Green tea and skin cancer: photoimmunology, angiogenesis and DNA repair

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Abstract

Human skin is constantly exposed to numerous noxious physical, chemical and environmental agents. Some of these agents directly or indirectly adversely affect the skin. Cutaneous overexposure to environmental solar ultraviolet (UV) radiation (290–400 nm) has a variety of adverse effects on human health, including the development of melanoma and nonmelanoma skin cancers. Therefore, there is a need to develop measures or strategies, and nutritional components are increasingly being explored for this purpose. The polyphenols present in green tea (*Camellia sinensis*) have been shown to have numerous health benefits, including protection from UV carcinogenesis. (−)-Epigallocatechin-3-gallate (EGCG) is the major and most photoprotective polyphenolic component of green tea. In this review article, we have discussed the most recent investigations and mechanistic studies that define and support the photoprotective efficacy of green tea polyphenols (GTPs) against UV carcinogenesis. The oral administration of GTPs in drinking water or the topical application of EGCG prevents UVB-induced skin tumor development in mice, and this prevention is mediated through: (a) the induction of immunoregulatory cytokine interleukin (IL) 12; (b) IL-12-dependent DNA repair following nucleotide excision repair mechanism; (c) the inhibition of UV-induced immunosuppression through IL-12-dependent DNA repair; (d) the inhibition of angiogenic factors; and (e) the stimulation of cytotoxic T cells in a tumor microenvironment. New mechanistic information strongly supports and explains the chemopreventive activity of GTPs against photocarcinogenesis.

Keywords: Green tea polyphenols; Photocarcinogenesis; DNA repair; Cyclobutane pyrimidine dimer; Immunosuppression; Contact hypersensitivity; Angiogenesis; IL-10; IL-12

1. Introduction

Human skin is the largest organ of the body (comprising a surface area of approximately 1.5–2.0 m^2), is an effective barrier against the detrimental effects of environmental and xenobiotic agents and thus protects the internal organs of the body. It is the first defense barrier of the body from external physical, chemical and environmental pollutants, including solar ultraviolet (UV) radiation [1]. The major layers in the skin include the epidermis, the dermis and the hypodermis (Fig. 1). Skin cancer is mainly associated with the epidermal layer and its cell types. The human epidermis is quite thick and comprises about 8–15 cell layers (Fig. 1A), while in laboratory animals, such as in mice, it is only two to three cell layers thick (Fig. 1B).

2. Solar UV radiation

Among several environmental and xenobiotic factors, exposure to solar UV radiation is the key factor in the initiation of skin disorders, such as wrinkling, scaling, dryness, mottled pigment abnormalities consisting of hypopigmentation and hyperpigmentation, and skin cancers [2,3]. Overexposure to solar UV radiation (290–400 nm) has a variety of adverse effects on human health, including basal and squamous cell carcinomas [4,5], melanoma [4,6], cataracts [5,7], photoaging of the skin [8] and immune suppression [9]. Such consequences are attracting considerable attention because of an alarming increase in the incidence of UV-radiation-induced skin and eye disorders. On the other hand, the skin is endowed with endogenous

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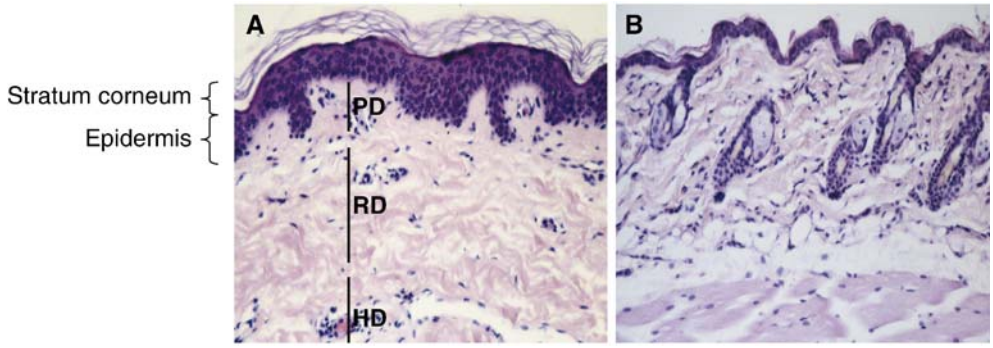

Fig. 1. The morphology of human skin (A) and mouse skin (B). The human epidermis is thicker than the mouse epidermis. PD = papillary dermis; RD = reticular dermis; HD = hypodermis.

defense systems that limit the potential damage caused by solar UV radiation. Light scattering by the stratum corneum, absorption of light by melanin, the presence of antioxidant defense methods and repair of UV-damaged DNA by repair enzymes can decrease the deleterious effects of UV radiation on the skin. However, these endogenous means of photoprotection are not fully capable of counteracting all adverse effects of overexposure to UV radiation.

3. UV radiation and skin cancer: strategies for prevention

Nonmelanoma skin cancers, including basal and squamous cell carcinomas, represent the most common malignant neoplasms in humans, particularly in Caucasians. Although several environmental and genetic factors contribute to the development of skin cancers, chronic exposure to UV radiation is an important etiological agent for both nonmelanoma and melanoma skin cancers and accounts for approximately 1.3 million new cases of skin cancers each year in the United States (reviewed in Katiyar [10] and Baliga and Katiyar [11]). Thus, skin cancers are currently a major burden on public health and health care expenditures. Therefore, the development of effective chemopreventive agents and strategies that can reduce or control the risk of UV-induced skin cancer is required to address this pressing public health issue.

In recent years, there has been great interest in the use of dietary supplements that are derived from naturally occurring botanicals for the photoprotection of the skin, including protection from skin cancers. Dietary botanicals, which possess anti-inflammatory, immunomodulatory and antioxidant properties, are among the most promising groups of compounds that can be exploited as ideal chemopreventive agents for skin cancer [11]. Among the agents that have been identified as having potential chemopreventive activities are retinoids [12,13], green tea polyphenols (GTPs) [10,11], grape seed proanthocyanidins [11,14,15] and silymarin [11,16]. Here, we will particularly discuss the beneficial effects of GTPs on skin photoprotection.

4. Green tea

Next to water, tea (*Camellia sinensis*) is the most commonly consumed beverage worldwide because of its characteristic aroma, flavor and health benefits [17]. Beverage-grade tea is manufactured from the leaves and buds of the plant *C. sinensis* and is commercially available in three forms: green, black and oolong tea [17–19]. Of the total tea production, approximately 78% is consumed as black tea mainly in Western and some Asian countries, while 20% is consumed as green tea primarily in Asian countries, including China, Japan, Korea and India. Approximately 2% is consumed in the form of oolong tea, mostly in southeastern China [17–19]. The basic steps of manufacturing the various forms of teas are similar, except in the development of their aroma and in the fermentation process, which is dependent on the oxidation states of catechins present in tea leaves. The term *green tea* refers to the product manufactured from the fresh leaves of the tea plant by drying and steaming at elevated temperatures, with care taken to avoid the oxidation and polymerization of catechin derivatives, which are commonly called polyphenolic components.

5. GTPs

The catechins present in green tea are commonly called polyphenols and are flavanols in nature. The major catechins found in green tea are: (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin-3-gallate and (−)-epigallocatechin-3-gallate (EGCG). The chemical structures of these catechins or polyphenols are shown in Fig. 2A. These polyphenols are antioxidant and anti-inflammatory in nature and have been shown to possess anticarcinogenic activity in several in vitro and in vivo systems [10,11]. Of these major polyphenols, EGCG has been shown to be the major and most effective chemopreventive agent and has been extensively studied (e.g., its use in skin photoprotective activity) in several disease models. It is noteworthy to mention that, during the manufacturing process of black tea, catechin derivatives are oxidized, polymerized and converted into a less well-defined group of compounds known as thearubigens (Fig. 2B). Thearubigen fraction is a mixture of substances

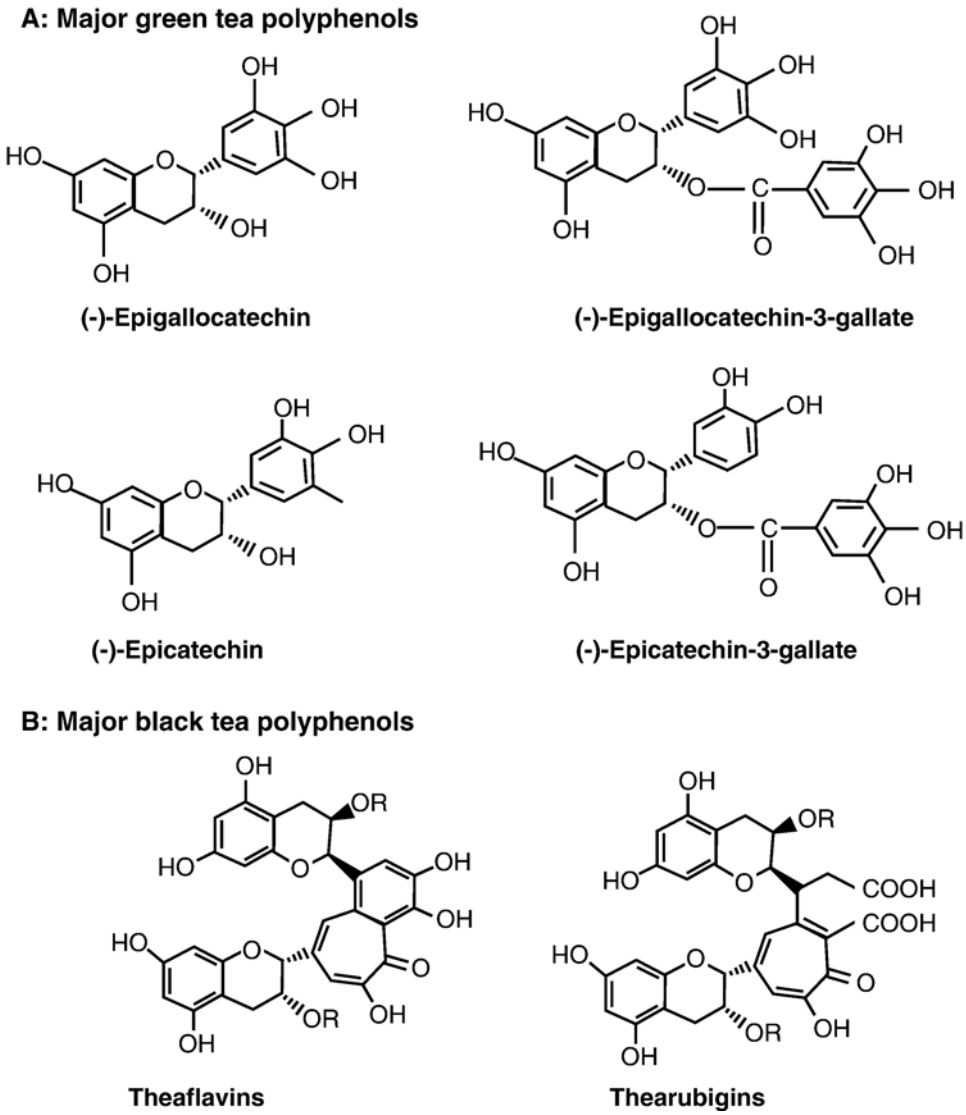

Fig. 2. Chemical structures of major polyphenols present in tea. (A) Major epicatechin derivatives or polyphenolic constituents present in green tea. (B) Major polyphenolic constituents present in black tea. R = galloyl group.

with a molecular weight distribution of 1000–40,000 and accounts for about 15% of the dry weight solids of black tea [17]. Experimental evidence from several in vitro and in vivo studies indicates that GTPs are better chemopreventive agents than those present in black tea. Hence, extensive studies were conducted with GTPs. Here we describe the antiphotocarcinogenic potential of GTPs and their mechanism of action, especially the recent developments on photoimmunology, antiangiogenic effects and DNA repair mechanism in the prevention of photocarcinogenesis by GTPs or EGCG, as discussed below.

6. GTPs as nutrients for the skin

Green tea is consumed as a beverage for its health benefits and thus can be considered a nutritional supplement. However, as far as the skin is concerned, most skin care lotions or sunscreens are applied topically for health benefits on the skin and skin cells. This indicates that the skin has the ability to consume its nutrition through the topical application of nutrients. Therefore, it is important to mention and understand that nutrition for the skin can be provided through both oral and topical administration. We should not be confused on these modes of nutrition, particularly in the case of the skin and its health.

7. GTPs prevent photocarcinogenesis

Extensive in vitro and in vivo studies have been conducted to determine the anti-UV carcinogenic effects of green tea. It has been found that the oral administration of GTPs (a mixture of polyphenolic components isolated from green tea) in the drinking water of mice results in significant protection against UV-induced skin carcinogenesis in terms of tumor incidence, tumor multiplicity and tumor size, compared to those mice that were not given GTPs in

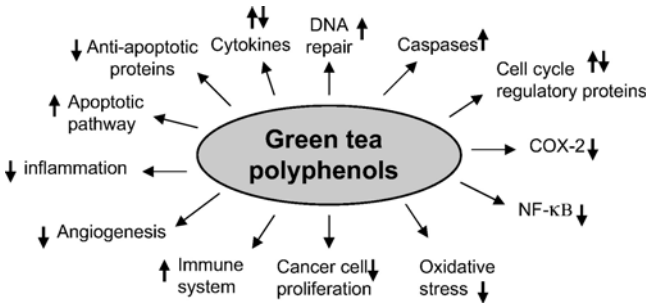

Fig. 3. Molecular targets of GTPs. (↑) Up-regulation; (↓) down-regulation.

drinking water [10,11,18,20]. The mice that were given crude water extracts of green tea as a sole source of drinking water developed a lesser number of tumors compared to those mice that were not given water extracts of green tea [21,22]. The administration of GTPs in drinking water or the topical application of EGCG also induced partial regression or inhibition of the tumor growth of established skin papillomas in mice [23]. The long-term oral administration or topical application of GTPs or EGCG did not show signs of visible toxicity. The oral administration of green tea as a sole source of drinking water resulted in a decreased number of papillomas (>80%), keratoacanthomas (53%) and squamous cell carcinomas (32%) induced by the chronic exposure of mice to UVB radiation. Our laboratory developed a hydrophilic-ointment-based formulation for the topical treatment of GTPs [24]. In this formulation, the topical treatment of SKH-1 hairless mice with EGCG resulted in exceptionally high protection from photocarcinogenesis. Protection from photocarcinogenesis was determined by tumor incidence (60% inhibition), tumor multiplicity (86% inhibition) and tumor growth, in terms of total tumor volume per group (95% inhibition) [24]. These results indicated that the use of EGCG in topical formulation might increase penetration or absorption capacity inside the skin layers and that the presence of a higher concentration may be responsible for higher photoprotection. The antioxidative or photoprotective effects of GTPs or EGCG by topical treatment were greater than those by oral administration, which may be due to the higher content of these polyphenols in topical application [25]. This information also suggests that nutrient supply to the skin through topical treatment may be better than oral administration. Record and Dreosti [26] have shown that green tea can protect against both UVA- and UVB-radiation-induced skin cancers in mice. Experimental studies conducted in in vitro and in vivo models indicate that GTPs or EGCG prevents photocarcinogenesis following several mechanisms involving multiple molecular targets, as summarized in Fig. 3.

8. GTPs prevent UVB-induced immune suppression through interleukin (IL) 12 induction

The immunosuppressive effects of solar UV radiation, in particular UVB, are well established, after having been demonstrated most clearly in the inhibition of contact hypersensitivity (CHS) induced by contact allergens, which is a prototypic T-cell-mediated immune response [27,28]. Many of the adverse effects of solar UV radiation on human health, including exacerbation of infectious diseases, premature aging of the skin and induction of skin cancer, are mediated, at least in part, by the ability of UV radiation to induce immune suppression [29–31]. As UV-induced immunosuppression is considered to be a risk factor for the induction of skin cancer [32,33], the prevention of UV-induced immunosuppression represents a potential strategy for the management of skin cancer. We have shown previously that topical treatment of C3H/HeN mice with GTPs resulted in significant protection against local and systemic models of CHS where 2,4-dinitrofluorobenzene was used as a contact sensitizer [34]. The chemopreventive effect of GTPs on the UVB-induced suppression of CHS response was dependent on the dose of GTPs used. Similar effects were also noted when water extracts of green tea were given to mice as the sole source of drinking water. Among the four major epicatechin derivatives present in GTPs, EGCG was found to be the most effective polyphenol affording protection against the UVB-induced suppression of CHS. The mechanisms involved in UV-induced immune suppression differ greatly. There are studies defining the role of the immunoregulatory cytokine, IL-12, in the induction and elicitation of CHS. CHS has been considered to be a Th1-mediated immune response [35]. Langerhans cells, which are critical antigen-presenting cells (APCs) in the induction phase of CHS [36], have been described as an additional source of IL-12 production. We were interested in determining whether topical treatment of EGCG blocks the UVB-induced infiltration of $CD11b^+$ cells (cell surface markers of macrophages and neutrophils) and whether it down-regulates IL-10 or up-regulates IL-12 in the skin and/or draining lymph nodes (DLNs) in mice, thereby preventing UV-induced immune suppression. The prevention of UVB-induced immunosuppression by EGCG treatment was found to be associated with a reduction in the number of infiltrating $CD11b^+$ cells in UVB-irradiated skin [37]. Hammerberg et al. [38,39] demonstrated that blockade of infiltrating leukocytes with anti-CD11b antibody or treatment with soluble complement receptor type I inhibited UV-induced immune suppression and tolerance induction in C3H/HeN mice. Therefore, it seems that the inhibition of UV-induced immunosuppression by EGCG is mediated, at least in part, through the inhibition of infiltrating $CD11b^+$ cells in the UVB-irradiated mouse skin.

IL-10 possesses immunosuppressive activity and inhibits antigen presentation [40,41] in in vitro and in vivo systems. In UVB-irradiated skin, IL-10 is primarily secreted by activated macrophages [42,43], thereby down-regulating CHS responses. In vivo studies have demonstrated the effects of IL-10 on T-cell-mediated reactions. Intraperitoneal administration of IL-10 in mice inhibits delayed-type hypersensitivity responses [44], whereas intraperitoneal

injection of anti-IL-10 antibody in mice prevented UV-induced tolerance induction [45]. In accordance with these observations, the treatment of mouse skin with EGCG resulted in a decreased level of IL-10 in UV-irradiated skin, as well as in DLNs, compared to mice that were not treated with EGCG. The number of IL-10-producing cells in UV-exposed skin increased in comparison to the skin not exposed to UV [37]. The treatment of mice with EGCG significantly reduces the number of IL-10-producing cells, which is accompanied with a reduction in infiltrating activated macrophages. This action of EGCG suggests a possible mechanism by which EGCG prevents UVB-induced immune suppression in mice [37].

IL-12 is another immunoregulatory cytokine. It regulates the growth and functions of T cells [46] and especially augments the development of Th1-type cells by stimulating the production of IFN-γ [47–49]. It has been shown that intraperitoneal injection of recombinant IL-12 in mice prevents UV-induced immune suppression [50]. These studies imply that a cytokine imbalance between Th1 and Th2 may be responsible for the development of UVB-induced immunosuppression. The topical treatment of EGCG prior to UVB exposure resulted in increased levels of IL-12 in the skin and in DLNs compared to non-EGCG-treated but UVB-exposed C3H/HeN mice [37]. Increased levels of IL-12 may contribute to the stimulation of immune responses; therefore, it appears that EGCG treatment is capable of promoting the development of Th1 immune response through IL-12 induction and may be one of the mechanisms responsible for inhibiting UVB-induced immune suppression in mice. To further confirm the role of IL-12 in the EGCG-mediated prevention of UV-induced immunosuppression, IL-12 knockout (KO) mice were used. Recently, Meeran et al. [51] have shown that topical treatment of EGCG prevented UV-induced suppression of CHS in wild-type (WT) mice, as shown by significant enhancement of CHS response (ear swelling). In contrast, UV-exposed IL-12 KO mice remained unresponsive to DNFB despite the application of EGCG on mouse skin, indicating that the immunopreventive effect of EGCG on UV-induced suppression of CHS requires IL-12 or is mediated through IL-12. To further confirm whether the prevention of UV-induced suppression of CHS by EGCG requires IL-12, WT mice were treated intraperitoneally with anti-IL-12 monoclonal antibody. In EGCG-treated mice, the intraperitoneal injection of anti-IL-12 antibody significantly reversed or blocked the preventive effect of EGCG on the UV-induced suppression of CHS. These studies provide convincing evidence that the prevention of UV-induced suppression of CHS by EGCG is mediated, at least in part, through IL-12.

9. Inhibition of UV-induced immunosuppression by green tea is mediated through IL-12-dependent DNA repair

UV-induced DNA damage, particularly in the form of cyclobutane pyrimidine dimers (CPDs), is an important molecular trigger for UV-induced immunosuppression [52], and reduction in UV-induced CPDs through the application of DNA repair enzymes can prevent UV-induced immunosuppression [53,54]. IL-12 has the ability to remove or repair UV-induced CPDs [55]. Schwarz et al. [56] reported that the prevention of UV-radiation-induced immunosuppression by IL-12 is dependent on DNA repair and acts through the induction of nucleotide excision repair (NER) mechanism. Based on these observations, our laboratory conducted experiments to examine whether IL-12 contributes to the ability of EGCG to prevent UV-induced immunosuppression by inducing the repair of photodamaged DNA [51]. The effect of EGCG was determined on UV-induced CPDs in WT mice and was compared with that in IL-12 KO mice. Twenty-four hours after UV irradiation, it was observed that the numbers of CPD^+ cells were significantly lower in EGCG-treated WT mice than in WT mice not treated with EGCG but exposed to UVB. As anticipated, the UVB-induced DNA damage in IL-12 KO mice that had been treated with EGCG did not differ from that in IL-12 KO mice that had not been treated with EGCG [51]. This information suggests that EGCG-induced IL-12 may contribute to the repair of UV-damaged DNA and that the difference in DNA repair between WT and IL-12 KO may be due to the absence of IL-12 in IL-12 KO mice.

It is recognized that UV-induced DNA damage is an important molecular trigger for the migration of APCs (i.e., Langerhans cells in the epidermis) from the skin to the DLNs. DNA damage in APCs impairs their capacity to present Ag, which in turn results in lack of sensitization [57]. CPD-containing APCs have been found in the DLNs of UV-exposed mice [58]. These APCs were identified to be of epidermal origin and to exhibit an impaired Ag presentation capacity. Since the treatment of EGCG induces IL-12 in mice [37] and since IL-12 has the capacity to induce DNA repair [55], the effect of EGCG on the migration of CPD^+ cells from the UV-exposed skin to the DLNs was studied. Immunohistochemical analysis of CPD^+ cells in DLNs after 36 h of UV irradiation showed significant numbers of CPD^+ cells in the DLNs in both UV-exposed WT and IL-12 KO mice; however, the numbers of CPD^+ cells in the DLNs of UV-exposed IL-12 KO mice were approximately fourfold higher than those in the DLNs of their WT counterparts. The lower percentage of CPD^+ cells in the DLNs of UV-exposed WT mice compared to that in IL-12 KO mice may be attributable to the presence of endogenous IL-12 in WT mice at levels that are capable of the partial removal of damaged DNA in migrating cells. Treatment with EGCG resulted in a significant reduction in the numbers of CPD^+ cells in the DLNs of UV-exposed WT mice compared to UV-exposed WT mice that did not receive EGCG (summarized in Fig. 4). In contrast, there was no significant difference in the number of CPD^+ cells in the DLNs between EGCG-treated and non-EGCG-treated UV-exposed IL-12 KO mice. This observation further supports the evidence that the reduction in the numbers of CPD^+ cells

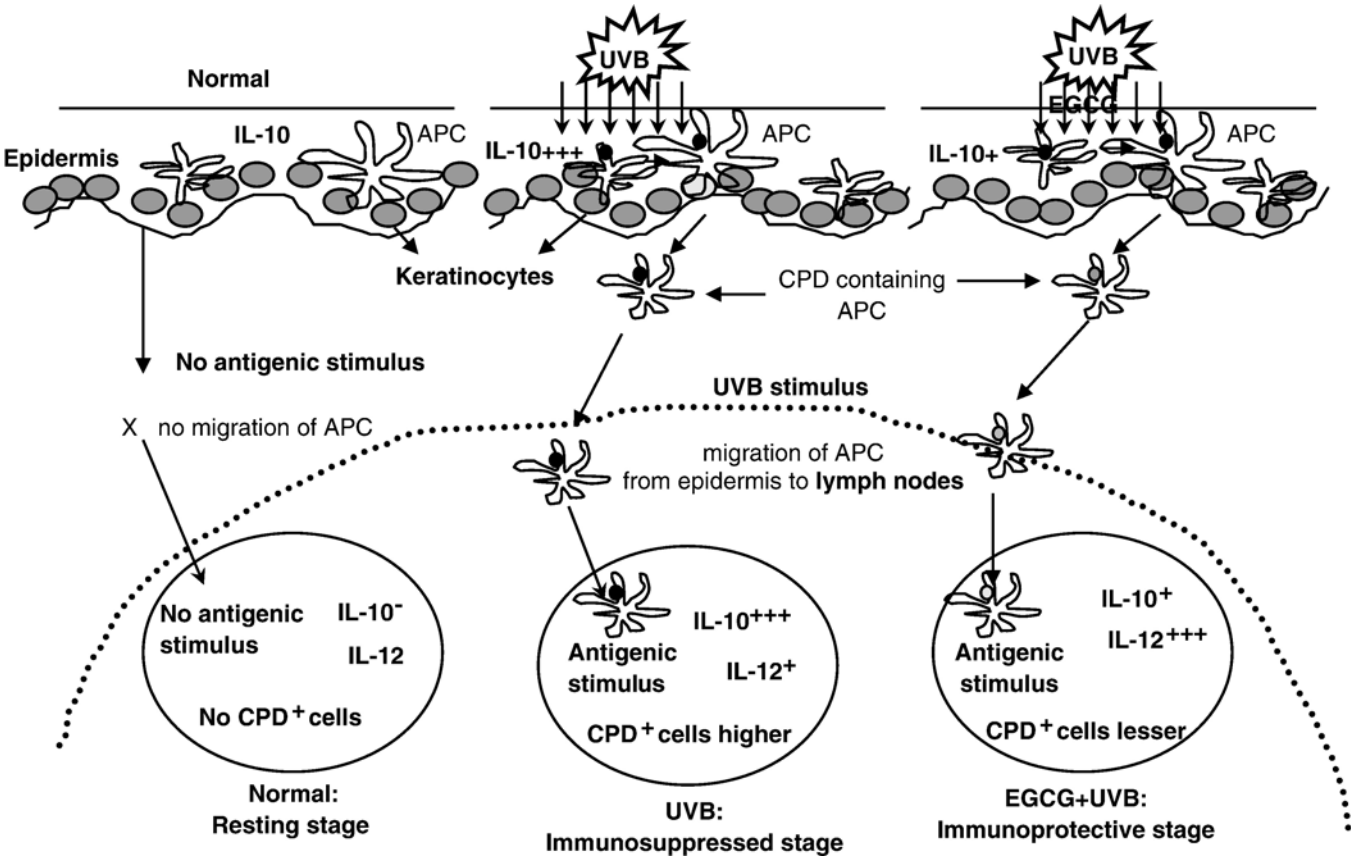

Fig. 4. Schematic diagram depicting EGCG-induced immunomodulatory changes in UVB-induced immunosuppression in mice. Treatment of mice with EGCG alters the levels of UVB-induced IL-10 and IL-12 in the skin and in DLNs. The treatment of EGCG reduces the number of CPD-containing APCs' migration from the skin to the lymph nodes, suggesting the removal or repair of UVB-induced CPDs in APC and thus protecting the mice from UVB-induced immunosuppression, which leads to protection from photocarcinogenesis. The process of EGCG-induced repair of CPDs in CPD-containing APCs is shown in the EGCG+UVB-treated group. (+) Comparative concentration of IL-10 or IL-12 in lymph nodes.

in the DLNs of WT mice after EGCG treatment may be due to EGCG-induced IL-12-mediated repair of CPD^+ cells.

10. Green tea prevents photocarcinogenesis through an IL-12-dependent DNA repair mechanism

Oral administration of GTPs in drinking water or topical treatment of EGCG inhibits photocarcinogenesis in mice. The antioxidant and anti-inflammatory effects of GTPs/EGCG have been described in detail [10,18,19]. As treatment of EGCG prevents UV-induced immunosuppression through increased levels of IL-12 and as IL-12 has antitumor activity and the ability to repair UVB-induced DNA damage, the effect of EGCG on photocarcinogenesis in the IL-12 KO mouse model was determined. Following photocarcinogenesis protocol [14,24], Meeran et al. [59] reported that topical treatment with EGCG significantly inhibits photocarcinogenesis in terms of tumor incidence, tumor multiplicity and tumor growth or tumor size in WT (C3H/HeN) mice, but not in IL-12 KO mice, indicating that the prevention of UVB-induced skin cancer by EGCG requires IL-12. As accumulation of UVB-induced DNA damage, particularly CPDs, has a role in the initiation of photocarcinogenesis, this study further demonstrated that treatment with EGCG removed or rapidly repaired UVB-induced CPDs in WT mice compared to IL-12 KO mice. Furthermore, the treatment of EGCG-treated IL-12 KO mice with recombinant IL-12 removes or repairs UVB-induced CPD^+ cells. This information further supports the finding that EGCG promotes the removal or the repair of damaged DNA in UVB-exposed skin through a mechanism that requires IL-12 activity.

The formation of sunburn cells after UVB irradiation is primarily a consequence of DNA damage [59,60]. Sunburn cells are keratinocytes that undergo apoptosis after they have received a physiologic UVB dose that has severely and irreversibly damaged their DNA or other chromophores. Using IL-12 KO and their WT counterparts as tool, Meeran et al. [59] have very recently shown that treatment with EGCG resulted in a significant reduction in the number of sunburn cells after time-dependent UVB irradiation in WT mice. In contrast to WT mice, EGCG treatment of IL-12 KO mice did not result in the rapid removal of sunburn cells after UVB exposure. This difference in the repair kinetics of

sunburn cells in IL-12 KO and WT mice may be attributed due to the EGCG induction of IL-12 in WT mice.

11. Removal or repair of UV-induced DNA damage through NER mechanism

To further elucidate the DNA repair mechanism by EGCG in the prevention of photocarcinogenesis, Meeran et al. [59] used fibroblasts from patients suffering from xeroderma pigmentosum (complementation group A; *XPA*-deficient) and from normal healthy persons. A distinct property of IL-12 was utilized in these studies. IL-12 has been shown to have the ability to repair UVB-induced CPDs in healthy cells, but not in cells from patients with *XPA* [51,55,59]. The *XPA* gene is an essential component of the NER; thus, cells with a mutated *XPA* gene completely lack functional NER. To examine whether the NER mechanism is required for the EGCG-induced IL-12-mediated repair of UVB-induced CPDs, NER-deficient fibroblasts from *XPA* patients and NER-proficient fibroblasts from healthy persons were exposed to UVB, with or without prior treatment with EGCG. When the cells were analyzed for CPDs immediately after UVB exposure, no differences were observed in the cells treated with or without EGCG in terms of the number of CPD^+ cells. This finding implies that EGCG does not prevent the immediate formation of CPDs after UVB exposure and excludes a UVB-radiation-filtering effect. However, when the cells were analyzed 24 h after UVB irradiation, the numbers of CPD^+ cells were significantly reduced in NER-proficient cells but did not significantly remove or repair CPDs in NER-deficient cells from *XPA* patients, suggesting that EGCG might accelerate the repair of UVB-induced CPDs through NER mechanism. Other studies have reported that UVB-caused DNA damage can be reduced by the application of exogenous DNA repair enzymes. The bacterial DNA repair enzyme T4 endonuclease V (T4N5) can be delivered into cells by liposomes [61]. Topically applied T4N5 liposomes penetrate the skin, increase the removal of CPDs and reduce the incidence of skin cancer [62,63]. In accordance with the accelerated removal of DNA lesions by T4N5, sunburn cell formation was also reduced [64]. In contrast to the external application of DNA repair enzymes, Meeran et al. [59] indicate that EGCG affects the cell's own NER system by inducing IL-12.

12. Stimulation of cytotoxic T cells in skin tumors

Mantena et al. [20] have shown that orally administered GTPs inhibit photocarcinogenesis in mice, and this activity of GTPs is mediated, at least in part, by the recruitment of cytotoxic T cells in a tumor microenvironment. IL-12 has been shown to stimulate the production of IFN-ã and to stimulate the development of cytotoxic T cells (e.g., $CD8^+$ T cells), which are tumoricidal and thus may result in the inhibition or regression of tumors. A study conducted in SKH-1 hairless mice indicates that oral administration of GTPs in drinking water enhanced the number of $CD8^+$ T cells in tumors treated with GTPs+UVB compared with non-GTP-treated UVB-exposed mice [20]. This study indicates another major pathway by which GTPs can inhibit tumor growth. $CD8^+$ T cells are effector cells in the cytotoxic response of the host to UV-induced skin tumor cells; they play an important role in protection against tumor immunity at least for skin tumors induced by chronic UV exposure [65]. The ability of the oral administration of GTPs to enhance the infiltration or recruitment of higher numbers of $CD8^+$ T cells in the tumor microenvironment may act to enhance the immunosurveillance mediated by these cells, thereby reducing the incidence of tumors. Similar observations were noted when mice were topically treated with EGCG and subjected to photocarcinogenesis protocol [66]; however, the degree of the chemopreventive effect of EGCG applied topically was greater than that of GTPs given in drinking water. Presumably, this difference may be due to the higher concentration of EGCG with topical application compared with the concentration of GTPs with oral administration. However, the chemopreventive effect of orally administered GTPs in mice was substantial; it can be as important as EGCG because GTPs are affordable, less costly than pure EGCG and easily obtained from green tea beverage for the prevention of UV-induced skin cancer and other harmful effects of UV radiation.

13. Inhibition of angiogenesis in skin tumors

Tumor angiogenesis is the proliferation of a network of blood vessels that penetrate into cancerous growths, supplying nutrients and oxygen and removing waste products. An important mechanism by which tumor growth can be inhibited or regressed by chemopreventive agents is the inhibition of angiogenesis. It has been identified that angiogenic factors, such as matrix metalloproteinases (MMPs) and vascular endothelial growth factors (VEGFs), are important regulators of tumor growth, both at the primary tumor site and at distant metastasis [67,68]. Hence, MMP and their regulatory pathways are considered promising targets for anticancer drugs or chemopreventive agents. In an effort to define the possible mechanism of inhibition of tumor growth in the photocarcinogenesis model by GTPs, Mantena et al. [20] recently demonstrated that oral administration of GTPs in drinking water inhibits the protein expression and activity of both MMP-2 and MMP-9 in tumors. The inhibition of MMPs was accompanied by an elevated expression of their natural inhibitor, TIMP1. Furthermore, the administration of GTPs inhibited the expression of vascular endothelial cell antigens, such as CD31 and VEGF, in UVB-induced tumors. The increased expressions of these proteins play an important role in tumor growth, invasion and metastasis due to the promotion of a new vasculature that supports tumor growth. Thus, the administration of GTPs in drinking water has significant antiangiogenic effects and has

the potential to reduce the growth — or to cause the regression — of tumors through this mechanism. Similar effects were also observed when SKH-1 hairless mice were topically treated with EGCG [66]. Again, the antiangiogenic effect of EGCG, when applied topically, was greater than that observed with GTPs given in drinking water [20,66]. Garbisa et al. [69] also reported that green tea inhibited the tumor invasion potential of tumor cells.

14. Conclusion

Extensive in vitro and in vivo laboratory evidence supports the antiphotocarcinogenic potential of green tea. The new mechanistic studies that have been discussed in this review article further support the potential nutritional value of green tea in skin photoprotection. It is effective through oral administration in drinking water, as well as through topical application on the skin. Moreover, GTPs, in combination with sunscreens or skin care lotions, may provide an effective strategy for reducing the risk of melanoma and nonmelanoma skin cancers and other skin disorders caused by excessive exposure to solar UV radiation. Importantly, green tea is pharmacologically safe because it is nontoxic to humans. It is an important factor because most modern medicines currently available for treating cancers are expensive, toxic and less effective in treating the disease. Clinical trials are needed to validate the usefulness of GTPs or EGCG, either alone or in combination with existing therapies of melanoma and nonmelanoma skin cancers, in high-risk human populations.

Acknowledgments

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