Overall study on molecular pathways of skin cancer derived from Ultraviolet radiation as an environmental threat

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ABSTRACT
An important part of solar radiation is considered to be Ultraviolet radiation. Though through passing ozone layer it is progressively filtered. Due to the depletion of the ozone layer, the filtering activity of the latter is reduced and as a result more UV radiation, UVB in particular, reaches the Earth’s surface. Ultraviolet radiation is composed of three different wavelengths: UVA, UVB and UVC. Although UVC isn’t a cause of skin cancer, UVA and UVB play different roles as for tanning, burning, and photo aging. As a matter of fact, Ultraviolet light can damage DNA in the epidermis. However, through apoptosis the damaged DNA is repaired or deleted in order to prevent the generation of cancer. It is believed that a deficient apoptotic mechanism might make individuals liable to skin cancer. The main factor for generating skin cancer is considered to be the UV radiation which could cause basal cell carcinoma, squamous cell carcinoma and possibly melanoma. For the maintenance of hemostasis, apoptosis plays a key role. This is done via many molecular pathways such as the pathways of tumor suppressor genes like P53, P21 and also the expression of BAX proteins. These pathways are involved in apoptosis after UV radiation. It is clear that the malfunction of these genes and proteins can lower the tolerance of body and cause cancer. The goal of this article is to investigate the molecular pathways of skin cancer derived from Ultraviolet radiation as an environmental threat.

1. Skin cancer
Cancer is a group of diseases that is defined by abnormal cell growth which can ultimately spread or invade other parts of the body (1-3). A variety of factors could cause cancer (4-7). Skin cancers are a group of cancers that are related to skin. The three main types of skin cancer are: Melanoma (pic1), Basal-cell cancer (pic2) and Squamous-cell cancer (pic3) (8-10). The first two of the latter, alongside some other less common skin cancers are known as non-melanoma skin cancer. Basal-cell cancer grows with a rather slow rate and can damage the tissue around it. Though it is unlikely to spread Squamous-cell cancer has a good potential to spread. It usually appears as a hard lump with a scaly top though it may also form an ulcer (14, 15). Melanomas are the most aggressive type. Signs include a mole that has changed in size, shape and color. It possesses irregular edges and usually has more than one color. Moreover, it is itchy or bleeds (16-19).

2. Ultraviolet radiation and DNA damage
Ultraviolet light results in DNA damage. If left unrepaired, it can give rise to several biological effects such as cell death, mutation and cancer (22, 23). Xeroderma Pigmentosum, A human related disease, is a remarkable example of how reduced DNA repair capacity can lead to a higher rate of cell lethality, higher mutation frequency and a predisposition to cancer (24-26). By nucleotide excision repair process, which is a complex interaction of more than 10 different types of gene products, the repair of UV-induced DNA damage is achieved. (27, 28). As shown by an increasing number of evidence DNA repair, like any phenotypic trait, would be heterogeneous distributed in the human population (29). As a result, specific individuals who possess low DNA repair capacity might be more susceptible to the adverse biological effects of environmental genotoxic agents, for example UV light (30,31). Apoptosis is a process which deals with the repair of damaged DNA in order to prevent the generation of cancer. (32). A deficient apoptotic mechanism is believed to make individuals susceptible to skin cancer. Thus, the reaction and response of normal
controls and patients with basal cell carcinoma to distant areas or cause death. It usually appears as a painless raised area of skin which in some occasions might be shiny and contain small blood vessels running over it or may show itself as a raised area with an ulcer (11-13).

3. Ultra violet radiation and its effect on skin cancer:
Solar radiation has many components, for example UV. Through passing the ozone layer, UV is progressively filtered. As a result of ozone layer depletion, such protective activity is reduced and therefore, more UV radiation will reach to the Earth’s surface. (35, 36). UV radiation has three wavelengths: UVA, UVB and UVC (37). Although UVC isn’t an initiative of skin cancer, UVA and UVB play different roles as for tanning, burning, and photoaging (38). Because there is no fully proven answer about the best way to get vitamin D, and also the controversy about tanning beds, we still face a great deal of misinformation regarding UV radiation. (39).

Though the fact that UV radiation is the main responsible factor for skin cancers, including basal cell carcinoma, squamous cell carcinoma and possibly melanoma remains true (41,42). This is further proven by the National Institutes of Health and the World Health Organization since they have categorized broad spectrum UV as a human carcinogen (43, 44). The solar UV spectrum is continuous, yet it would be scientifically convenience to describe the light within three specific wavebands; UVA, UVB and UVC based on their wavelength. They are different due their biological impact and the depth of which they can penetrate skin. (45-48).

UVA has a wavelength of 320-400 nm and is responsible for up to 95 percent of the solar UV radiation that reaches the Earth’s surface. Due to its strong penetration through skin, for many years it has been hold responsible, as a major factor, for skin aging and wrinkling. In addition, recent studies’ findings suggest that UV radiation might initiate and exacerbate the development of skin cancers (49-50). UVA radiation is present during all daylight hours and alongside winter months. Also, it can pass through glass and clouds. Therefore the exposure of humans to UV radiation in their lifetime is great. (51, 52). Recent findings propose that UVA exposure could deal the same amount of damage to skin as UVB. Until recently scientists believed that although UVA penetrates more deeply through the skin compared to UVB, it would be absorbed less by DNA and therefore, would do a lower damage when compared to UVB. (53, 54). However based on a recent Australian-US study, UVA is more harmful than UVB to the genetic material of skin cell where most skin cancers arise which is the keratinocytes in the basal layer of the epidermis (55, 56). Superficial epidermal layers are more susceptible to UVB radiation (picture5). Being responsible for burning, tanning, acceleration of skin aging, UVB has a wavelength of 290-320 nm. In addition, it plays a key role in the development of skin cancer. (57,
58). The intensity of UVB depends on many factors like season, location and time of day. UVC has the shortest wavelength of the three (less than 290 nm) and as a result, it possesses the highest amount of energy. It should be stated however, since UVC is filtered and is not able to pass through the ozone layer, these wavelengths do not reach the Earth’s surface and aren’t able to do harm to human skin. The differences between the effects of UBV and UVA are yet to be fully uncovered. But when these two are combined, they are to pose a serious threat to the skin (59). It can create irreversible damage that varies from sunburn to premature aging and ultimately to skin cancer. In order to avoid such harm, protection from these rays seems to be the only solution.

5.P53 and P21 genes functions against UV exposure:
P53 and P21 genes are tumor genes which function against the occurrence of cancer (72,73). After and UV radiation, P53 gene prevents cancer formation and maintains the cellular genetic stability (74). The amount of p53 protein is increased after UV radiation. This response is believed to induce cell cycle arrest, support nucleotide excision repair (NER) and apoptosis (75, 76). Also, the NER increases when low doses of radiation are involved. In contrast, apoptosis takes place only after high doses of radiation are received by cells (over 200 J/m²). P21 is a tumor suppression gene which is tightly controlled by p53 gene. This protein mediates the p53-dependent cell cycle G1 phase arrest as a response to a variety of stress inducers (picture 6) (77-79). This was a major discovery in the early 1990s since it revealed how cells stop dividing after the exposure to harmful agents such as radiation. P21waf1/cip1 is induced by low dosages solely. Bax though, is induced only after high doses of UV radiation and thus, supporting the roles of p21waf1/cip1 and bax in NER and apoptosis, respectively (80, 81). These results show that UV dose, DNA repair after low doses and apoptosis after high doses are the main factors that determine cellular stress response to UV radiation. Both of the aforementioned mechanisms are dependent on wild-type p53 function.

Picture5: Penetration of UVA, UVB and UVC into different layers of superficial epidermal layers (40).

4.Efficiency of biomarkers in detection of cell damage
Biomarkers are cellular, biochemical, or molecular alterations. Such molecules are measurable in biological media such as human tissues’ cells or fluids (60, 61). Some carcinogens affect living cells by altering genes while some others are able to cause reactive chemical compounds that result in oxidative stress. (62, 63). UV radiation affects a range of molecules in living tissues including DNA. Therefore, using biological exposure markers could give us many advantages in terms of understanding exposure estimates. In addition, it would give us the ability to validate other measures of exposure and also increase the knowledge of intermediate steps in pathways regarding the exposure to disease. UV response is a stress response as DNA damage when the mammalian cells are exposed to Ultraviolet radiation. Several transcription factors are involved in such induction, including AP-1, NF-kB and p53 (64-66). It seems that only p53 is directly induced in response to UV-damaged DNA. On the other hand, AP-1 and NF-kB are activated through signal transduction cascades which appear to be elicited by effects of short wavelength UV on the cell surface, separately from DNA damage (67, 68). Specific signal-responsive protein kinases are of utmost important in such pathways. It should be mentioned that the protein kinase involved in NF-kB activation is not molecularly identified. The activation of AP-1 and NF-kB have both been suggested to play roles in diverse and conflicting responses including apoptosis, tumor promotion, protection against radiation induced damage and finally, aging (69-71). Since UV light is a common carcinogen and genotoxic agent to which patients are exposed, understanding the function of UV activated protein kinases seems to be of utmost importance for both physiological and clinical purposes.
6. Conclusion:
Ozone layer depletion has resulted in many harmful events. One of which is skin cancer. UV exposure in specific parts of the planet with lower protection levels due to the ozone layer depletion has resulted in different types of skin cancer. Studying the molecular pathways that are related to the occurrence and progress of different kinds of cancers is without debt, a crucial matter and needs urgent and in depth further studies, for both research and clinical purposes.

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