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Inhibition of hTERT and telomerase activity via hampering MAPK kinase signaling in renal cell carcinoma cell lines

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Background: Telomerase adds species specific telomeric repeats onto chromosome termini, thereby counterbalancing sequence loss that would ensue as a result of semiconservative DNA replication by the conventional DNA replication machinery. Inhibition of telomerase is an exciting therapeutic target, since it is required for the long term proliferation of most cancer cells but not present in most somatic cells. Human telomerase reverse transcriptase (hTERT) is a catalytic subunit of telomerase and it is a major target for the development of anticancer methods because of the high concentration of TERT in almost all cancer cells, the dependency of most cancer cells on TERT activity. Previous studies have shown that EGF activates hTERT expression in which Ras/MEK/ERK pathway plays major role. In this study we use hTERT inhibition as a anticancer approach in renal cell carcinoma.

Materials and Methods: Total 100 cases of RCC treated by surgery under advanced Urology services of Nehru Hospital, at Postgraduate Institute of Medical Education and Research, Chandigarh were included in the present study. For comparison, normal renal cortex samples were taken in each case. Relative telomerase activity was measured by Telo TAGGG Telomerase PCR ELISA ^{PLUS} supplied kit by Roche applied science as per the manufacturer's instruction. Transcriptional expression of hTERT was estimated by real time PCR. RCC cell lines ACHN and A498 were maintained in DMEM medium supplemented with 10% FCS, 100U/ml ampicillin, 100mg/ml streptomycin at 37°C, 5% CO₂ in a humidified chamber. Activator and inhibitor of MAPK pathway EGF and U0126 were used at 80ng/ml and 20µM concentration respectively. To confirm the activation and inhibition of MAPK ERK phosphorylation was checked by RayBio cell based ERK1/2 (Thr202/Tyr204) ELISA kit as per manufacturer's instructions. Effect of hTERT inhibition on cancer properties of RCC cell lines ACHN & A498 were tested by MTT assay, Propidium iodide staining and cytofluorimetric analysis. Statistical analysis was performed with SPSS program (version 11.5; SPSS Inc., Chicago, IL). The significance level was set at P<0.05.

Results: The expression of hTERT and telomerase activity were significantly higher in the tumor tissue in comparison with normal renal parenchyma (p=0.000). Cell proliferation was inhibited significantly after treatment with U0126 in ACHN and A498 cells as compare to untreated cells (p=0.001). Cell cycle analysis by Propidium iodide staining showed that the growth of the U0126 cells was arrested in SubG0/G1 phase (p=0.001). Whereas Cytofluorimetric analysis of the AnnexinV-FITC versus PI staining revealed that U0126 treatment induced apoptosis in ACHN and A498 cells (p=0.001).

Conclusion: Our result suggests the expression of hTERT was significantly higher in tumor tissue as compare to normal renal tissue. Inhibition of hTERT, a catalytic component of telomerase enzyme drove RCC cancer cells into crisis and death. This inhibition of hTERT via inhibition of MAPK pathway may offer new opportunities for realizing the promise of telomerase inhibition therapy.

Dimensions of loneliness

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In greater numbers our aging population is living both longer and at home. Many have a paucity of supports and affiliations exposing them to the experience of loneliness. This presentation examines the progression from alone to lonely to loneliness. Some theoretical constructs which help develop insights into lonely will be discussed. Finally suggestions for adaptive interventions will be identified.

Biography

Tom Adamski is the Director of Psychiatric Programs for Jewish Home Lifecare, Community Services. He completed his Doctorate in Psychiatric Nursing at Teacher's College Columbia University. He is nationally and internationally recognized in the areas of Mental Health, HIV, Addiction and Bereavement. He is a practicing Psychotherapist in New York City and lectures extensively. He is a past Professor of Psychiatric Nursing at New York University and currently a preceptor of Graduate Nursing Students at Hunter College of the City of New York.