, if UV-B provokes the suppression of CHS and DTH, it does not negatively interfere with the production of antibodies against specific antigens in the course of a vaccination (19).

ENERGETIC METABOLISM

When DNA is damaged by UV, the metabolism of the cell is affected. In particular Nicotinamide Adenosine Dinucleotide (NAD) is split in ADP ribose and nicotinamide, glycolysis is arrested and ATP synthesis impaired. The consequence of this is cell death, with the possible triggering of the arachidonic acid cascade and the inflammatory consequences, of which erythema is but one aspect.

It has been shown that the topical application post-UV, of liposomes containing NAD reduces dramatically the intensity of the erythema (8) as if the addition of NAD could help maintaining electron transport and synthesis of ATP at a le-
vel sufficient for keeping the cells alive. Strategies for maintaining the level of energetic metabolism in UV aggressed cells can be designed and ingredient have been found to boost the synthesis of ATP.

**HEAT SHOCK PROTEINS**

When a cell is subjected to stress (temperature increase, treatment with heavy metals, exposure to modified amino acids, treatment with pro-oxidants) it stops the synthesis of all proteins except those belonging to a family which, for historical reasons, has been termed the family of heat shock proteins (hsp).

It has been reported that exposure to solar simulators provokes the accumulation of heat shock mRNA (6) and heat shock proteins (7). The role of these proteins is to help nascent polypeptides to fold in the correct tertiary structure upon leaving the ribosomes where they are synthesized, and also to help refolding those proteins the structure of which has been somehow perturbed by the stress. The synthesis of heat shock proteins requires a few hours after the stress and is a response to an aggression, not a prevention against it. It can be surmised that sun protection might be improved by achieving the prevention against solar aggression by using gratuitous inducers of hsp synthesis.

Gratuitous inducers of hsp synthesis are innocuous substances able to stimulate the response of self-defense without representing, per se, an aggression to the skin. Topical application of gratuitous inducers of heat shock proteins a few hours before exposing one-self to the aggression of sunlight or of other environmental aggressors could be one of the newest and most efficient ways to accompany sunscreens and anti-oxidants to achieve sun protection.

**DISCUSSION**

The effects of solar radiation, in particular of ultraviolet radiation have been studied for more than a century on a variety of organisms, ranging from bacteria to plants to man. A part of our knowledge on the effects of solar radiation on human skin, hair and eye is summarized in a monograph of the European Society for Photobiology, published in 2001, which I was asked to be the editor of. The majority of information in this paper is described in full detail in chapters of that monograph.

When learning about the effects of an aggression on an organism, as well as when learning about the endogenous reactions of the organisms to those aggressions, it comes spontaneously to the mind how to design a certain amount of strategies to help fighting the aggression.

In this paper I have exposed a Three Step method to achieve sun protection, which consists in averting impinging photons, scavenging reactive species generated by non-averted photons and boosting the endogenous defense mechanisms. This third step might be divided in two sub-steps, i.e. enhancing the self defense (activate DNA repair, induce the synthesis of heat shock proteins) and restoring physiological functions which are impaired by the aggression (boost energetic metabolism, restore immune response).

Active ingredients can be added to cosmetics to achieve the three steps of sun protection. Others will be found in the future, to make protection and repair as complete as possible.
References


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