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Regulation of transcription factor E2F3b and its clinical relevance in breast cancer

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Initial studies evaluated the MCF7 cell uptake of a Cy3-labeled siRNA following intravenous administrations. The present findings showed representative 2-photon images collected at 0 and 5 min from the same MW (Swiss mice). Following intravenous injection, there was rapid accumulation of the Cy3- siRNA, Within 4-5min, extensive binding to the apical membrane had occurred and early endosomes on the outer aspects of the apical membrane could be visualized. Interestingly, the minimal Cy3-siRNA label in the cells at 5min indicated rapid clearance of siRNA. Recently we showed a mutant Retinoblastoma (mRb)–E2F3b signaling pathway, in which E2F3b was found to be essential in mRb-mediated proliferation in breast cancer cells. The present work evaluates the clinical relevance of this novel axis and of E2F3b itself in a large set of 73 breast cancer specimens. For this purpose E2F3b and its counterpart, E2F3a, were measured by RT–PCR and activated Rb was assessed by immunohistochemistry in MCF7 cellsWe further identified two Rb-independent mechanisms that regulate E2F3b expression, namely one, acting by promoter methylation of miR-22b, which by its physical interaction with E2F3b transcripts causes their degradation, and the second based on 6p22 gene locus amplification. MiRIDIAN-based knockdown and induction of miR-22b evidenced a direct regulatory link between miR-22b and E2F3b, and the tumor-suppressive character of miR-22b was documented by its association with improved survival. Although, 6p22 gene locus amplification was detected in a significant number of breast cancer specimens, 6p22 ploidy was not relevant in predicting survival. In Cox regression analysis, E2F3b, but not activated Rb or miR-22b expression, retained independent prognostic significance. These clinical findings highlight the relevance of E2F3b in the biology of breast cancer. Moreover, identification of Rb-independent mechanisms in E2F3b control can be helpful in explaining the non-responsiveness of therapeutic Rb targeting in breast cancer.

Biography

Dr. S.Kannan Ph.D (Zoology), Ph.D (Biotechnology) has obtained Ph.D Degrees from Bharathidasan University and having a wealth of experience in animal cell culture, protein expression and characterization in prokaryotic and eukaryotic cells. His research team is working on synthesis and manipulation of nanoparticles like silver, ORMOSIL and mesoporous silica nanoparticles towards the development of gene delivery as well as anticancer drug delivery systems. Our activity also leads to the development of novel anticancer agents and proteomic characterization of lung, colorectal and breast cancer in collaboration with Industries and Hospitals. He has successfully completed 3 major research projects and published more than 40 research articles in his field of interest. Currently running research projects funded by DST, Ministry of Science and Technology and University Grants Commission, Govt. of India.