Seminars in Biotechnology BTEC 592 & BTEC 692

"Importance of Tissue Transglutaminase Transamidation and GTP Binding Activity on Metastatic Potential and Drug Response in Renal Cell Carcinoma"

Thursday, March 31, 2022
13:30
GTU Congress Center, Blue Hall

Prof. Dr. Dilek TELCİ TEMELTAŞ
Yeditepe University, Genetics and Bioengineering Department, İstanbul, Turkey

Prof. Dr. Dilek Telci Temeltaş got her B.Sc. from Middle East Technical University (METU) at Molecular Biology Department in 1999. Then, she studied medical genetics with immunology during her graduate education and got her M.Sc. from Brunel University in England. She studied cell biology and biochemistry during her Ph.D. and got her Ph.D. degree from Nottingham Trent University in 2004. She continued her postdoctoral studies at Sabancı University between 2004 and 2007. At the same time, during this period she contributed to the studies at Aston University as a research associate. In 2008, she joined the Department of Genetics and Bioengineering at Yeditepe University. Her research areas include molecular mechanisms in cancer progression and metastasis, endometrial stem cells and infertility, cell signaling, wound healing, extracellular matrix turnover, fibrosis.

Abstract

Renal cell carcinoma (RCC), the most common form of kidney cancer, has been stated as the 6th severe cause of cancer-related death. Despite recent advances in cancer treatment, recurrence of tumor, chemoresistance, and metastasis remain to be significant consequences of aggressive RCC. As a result, new treatment alternatives that necessitate the discovery of novel therapeutic targets are still needed. From this point of view, tissue transglutaminase (TG2) draws attention by its involvement in the progression, development, survival of various neoplasms including RCC. Our previous findings indicate that the increased expression of TG2 in RCC results in tumor metastasis with a significant decrease in disease- and cancer-specific survival outcome. Given the importance of the pro-metastatic activity of TG2 in RCC, in the present study, we aim to investigate the relative contribution of TG2's transamidase and guanosine triphosphate (GTP)-binding/GTPase activity in the cell proliferation, migration/invasion,

and cancer stemness as well as drug resistance in RCC. For this purpose, the mouse RCC cell line RenCa was transduced with wild-type-TG2 (wt-TG2), GTP-binding deficient-form TG2-R580A, transamidase-deficient form with low GTP-binding affinity TG2-C277S, and transamidase-inactive form TG2-W241A constructs. Based on our data, catalytically inactive transamidase domain-containing but GTPase active form TG2-W241A expressing RenCa showed the highest cell proliferation rate and increased cell cycle activity. In addition, GTP-binding activity of TG2 was shown to be responsible for cell migration and invasion as well as epithelial−mesenchymal transition. CD marker analysis and spheroid assay confirmed that GTP binding/GTPase activity of TG2 is important in the maintenance of mesenchymal character and the cancer stem cell profile. To elucidate the importance of TG2 transamidase/GTPase activity on the drug response to kinase inhibitors Sorafenib and Everolimus, which are the first line treatments for RCC, cell proliferation assay and Annexin V staining were performed following the drug treatments. Our results showed that non-transduced, wild-type TG2, TG2-C277S and TG2-R580A mutant RenCa cells demonstrated a similar cell viability pattern against Everolimus and Sorafenib. On the other hand, 2 to 3-fold increase in the cell survival was detected for the TG2-W241A cells after drug treatments. These findings support a pro-metastatic role for TG2 in RCC that is dependent on the GTP binding/GTPase activity of the enzyme.