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A survey of in-vitro and in-vivo effects of steroids on melanoma growth and its implication on the nature of the disease

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Melanoma, a fatal form of skin cancer accounts for less than 2% of skin cancer, but is responsible for 75% death due to skin cancer [1]. UV rays in the Sun is believed to be responsible for 90% of melanoma incidence [2], with only 10% inherited in the family. Epidemiological studies showed that mortality rate was higher in males than in females [3]. Current targeted therapy and immuno-therapy are accompanied by serious side-effects such as endocrinopathies and other allergic and autoimmune disorders [4,5]. This situation warrants an understanding of the fundamental nature of the disease before developing any treatment. At this juncture, a survey of in-vitro and in-vivo effects of steroids on melanoma growth [6] provided a basis for the nature of this disease.

Apart from being the largest organ in the body, skin is also an endocrine gland which secrets various hormones [7,8]. Skin has an analogous hypothalamus, pituitary and adrenal axis with the production of POMC, ACTH and glucocorticoid steroidogenesis [9]. Studies showed that local production of hormones in the skin not only influenced regionally, but also affected systemically [10]. In addition, skin is also the site for production of sex steroids such as testosterone and estrogen. Sex steroids such as progesterone, estrogen and androgens are essential for a healthy skin [11]. In fact, melanocyte, which produces melanin pigment in skin is under the influence of melanocyte stimulating hormone (MSH) from pituitary [8]. Hence, these observations raise the question whether melanoma is a hormone dependent cancer like breast, endometrial and prostate cancers. So far UV rays from the sun and other radiations are considered as the major cause for melanoma, but not hormones as the cause for this disease. However, various in-vitro experiments showed that steroid hormones decreased melanoma cell growth [12,13]. Our lab also showed that progesterone, a female sex hormone inhibited melanoma cell growth significantly in-vitro [14,15]. Other researchers, Fang et al. [16] from China also showed the effect of progesterone on melanoma cell growth in-vitro. Later the study was repeated by Moroni et al. [17] from Italy using progesterone concentration up to 1000 µM and showed the inhibition of melanoma cell growth. Earlier Kanda and Watanbe [18] from Japan also demonstrated the inhibitory effect of progesterone on melanoma cell growth. So, these in-vitro studies suggested that progesterone might regulate melanoma cell growth. This raised the question whether there were in-vivo evidences for the effect of progesterone on melanoma. To that end, previous clinical studies showed that menstruating females were better protected in melanoma than post-menopausal women and men of any age [19,20]. But these clinical studies were not correlated with steroid status in females and did not demonstrate any direct effect of steroids on melanoma cells. In addition, there were in-vivo experiments with small animals where steroids were used to treat melanoma [21,22]. So, in-vitro and in-vivo studies suggested that melanoma could be a hormone responsive cancer, where hormones were needed for survival in melanoma. Progesterone could be the steroid hormone protecting menstruating females in melanoma, as progesterone level peaked in menstruating females between 1000 – 1500 ng/dL [23]. Whereas, progesterone level in post-menopausal women ranged between 20 – 100 ng/dL [23]. Further, epidemiological data showed that mortality rate was higher in males than in females [3]. Progesterone level in males ranged between 27 – 90 ng/dl and its function was not known in males. So, the two groups which were not protected in melanoma had low progesterone level in circulation. But, this observation could be a mere coincidence between progesterone and melanoma growth. A valid biochemical evidence mediated by a biomolecule is needed to make the connection between progesterone and melanoma growth. In this context, our further in-vitro research revealed that progesterone action was mediated by a specific suppression of pro-inflammatory cytokine IL-8 [24]. When IL-8 level was decreased, melanoma cell growth was decreased. There were several in-vitro and in-vivo studies connecting IL-8 level with melanoma growth such as IL-8 acting as an autocrine growth factor for melanoma cell growth and IL-8 conditional expression increased melanoma growth and metastasis in a mouse model [25,26].

In summary, in-vitro and in-vivo animal studies along with clinical and epidemiological studies suggested that melanoma could be a hormone (progesterone) responsive cancer and that progesterone action was mediated by a suppression of pro-inflammatory cytokine IL-8. IL-8 in turn was shown to regulate melanoma cell growth. So, IL-8 could be a mediator molecule of progesterone action on melanoma growth, providing a biochemical basis for previous clinical findings that menstruating females (with a peak progesterone level of 1000-1500 ng/dL) were better protected in melanoma. Understanding this basic nature of melanoma is important in developing a future treatment for melanoma.

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