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Hsp90 Inhibitor Can Inhibit UV-Carcinogenesis

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Abstract

Extensive exposure to solar ultraviolet radiation (UVR) is a well-recognized etiologic factor for cutaneous non-melanoma skin cancer. In this issue of the Journal, Singh *et al.* show that topical treatment of skin with 17-[allylamino]-17-demethoxygeldanamycin (17AAG), a heat-shock protein 90 (Hsp90) inhibitor, prevents UVR-induced squamous cell carcinomas (SCC) in mice. The inhibitory effect of 17AAG on SCC was associated with the inhibition of the UVR-induced: (i) hyperplastic response, (ii) Hsp90β-PKCε interaction, and (iii) pStat3 and pAkt expression in mouse skin.

Epidemiological, clinical and laboratory studies have implicated solar ultraviolet radiation (UVR) in tumor initiation, tumor promotion and complete carcinogenesis. Excessive exposure to UVR can lead to the initiation and development of several skin disorders/diseases and increase the risk of melanoma and non-melanoma skin cancers (Baliga and Katiyar, 2005). UVR exposure induces inflammatory responses, oxidative stress, immunosuppression, DNA damage and gene mutations. Individually, each of these effects can contribute to the risk of skin cancer and collectively they heighten that risk considerably. Multiple molecular targets and biomarkers have been identified that play significant roles in skin disease. Efforts have been made to develop new and more effective strategies for the treatment and/or prevention of these diseases. For more than two decades, efforts have concentrated on screening and testing the chemopreventive effects of natural plant products or phytochemicals using various animal models. Phytochemicals, including dietary plant products, offer promising options for the development of more effective chemopreventive and chemotherapeutic strategies for cancers of different organs, including skin. These alternative strategies are based on the specific characteristics of the individual phytochemicals, such as their anti-inflammatory, antioxidant, DNA repair activities and their ability to stimulate the immune system. In line with these investigations and strategies, green tea polyphenols, grape seed proanthocyanidins and silymarin have been studied extensively, and these phytochemicals have shown significant anti-skin carcinogenesis effects both in *in vitro* and *in vivo* in animal models (Baliga and Katiyar, 2005; Nichols and Katiyar, 2010).

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CONFLICT OF INTEREST

The author states no conflict of interest.

Multiple molecular targets, including inflammatory mediators, oxidative stress, DNA damage and repair, and immunological responses, have been identified that are responsible for the prevention of UVR-induced skin carcinogenesis by these phytochemicals.

The research laboratory of Dr. Verma and colleagues reported the activation of PKCε, a novel PKC isoform, in UVR-exposed skin and demonstrated that PKCε activation mediates UVR-induced TNFα release, which is linked to the development of SCCs (Wheeler *et al.*, 2004). PKCε is among the six PKC isoforms (α, δ, ε, μ, ξ, η) that are expressed in both human and mouse skin. PKCε overexpression has been shown to decrease the latency, while increasing the incidence and multiplicity of the SCCs in PKCε transgenic mice (Wheelar *et al.*, 2004). It has been reported that the possible mechanisms by which PKCε mediates susceptibility to SCC induction include PKCε-mediated anti-apoptotic and cell survival signals (Aziz *et al.*, 2007). The PKCε-mediated cell survival signal may involve interaction of PKCε with Stat3, which also has been linked to the induction of skin cancer (Goetz *et al.*, 2005).

In this issue of the Journal, Singh and colleagues (2014) have shown that UVR exposure increases the interaction of PKCε with heat-shock protein 90β (Hsp90β) and that this interaction may play an important role in UVR-induced SCCs. The chaperone Hsp90 mediates the maturation and stabilization of PKCε as a client protein (Gould *et al.*, 2009), and it also plays a significant role in cell transformation, proliferation and cell survival (Miyata *et al.*, 2013). Hsp90 is of considerable interest as an oncogenic target since tumor cells and oncogenic proteins are heavily dependent on its activity (Soti *et al.*, 2005). By inhibiting Hsp90 one can target a large number of downstream proteins and thereby attack the neoplastic process at several points as illustrated in Figure 1. Consequently, several Hsp90 inhibitors have been developed and are being evaluated for treatment of various human cancers (Cullinan and Whitesell, 2006). Geldanamycin, the first Hsp90 inhibitor to be tested in a clinical trial, failed due to hepatotoxicity. Second-generation derivatives, such as 17-[allylamino]-17-demethoxygeldanamycin (17AAG), do not cause liver toxicity and currently are being evaluated in phase II clinical trials (Heath *et al.*, 2008; Pacey *et al.*, 2012). A large number of clinical trials are exploring the use of 17AAG and other Hsp90 inhibitors in various cancers including melanoma (Cullinan and Whitesell, 2006); however, Hsp90 inhibitors have never been investigated in terms of the prevention and treatment of UVR-induced SCC. As many of the molecular targets in UVR-induced skin carcinogenesis are dependent on Hsp90 for maturity, stability and activity, Singh and colleagues formulated the hypothesis that treatment of Hsp90 inhibitor in conjunction with UVR exposure will prevent development of cutaneous SCCs. They demonstrate that topical treatment with the Hsp90 inhibitor, 17AAG, was not toxic and that it was effective in preventing UVR-induced SCC development in mice in terms of: 1) inhibition of tumor incidence and tumor multiplicity and 2) increased latency for first tumor appearance. These results concerning tumor development were verified in three mouse models: SKH-1 hairless, wild-type FVB, and PKCε overexpressing transgenic FVB mice.

17AAG is an ATP antagonist that inhibits Hsp90 and ATPase activity. This inhibition of Hsp90 ATPase activity affects the maturity and stability of its client proteins, including PKCε. Interestingly, Singh and colleagues found that UVR exposure of mouse skin results

in increased expression of PKCε, possibly due to its increased synthesis. They also demonstrate that topical application of 17AAG to mouse skin inhibits UVR-induced Hsp90β-PKCε interaction as well as expression levels of pStat3 and pAkt. These findings are consistent with the requirement for sequential phosphorylation of newly synthesized PKC and its binding to Hsp90, which is a required step in its maturation and stability (Gould *et al.*, 2009).

In this issue of the Journal, Singh and colleagues also report the effects of 17AAG on the biomarkers of chronic UVR-induced photoaging of the skin. Overexpression of matrix metalloproteinases (MMP) in UV-exposed skin has been implicated in the wrinkling of skin or premature aging that is known as photoaging. Topical treatment of SKH-1 hairless mouse skin with 17AAG before and after UVR exposure resulted in decreased levels of MMP-2 and MMP-9 proteins as compared with mouse skin that was not treated with 17AAG but exposed to UVR. These results suggest that 17AAG treatment may protect the skin from photoaging through inhibition of MMPs.

Singh and colleagues have demonstrated convincingly that 17AAG has the ability to inhibit UVR-induced SCCs development and also to inhibit selected biomarkers of photoaging. However, UVR-induced development of SCCs accompanies expression and activation of several oncogenic signal transduction pathways, as summarized in Figure 1. Thus, more rigorous, mechanism-based studies are warranted to establish the molecular mechanisms underlying prevention of UVR-induced SCCs in the skin by 17AAG. Further studies may reveal broader mechanisms of action of the Hsp90 inhibitor, 17AAG.

Acknowledgments

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References

Aziz MH, Manoharan HT, Verma AK. Protein kinase C epsilon, which sensitizes skin to sun's UV radiation-induced cutaneous damage and development of squamous cell carcinomas, associates with Stat3. Cancer Res. 2007; 67:1385–94. [PubMed: 17283176]

Baliga MS, Katiyar SK. Chemoprevention of photocarcinogenesis by selected dietary botanicals. Photochem Photobiol Sci. 2006; 5:243–53. [PubMed: 16465310]

Cullinan SB, Whitesell L. Heat shock protein 90: a unique chemotherapeutic target. Semin Oncol. 2006; 33:457–65. [PubMed: 16890800]

Goetz MP, Toft D, Reid J, et al. Phase I trial of 17-allylamino-17-demethoxygeldanamycin in patients with advanced cancer. J Clin Oncol. 2005; 23:1078–87. [PubMed: 15718306]

Gould CM, Kannan N, Taylor SS, et al. The chaperones Hsp90 and Cdc37 mediate the maturation and stabilization of protein kinase C through a conserved PXXP motif in the C-terminal tail. J Biol Chem. 2009; 284:4921–35. [PubMed: 19091746]

Heath EI, Hillman DW, Vaishampayan U, et al. A phase II trial of 17-allylamino-17-demethoxygeldanamycin in patients with hormone-refractory metastatic prostate cancer. Clin Cancer Res. 2008; 14:7940–6. [PubMed: 19047126]

Miyata Y, Nakamoto H, Neckers L, et al. The Therapeutic Target Hsp90 and Cancer Hallmarks. Curr Pharm Des. 2013; 19:347–65. [PubMed: 22920906]

Nichols JA, Katiyar SK. Skin photoprotection by natural polyphenols: Anti-inflammatory, anti-oxidant and DNA repair mechanisms. Arch Dermatol Res. 2010; 302:71–83. [PubMed: 19898857]

Singh A, Singh A, Sand JM, Bauer SJ, Hafeez BB, Meske L, Verma AK. Topically applied Hsp90 inhibitor 17AAG inhibits ultraviolet radiation-induced cutaneous squamous cell carcinomas. J Invest Dermatol. 2014

Soti C, Nagy E, Giricz Z, et al. Heat shock proteins as emerging therapeutic targets. Br J Pharmacol. 2005; 146:769–80. [PubMed: 16170327]

Pacey S, Gore M, Chao D, et al. A Phase II trial of 17-allylamino, 17-demethoxygeldanamycin (17-AAG, tanespimycin) in patients with metastatic melanoma. Investigational New Drugs. 2012; 30:341–9. [PubMed: 20683637]

Wheeler DL, Martin KE, Ness KJ, et al. Protein kinase C epsilon is an endogenous photosensitizer that enhances ultraviolet radiation-induced cutaneous damage and development of squamous cell carcinomas. Cancer Res. 2004; 64:7756–65. [PubMed: 15520180]

Clinical Implications

- Topical application of the Hsp90 inhibitor (17AAG) significantly inhibits UVR-induced cutaneous squamous cell carcinoma (SCC) development in mice.
- Therapeutic blockade of the interaction between PKCε and Hsp90 by 17AAG is a promising approach to prevent UVR-induced skin carcinogenesis.
- 17AAG might be supplemented with the use of sunscreens to reduce UVR-induced adverse effects, such as hyperplastic skin diseases (*e.g.*, actinic keratosis) and/or photoaging of the skin.

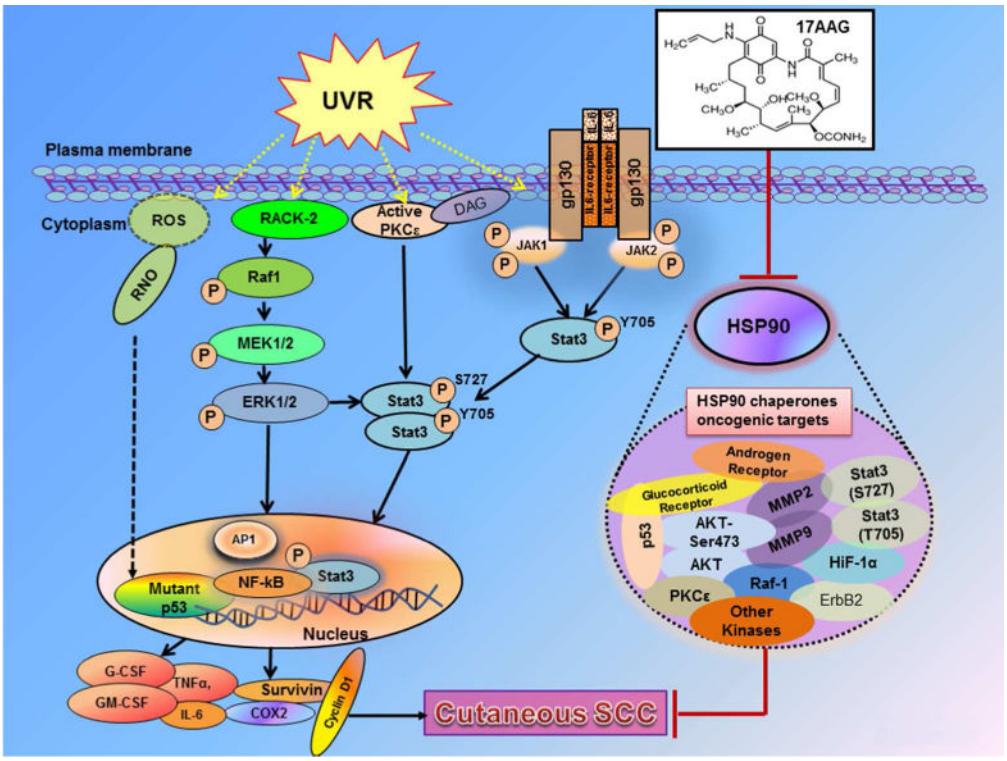

Figure 1. Schematic illustration showing the molecular targets of 17AAG, an inhibitor of Hsp90, in UVR-induced skin carcinogenesis

Skin exposure to UVR induces the activation of multiple signal transduction pathways culminating in activation of transcription factors (AP1, NF-κB, Stat3, etc.) and constitutive expression of genes (e.g., cytokines, COX-2, cyclin D1, Survivin, etc.), essential for SCC development. The molecular targets in UVR-induced skin carcinogenesis require Hsp90 for their maturity, stability and activity. 17AAG inhibits UVR-induced SCC via inhibition of Hsp90 ATPase activity essential for the stability of UVR-activated signal transduction pathways.