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Development of novel targeted therapies for triple negative breast cancer: Targeting EF2-kinase

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Triple-negative breast cancer refers to any breast cancer which is clinically characterized as more aggressive and less responsive to standard treatments, and is associated with poor overall patient prognosis. Therefore, there is an urgent need to develop effective and safe therapies against triple negative breast cancer due to poor prognosis and lack of targeted therapies. Recently, we found that EF2-Kinase (EF2K) is significantly overexpressed in breast cancer cell lines compared with normal breast epithelium and its expression is associated with poor patient overall survival. However, its regulation and the role in breast cancer progression and tumorigenesis are not known. We demonstrated, for the first time, that inhibition of EF2K blocked proliferation, colony formation and invasion and tumorigenesis of TNBC tumors. We also discovered that FOXM1 and a microRNA directly binds and regulates EF2K gene expression and targeting of these molecules recapitulates the effects of EF2K targeting inhibit proliferation, invasion migration and tumor growth in TNBC models. We demonstrated blocked tumor growth tumor xenografts and significantly enhanced the *in vivo* efficacy of chemotherapy. Inhibition of FOXM1-miRNA/eEF2K axis significantly reduced Src/Fak/Paxillin, IGF-1R, PI3K/Akt/mTOR, cyclinD1, c-myc, HIF1 alpha and VEGF and induced significant apoptosis in tumors. Overall, our studies suggest that EF2-Kinase plays an important role in TNBC tumorigenesis and progression and EF2K targeted therapies provide the proof of concept for translation into Phase-I clinical trials in patients.

Biography

Bulent Ozpolat is an Associate Professor at the Department of Experimental Therapeutics at MD Anderson Cancer Center, Houston, TX, USA. He earned his PhD degree in Immunology from The University of Texas, M.D. Anderson Cancer Center, Houston Graduate School of Biomedical Sciences after getting his MD degree from The University of Dokuz Eylul University, Izmir, Turkey. He completed his graduate and Post-doc Training at the departments of Cancer Biology and Immunotherapy at MD Anderson Cancer Center. His research focuses on identification of novel survival pathways including EF2-Kinase (eEF2K) and autophagy pathways as well as regulation of cell death mechanism such as autophagic and apoptotic cell death; and development of molecularly targeted therapies using tumor-targeting nanotherapeutics (i.e. liposomes, immunoliposomes and metal-magnetic nanoparticles) in aggressive type of solid tumors (i.e. breast, pancreatic and ovarian cancers) and hematological cancers such as leukemia and lymphoma for the delivery of therapeutic cargo including siRNA, microRNA small molecule inhibitors, peptides, proteins, cytokines and anticancer agent. He is a Member of Center for Targeted Therapy and Non-Coding RNA Center and received many research awards in recognition of research excellence. He has published more than 50 papers, 9 book chapters and 12 review articles in peer-reviewed high impact journals and contributed to textbooks.

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