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Effect of all-trans-Retinoic Acid and Conjugate with Spermine on Human Endothelial and Prostate Cancer Cell Growth *in Vitro* and Angiogenesis *in Vivo*

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SUMMARY.Retinoids constitute a large family of organic compounds structurally related to the naturally occurring vitamin A. All-trans-retinoic acid (atRA) is known to modulate a wide range of cellular biological processes through binding to and activation of specific receptors, the retinoic acid receptors (RAR) α, β and γ. Retinoids are being used for the treatment of various diseases, ranging from acne vulgaris to acute promyelotic leukemia. Their use however is limited due to serious adverse effects and there is a great need for analogues with minimized adverse effects. Towards this direction, we have previously synthesized a series of atRA conjugates with polyamines like spermine (SPM) and have tested them against RNase P activity. Among the molecules tested, the most potent inhibitor was the N^1,N^{12}-bis(*all-trans*-retinoyl)spermine (RA_2SPM). In the present work we studied the effect of RA_2SPM on angiogenesis in vivo and on human endothelial and prostate cancer cell growth in vitro. Both atRA and RA_2SPM dose-dependently inhibited angiogenesis in the chicken embryo chorioallantoic membrane model, with RA_2SPM being more effective and less toxic for the tissue. Similarly, both atRA and RA_2SPM decreased the number of human endothelial and prostate cancer LNCaP and PC3 cells in a concentration-dependent manner. In all cases, RA_2SPM was more effective and potent compared with atRA. Interestingly, the effect of RA_2SPM was mediated by RARα and was higher in PC3 cells that do not express RARβ and are considered more aggressive, while in cells that express RARβ it was less effective. Both atRA and RA_2SPM decreased expression of the growth factor pleiotrophin (PTN), which is known to be significant for prostate cancer cell growth. Further studies are in progress in order to elucidate whether the effect of atRA and RA_2SPM is related to their effect on the expression of PTN, as well as their mechanism of action on tumor and endothelial cells.