

Minireview Article

Reactive Sulphur Species and Exposome: A Perspective on Potential Role in Alleviating UV-induced Stress

ABSTRACT

Exposome is a field of study in identifying and recognizing the impact of environmental exposures towards a person health and development starting from prenatal period onward. Oxidative stress due to overproduction of reactive oxygen species (ROS) in the body is commonly associated as one of the underlying mechanisms of ultraviolet radiation (UV)-induced damage in the skin. Evidently, an overexposure of UV radiation will cause disturbance in balancing the ROS level in the body leading to damaging effects such as protein modifications, lipid peroxidation, and DNA mutation which will progress into cell death. Reactive sulphur species (RSS) are molecules that have the capability of oxidizing or reducing biomolecules under physiological conditions. In this review, we will discuss on the mechanism of UV-induced cellular damage and relate on the potential role of RSS in combating oxidative stress induced by UV exposure.

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Keywords: exposome, ultraviolet radiation, reactive sulphur species, oxidative stress, skin

INTRODUCTION

1. EXPOSOME 1.1 Overview of exposome

The world is moving towards the personalized medicine era ([ref](#)). Huge efforts and money were invested in sequencing and mapping human genome for better understanding of the gene expression, protein function and metabolic processes which have been implicated with major chronic diseases. Genetic variability is commonly implicated to the biological detoxification system which is known as metabolic polymorphism. Despite of its low penetrant, metabolic polymorphism is commonly existed which it is expected that it can significantly contribute to the population disease burden [1]. Therefore, venturing into pharmacogenomic is thought to offer high precision measure to be employed in the management of the diseases. In the context of "non-genetic", broad range of pathological conditions has been associated with the exposure towards the environmental electrophiles yet nonetheless much aspects of current fundamental understanding on such occurrence remains ill-defined [2]. The concept of exposome was first coined by ~~Professor~~ Wild in 2005 as a "highly dynamic and variable entity that evolves during the lifetime of a person". Exposome refers to a variety of exposures ranging from environment and biological residues such as radiation, chemical or biological agents, and determinants from conception to death [3-5]. Exposome is divided into three classifications; internal (such as ageing, hormonal system and metabolic processes), specific external (for example chemical waste, radiation and lifestyle factors), and general external (for instance socioeconomic status and physiological situations) [6-7]. Exposome is an intricate concept that r

complex approaches as it involves a lifetime exposure, from prenatal period onwards. Hence, a continuous assessments of multiple time exposure over the course of a person's life are required to measure the exposome to scientifically understand on its nature and the possible outcomes [8]. The life sequence exposome is often derived by an exposure at certain time points and the health impacts of certain exposure may be different [8]. In fact, co-exposure and involvement of other elements can somewhat change the severity of a condition due to interactive or synergistic effects [9]. In 2016, it

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was estimated that approximately 80% of chronic diseases recorded worldwide potentially originated as the negative effects of exposome (ref). The genome wide related diseases, on the other hand, are less than 20% [10]. Indeed, exposome offers important broad and transdisciplinary/trans disciplinary studies permit the discovering factors lead to complex chronic diseases over time.

1.2 Ultraviolet (UV) radiation as a skin exposome

The skin is the largest organ in human and plays as the most important role as primary defense system against harsh external environment and pathogens [11]. Sun radiations comprise of UV radiation, infrared radiation, and visible light (ref). Exposure to these sun radiations is a naturally occurring process. In fact, exposure to UV radiation has been associated with several health benefits [12]. For example, sufficient amount of UV exposure is good for vitamin D synthesis. Vitamin D supplies calcium to the body which is very important in maintaining the skeletal health [13]. However, overexposure of UV can cause many skin pathological conditions, for example malignant melanoma and skin cancer as reported in previous studies [14-15]. According to the US Environment Protection Agency (EPA), the UV index scale is divided into several categories; 0-2 (low), 3-5 (moderate), 6-7 (high), 8-10 (very high) and more than 11 (extreme). UV index increases with increasing altitude and decreasing latitude. In Europe, the UV index is recorded high during summer and can reach up to 12.1 in South Spain [16]. However, in tropical countries, the sun shines directly and experience high temperature all year round. The average UV index recorded in these countries can be more than 7, which is close to "very high" category [17]. UV exposure is high in some of these regions, but the skin pigmentations of the inhabitants is often associated with the low incidence of melanoma compared to the people of other regions [18]. Statistically, almost 5 million people in the United States undergo skin cancer treatment each year that cost approximately USD 8.1 billion [19].

Indeed, the most general risk factor for skin cancer that is modifiable is UV exposure [20]. UV radiation is part of the exposome that contribute to the emerging of deleterious effects on human skin including sunburn, cancer, immune suppression, and photoaging which leads to individual premature aging [4]. UV photons is as a part of the electromagnetic spectrum and it falls between gamma and visible light radiation wavelengths [21]. Ozone (O_3) plays a role as selective filters that absorb UVC and UVB which make up the radiation of UVA (90- 95%) to reach the earth [22]. Some UVB (5-10%) can pass through the ozone layer and reach to the earth [21]. UVC radiation with the highest energy and shortest wavelength induces the mutagenic DNA lesions to form and substantially increases the risk of emerging cancer when the skin is exposed to it [21,23]. However, almost no UVC can penetrate atmosphere of the earth as its rays are completely hindered by the ozone layer which makes the effect of its radiation less concerning [22,24]. UV radiation penetrates into the skin depending on the wavelength of each type (35). UVA with a longer wavelength and least energetic photons penetrates deeply into the dermis while UVB with a shorter wavelength is almost entirely absorbed by epidermis and relatively slight that reaches to the dermis [21].

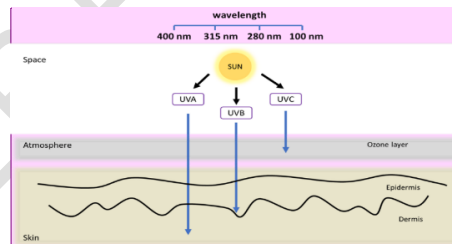


Figure 1: The pathways of UV radiation through atmosphere into the skin

2. MECHANISM OF UV-INDUCED CELLULAR DAMAGES

UV radiation possesses an important ionizing molecular property and chemical reaction induction makes it distinguishable from visible rays. It performs as a powerful environmental mutagen by giving harm to components of cells, which can contribute to immunodeficiency-related diseases and causes fatal diseases such as cancer [22]. Immunosuppression induced by UV leads to skin cancer due to DNA damage and inhibited skin defense mechanisms via multiple pathways [24]. In cellular DNA, the most common UV-induced lesions are dimeric photoproducts which involves adjacent pyrimidine bases [25]. When the UV-induced DNA damage is too severe and not able to be repaired, p53 as a protein that has a significant role in apoptotic pathways is activated [26]. Therefore, this will lead to induction of apoptosis to eliminate damaged cells. UVB was identified to cause damage to epidermal proteins. Aromatic amino acids such as tryptophan (Trp), tyrosine (Tyr), and cysteine largely absorb UVB [27,28]. The absorption can lead to excited species. Several

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additional interactions involving excited Trp and Tyr are proposed, which could result in skin cell constituent disintegration and oxidative stress [27].

UV radiation is commonly known to cause DNA injury in a manner of oxygen-dependent involving photosensitization. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) induced by UVA radiation will lead to single strand breaks (SSBs) and base lesions such as 8-oxo-7,8-dihydroguanine (8-oxoGua) [25]. UVA-excited photosensitizers can produce singlet oxygen that can further reacts with protein and resulting in protein modification [27]. Aggregation of modified proteins can cause harm to the cell and associated with many diseases and aging process.

UVA and UVB are both capable of generating comparable singlet oxygen (1O_2) and/or free radicals either directly when interacting with components of the cell or when there is presence of photosensitizers [29]. At their ground state or lowest energy, these photoactive chemicals absorb incident radiation (UVA/UVB) within their absorption range. For instance, UVA light penetrates the skin and cellular chromophores such as bilirubin, urocanic acid, melanin, riboflavins, heme, pterins, and porphyrin absorb the UVA light [30–32]. Then, the photons/energy absorbed by these photosensitizers give rise to singlet excited state which is the excited state of chromophores [33]. An excited state molecule is created from the energy of the absorbed photon. This molecule is not stable under ambient conditions [29]. Energy is transferred from excited species to adjacent intracellular chemical moieties, especially molecular oxygen (O_2), when returning to the ground state, and thus convert it into ROS (e.g. superoxide, singlet oxygen, hydroxyl radical or hydrogen peroxide) [29,32]. These ROS act on plasma membranes rich in lipids and begin a reaction known as lipid peroxidation [32].

ROS are chemical species that formed from the incomplete oxygen reduction, namely superoxide anion (O_2^-), hydroxyl radical (HO^\cdot), and hydrogen peroxide (H_2O_2) [34]. ROS contains unpaired valence electrons or unstable bonds [35]. ROS is commonly described as electrophilic, that tend to attack other molecules to achieve stabilization, particularly the nucleophiles that rich with electrons. ROS reactivity has been noted to be involved in various essential physiological processes. ROS plays a part in different signaling cascades for instance, response to stimulation of the growth factor and regulation of inflammatory responses [35]. Besides, they also responsible in regulating numerous biological processes such as immune function, thyroid function and cognitive function. In contrast, ROS can also cause permanent functional modifications or even complete damage to cell as it reacts easily with carbohydrates, proteins, lipids, and nucleic acids at high concentrations [35]. Overoxidation of protein thiol group, which leads to the formation of sulfinic acid (RSO_2H) and sulfonic acid (RSO_3H) have been implicated with irreversible posttranslational modification [36–38]. Such modification can render the enzymes or proteins to be dysfunctional. Moreover, nucleotides are prone to mutation by ROS (e.g., HO^\cdot , H_2O_2 and O_2^-) generated by UV radiation [22]. Nucleotide bases oxidation stimulates in mismatch of base pair resulting to mutagenesis [39–40]. For instance, base mispairing prompted by ROS is guanine to thymine transversion. This occur when the 8th position of guanine undergo oxidation, forming 8-hydroxy-2'-deoxyguanine (8-OHdG) [40–41]. Instead of pair with cytosine, 8-OHdG will tend to pair with an adenine thereby G/C pair will be mutated into an A/T pair [21].

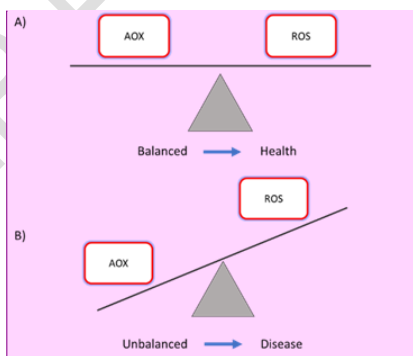


Figure 2: (A) Equilibrium between antioxidant (AOX) defence and reactive oxygen species (ROS) production. (B) The imbalance between ROS and AOX, which is correlated with many pathologic conditions.

3. REACTIVE SULPHUR SPECIES (RSS)

3.1 Overview of RSS

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Endogenous reactive sulphur species (RSS) was recently discovered in an appreciable amount in body and plays vital role in cell signalling, metabolic regulation and redox homeostasis [42]. RSS can be described as a redox-active sulphur-containing molecule capable of reducing or oxidizing biomolecules under physiological conditions [43]. RSS are good reducing agents and nucleophiles in their most reduced state (S^{2-}) and these S^{2-} species may convert to S^{1-} state by undergoing a one electron oxidation to generate thiyl radicals (RS^{\cdot}), or sulphhydryl (HS), that combined to form hydrogen disulphide (HSSH), disulphides (RSSR), or related hydrosulphides/persulphides (RSSH) [42].

The RSS are biologically present in different forms including hydropersulphide (RSSH), organic persulphides (RSSR) and inorganic persulphide (HSSH), and corresponding higher order polysulphides ($HSS_{(n)}SH$, $RSS_{(n)}SH$ and $RSS_{(n)}SR$) with $n > 1$ and R ranges from low- to high molecular compounds [44]. RSS are stronger acids, nucleophiles and reductants compared to the corresponding thiols. The only plausible explanation underlying this mechanism is due to the α -effect. To current understanding, α -effect is described as the presence of unshared electron pairs or in this case the sulfur atoms adjacent to the nucleophilic centre causing the RSS to exert higher nucleophilicity compared to the traditional thiol [45]. Consequently, the longer sulphur chain present, the higher nucleophilicity it will become. Moreover, the pK_{a1} value of a sulfur-containing compound is inversely proportional following the number of sulfur atom [46].

The mitochondrial cysteinyl-tRNA (CARS2) was discovered to play a major role in producing endogenous low- (such as cysteine persulphides, CysSSH, cysteine trisulphides, CysSSSH) and high molecular weight RSS (such as protein bound polysulphides, RS_nSH) [47]. Production of cysteine persulphide (CysSSH) is catalysed by CARS2 from CysSH and it can also directly incorporate the persulfidated amino acid into proteins [48]. Other enzymes such as cystathionine β -synthase (CBS), cystathionine γ -lyase (CSE), thioredoxin and sulfide:quinone reductase have been reported to produce low molecular weight RSS as well [49-52]. Till date, the RSS has been recognized to be critically involved in several critical physiological function including redox signaling and xenobiotics metabolism [53].

2.3.2 RSS and UV-induced cellular damage

RSS is highly nucleophilic and can readily scavenges ROS and various electrophiles [54]. For instance, RSS reacts with 8-nitroguanosine 3'-5'-cyclic monophosphate (8-nitro-cGMP). 8-nitro-cGMP is a secondary messenger of nitric oxide (NO) signaling mechanism derived from the nitration of cGMP by NO [55]. The reaction of RSS with 8-NO-cGMP can result in the formation of 8-SH-cGMP, with nitrite anion being released [56]. In fact, several studies have indicated that RSS including the glutathione and hydrogen sulphide-derivatives contribute to the cellular detoxification system. RSS has been known to protect the cells against electrophiles such as heavy metals [54,57-58].

Our skin owns a dynamic and powerful network of antioxidant molecules that detoxify reactive species to resist free radical modifications towards DNA and other macromolecules. GSH is undoubtedly one of the highly significant molecules with antioxidant properties in skin cells. The sulphhydryl group of GSH performs a leading role in detoxification and antioxidation of exogenous and endogenous compounds, including preserving the intracellular redox status [59]. As a reducing agent, GSH donates electrons to another reactive molecules which stabilize the reactivity of free radical. GSH is oxidized to GSSG during the process but with the presence of glutathione reductase, it can be reduced to its basal state through NADPH as an electron donor and being recycled [59]. Hence, both forms (GSH and GSSG) of glutathione can be found in cells. Oxidative stress can be indicated when the reduced to oxidized glutathione ratio become abnormal [21]. The action of glutathione against ROS is commonly known to be promoted by interactions with glutathione reductase and glutathione peroxidase [59]. With recent evidences indicating the existence of RSS in a form of free RSS or protein-bound RSS, that can readily react with oxidative stress somewhat can shift our understanding on available cellular protection mechanisms. The RSS can provide better protection against overoxidation of protein. As aforementioned, the formation of RSO_2H and RSO_3H on cysteine moieties is an irreversible enzyme or protein modification that can lead to dysfunction. However, polysulfurated cysteine residue, for example $RS-S-SH$, whenever exposed to overoxidation, can form $RS-S-SO_nH$ ($n = 1-3$), to which such derivative can somewhat be reduced back to the original thiol [60].

The skin also possesses several other both enzymatic and non-enzymatic antioxidant mechanisms. Catalase for example is an enzyme that has been attributed with the function of metabolizing H_2O_2 to H_2O , mitigating the ROS-induced toxicity. Interestingly, Olson and his team further discovered that catalase has another function as a sulfide-sulfur oxido-reductase, making catalase as another key regulator of RSS [61]. The team further work on another antioxidant enzyme, superoxide dismutase (SOD), attempting to see whether the enzyme possible involvement in RSS metabolism. Unlike catalase, the SOD was found to unidirectionally oxidize H_2S and produce little amount of H_2S_2 [62]. The Kelch-like ECH-associated protein 1 (KEAP1)-NF-E2-related factor 2 (Nrf2) is a master regulator of antioxidant and detoxification enzymes [63]. KEAP1 is a repressor protein of Nrf2 and it contains 5 cysteine residues in its intervening region that has been implicated with KEAP1-dependent Nrf2 ubiquitination [64]. Oxidative insult or covalent modification on these cysteine residues was identified the cause of dissociation of Nrf2 from the KEAP1 [65]. The loss of Nrf2 has been associated with increased risk of developing cutaneous squamous cell carcinoma in mice [66]. The KEAP1-NRF2 system however, was said to only

prevent the harmful effects of UV irradiation caused by the UV-A that has long wavelength, compared to UV-B or UV-C. UV-A induces cellular damages through ROS-dependent pathway which leads to KEAP1-Nrf2 orchestrates the activation of sequential antioxidant systems [67]. Interestingly, Nrf2 can work with CSE in a parallel manner in the repression of the electrophile-induced toxicity. Nrf2 detoxifies electrophiles via formation of GSH adducts, while the CSE mediates sulfur adduct formation by RSS, suggesting that there is a canonical and non-canonical pathway of detoxification of environmental electrophiles conducted by Nrf2 and CSE respectively [68].

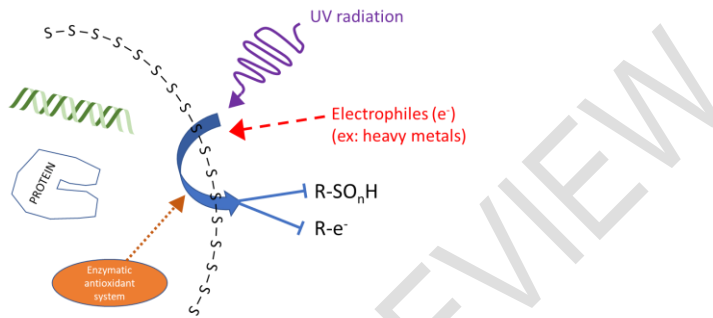


Figure 3: Potential role of RSS in alleviating UV-induced cellular damage.

3. CONCLUSION

Several protective interventions including the use of pharmaceutical products and dietary antioxidants are commonly recommended in managing the risk of UV exposure. The application of both endogenous and topical photoprotection is sought to create a better prevention strategy in this scenario. In this review, the authors provided a brief perspective on the potential role of RSS in preventing and alleviating UV-induced damage (Figure 3). The study of polysulfidomic is indeed far from fully understood. There is much to understand on sulphur biology and how it potentially contributes in understanding pathogenesis related to UV-exposure. Despite a lot of research on the crosstalk between ROS and RSS have been done, the direct relationship between UV irradiation with endogenous RSS will be an interesting subject to look into. Indubitably, precise evaluation on the role of RSS in regulating ROS-dependent UV-induced dermal toxicity still requires detailed studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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