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Anticancer activity of polyphenolic acetates mediated by calreticulin transacetylase in lung cancer: An epigenetic modulation

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Background: Cancer is a group of diseases involving abnormal cell growth, occasionally having metastasis. This underlying genetic disease is initiated either by mutation or epigenetics. We are targeting lung carcinoma, most common cause of cancer-related death in men and women. Our new drug discovery is targeted on Calreticulin Transacetylase (CRTAase). We intend to treat lung cancer *in-vivo* and *in-vitro* by inducing hyperacetylation and upregulating the expression of genes important in tumor suppression. The polyphenolic acetates in combination with HDAC inhibitors are known to promote hyperacetylation, leading to apoptosis in lung cancer cells.

Aim: To determine the anticancer activity of 7, 8-Diacetoxy-4-Methyl Coumarin (DAMC), Polyphenolic acetate targeting acetylated histone interaction.

Methodology: DAMC showed anticancer activity both *in-vitro* and *in-vivo*. The hyperacetylation activity of DAMC on CRTAase induced epigenetic modulations were observed in A549 cells, as well as mice with Ehrlich ascites tumor (EAT) cells. The *in-vitro* and *in-vivo* data was validated by the apoptosis. Additionally specific target based anticancer property of DAMC was evaluated using microarray and RTPCR prior and after demethylation.

Results: In A549 cells, highest transfection efficiency was obtained after 72 hrs. Significant increase ($p<0.01$) in expression of H3 (2.67±0.02) and H4 2.755±0.016) was observed in DAMC treated CRTAase gene transfected A549 cells as compared to non-transfected A549 cells treated with DAMC (2.14±0.023) and (2.161±0.011) respectively. High apoptotic index was observed in The EAT cells *in-vivo* as well as in A549 cells *in-vitro*. RNA having RIN (RNA Integrity) values between 8.5 and 9.8 on electropherogram were subjected to microarray and RTPCR. A549 cells treated with DAMC and Valproic acid (VA) were suggestive of synergistic upregulation of tumor suppressor genes viz. ING4, TCF21, MFSD2A, FHIT and metalloproteinase inhibitor 3 i.e.TIMP3 and downregulating the oncogene Skp2.

Conclusion: The *in-vivo* as well as *in-vitro* findings suggest that DAMC and VA can potentiate the apoptotic pathway via CRTAase and thus can be a very promising anticancer drug candidate. In further ongoing studies we are screening more drugs targeting similar/more molecular targets and extending correlation with clinical applications.

Biography

Vishwajeet Rohil has obtained his MBBS degree from University College of Medical Sciences, Delhi and MD in Biochemistry from V P Chest Institute and has joined the Department of Clinical Biochemistry, V P C I, University of Delhi in 2001 as Assistant Professor, after doing Senior Residency at Maulana Azad Medical College, New Delhi. He has more than 24 years of Professional experience in the medical profession out of which 16 years of experience he has got in Teaching, Diagnostics and Research in the field of Biochemistry, Clinical Biochemistry and Molecular Biology. He is Supervisor and In-charge of the Clinical Biochemistry Autoanalyzer Laboratory for patient care at the Viswanathan Chest Hospital at V P C I and he is actively involved in Research and Teaching and guiding Post-graduate MD and PhD Students. He was selected as Govt. of India Expert, Medical Faculty under Govt. of India assistance programme by Ministry of External Affairs on special deputation to work at the Dept. of Biochemistry at B P K I H S, Dharan, Nepal and taught Medical graduates and Post-graduates for three years in an integrated setup, thereby he has acquired skills in structured interactive session [SIS], laboratory exercises [LABEX], problem based learning [PBL], multi-system seminars [MSS] with integrated teaching along with newer improved assessment techniques like OSPE [Objective structured practical examination], MCQ, Item analysis, SAQ, MEQ etc.

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