

7th European Dermatology Congress

June 13-14, 2016 Alicante, Spain

Topically applied Hsp90 inhibitor 17AAG inhibits ultraviolet radiation induced cutaneous wrinkles and squamous cell carcinomas

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We present here that Heat shock protein 90 β (Hsp90 β) interacts with protein kinase C ϵ (PKC ϵ); a predictive biomarker of various human cancers including ultraviolet radiation (UVR) induced cutaneous squamous cell carcinoma (SCC). Hsp90 inhibitor 17-(allylamino)-17-demethoxygeldanamycin (17AAG), when topically applied to mouse skin, inhibits ultraviolet radiation (UVR) induced Hsp90 β -PKC ϵ interaction, wrinkle formation and development of SCC. In these experiments, DMSO:Acetone (1:40 v/v) solution of 17AAG (500 nmol) was applied topically to mouse skin in conjunction with each UVR exposure (1.8 kJ/m²). The UVR source was Kodacel-filtered FS-40 sun lamps (approximately 60% UVB and 40% UVA). In independent experiments with three separate mouse lines (wild-type FVB, PKC ϵ over expressing transgenic FVB and SKH-1 hairless mice), 17AAG treatment increased the latency and decreased both the incidence and multiplicity of UVR induced SCC. Topical 17AAG did not elicit any toxic effects. 17AAG caused inhibition of SCC induction accompanied decrease in UVR-induced: Hyperplasia, wrinkle formation and Hsp90 β -PKC ϵ interaction, Hsp90 β , PKC ϵ , Stat3, pStat3Ser727, pStat3Tyr705, Akt, pAktser473 and matrix metalloproteinase (MMPs) expression levels. The results presented here indicate that topical Hsp90 inhibitor 17AAG is nontoxic and is effective in prevention of epidermal hyperplasia, wrinkle formation and SCC.

Biography

Ajit K Verma has obtained his PhD in 1972 at the Flinders University of South Australia, Adelaide, Australia and Postdoctoral training in 1976 at the McArdle Laboratory, University of Wisconsin, USA. Currently, he is a full Professor in the Department of Human Oncology, University of Wisconsin, USA. His major findings include generation of PKC ϵ transgenic and conditional PKC ϵ knockout mice, identification of PKC ϵ downstream molecular targets (Hsp90, Stat3, cytokines) and their role in ultraviolet radiation carcinogenesis. He was the first to report that Hsp90 inhibitor 17AAG can be topically applied to prevent development of SCC.

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