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In-vitro determination of the protective function of progesterone and its receptor antagonist RU-486 in melanoma using a human melanoma (BLM) cell model

Melanoma is a fatal form of skin cancer, which showed an increased mortality rate in males than females, suggesting a sex difference. Clinical studies showed that menstruating females were better protected in melanoma than post-menopausal women and men of any age, suggesting the involvement of sex steroid hormones. But clinical studies did not show a direct effect of sex steroids on melanoma. Our *in-vitro* studies using a variety of steroids showed that progesterone a female sex hormone and its receptor antagonist RU-486 (a synthetic steroid) significantly killed both mouse (B16F10) and human (BLM) melanoma cells. Progesterone killed human (BLM) cells by autophagy and RU-486 killed human cells by apoptosis. But, actions of these two steroid hormones were not mediated through progesterone receptor. The observation that progesterone a natural female sex hormone killed melanoma cells, raised the question, whether androgens (present at high concentrations in males) were responsible for increased male mortality in melanoma? Dose curve studies of androgens (androstenedione and testosterone) showed a dose-dependent inhibition of mouse melanoma cells, suggesting androgens also killed melanoma cells and might not be responsible for increased male mortality in melanoma. Since, we already showed progesterone had killed mouse melanoma cells; co-incubation of progesterone with androgens was carried out. Addition of progesterone (as low as 10 βM) to androgens showed an additive effect on mouse melanoma cell growth inhibition. Results suggested that perhaps lack or deficiency of progesterone in males could be responsible for increased male mortality.Literature survey showed that progesterone level was very low in males and its level was drastically low in post-menopausal women, the two groups which lacked protection in melanoma as per the clinical studies. Our *in-vitro* experiments along with literature survey and clinical findings suggested that progesterone could be involved in the protection. So the study was extended to human melanoma (BLM) cells. Androgens showed inhibition of human melanoma cell growth also, though at higher concentrations (100 and 200 μM). Addition of 10 μM concentration of progesterone to androgens showed an additive effect on human melanoma cell growth inhibition, indicating a protective function of progesterone. However, addition of RU-486 to androgens did not show any additive effect on human melanoma cell growth inhibition, indicating a lack of protective function. Perhaps, lack of protective function of progesterone due to very low level of progesterone in males could be responsible for increased mortality in melanoma. A similar kind of study showed a significant correlation between estrogen level and male breast cancer. Though RU-486 individually inhibited human melanoma cell growth *in-vitro*, it lacked protective function.

Biography

Pandurangan Ramaraj obtained Master's degree in Medical Biochemistry from JIPMER and PhD in Biochemistry from Indian Institute of Science, India. His Post-doctoral research work in US involved gene and function studies involving transgenic & knockout mice, oncogene transfer into human hematopoietic stem cells and transdifferentiation of murine mesenchymal stem cell. He started teaching career as an Instructor at Cleveland Chiropractic College, Los Angeles before joining Kirksville College of Osteopathic Medicine as an Asst. Prof, where currently he is teaching Medical Biochemistry to DO students. He is interested in studying the effect of steroid hormones on cancer using mouse and human melanoma cell lines as model systems.

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