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Oxidative stress induced NRF2 regulation in BxPC-3 pancreatic cancer cells and identification of therapeutic targets

Hem D Shukla
University of Maryland, USA

Pancreatic cancer is one of the most aggressive human malignancies and ninth leading cause of cancer death in the world. Estimated new cases and deaths from pancreatic cancer in 2013 in the United States would be 45,220 and deaths 38,460. Most patients diagnosed with pancreatic cancer die within 6 months, and only 4% survive 5 years after diagnosis. Pancreatic cancer is characterized by colossal local invasion and early metastatic growth to the liver and regional lymph nodes. Expression of Nrf2 was up-regulated in oxidatively stressed BxPC-3 cell line and ductal adenocarcinomas. Furthermore, the BxPC-3 cell line responds to stress signals and resist chemotherapeutic interventions and have shown drug resistance. The Nrf2 has also been implicated in proliferation in certain pancreatic adenocarcinomas. Normally, ROS levels are tightly controlled by an inducible antioxidant program that responds to cellular stressors and is predominantly regulated by the transcription factor Nrf2. We have also identified the presence of a number of gene products involved in integrin signaling pathways. The comparative proteomic analysis using Protein Center and Ingenuity Pathway Analysis have shown the activation of DNA repair pathway genes like RAD50, ApeX, damage-specific DNA binding protein, which have the capability to repair DNA damage. The activation of NRF2 transcriptional factor and its phosphorylation in BxPC-3 treated cells shows that it may bind to the DNA at the location of the Antioxidant Response Element (ARE) or also called hARE (Human Antioxidant Response Element), which is the master regulator of the total antioxidant defense system. The proteomic data have also shown the activation of INT-ILK-PT3K-ILKAP-AKT and Cav-1-GRB2-SOS-cRas-Raf-MEK cascades. These results may have some promise in therapeutic intervention in the treatment of pancreatic cancer adenocarcinoma.

Biography

Hem D Shukla is a Research Scientist in the Department of Pharmaceutical Sciences at University of Maryland and adjunct Professor of Genomics in Notre Dame of Maryland University. He has also worked as Research Faculty in Department of Biology at Johns Hopkins University. He has worked on proteomic analysis of oxidative stress response in BxPC-3 pancreatic cell lines and identification of biomarkers for early detection of pancreatic cancer. He has worked on "The Nrf2 mediated antioxidant defense against oxidative stress in pancreatic cancer cell lines and targets for therapeutic intervention". He has shown elevated level of Nrf2 transcriptional factor in pancreatic cancer cell lines under oxidative stress, which is phosphorylated by protein kinase C and affects phosphatidylinositol 3-kinase and MAP kinase pathways. After phosphorylation, Nrf2 translocates to the nucleus, binds AREs and transactivates detoxifying enzymes and antioxidant enzymes, such as glutathione S-transferase and superoxide dismutase. The IPA analysis has suggested a potential role of Nrf2 under oxidative stress conditions. His research interests are: proteomic analysis of oxidative stress response in BxPC-3 pancreatic cell lines, identification of biomarkers for pancreatic cancer and Nrf2 mediated antioxidant defense against oxidative stress in pancreatic cancer cell lines.

hshukla@ndm.edu

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