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Lina Elsalem, J Cancer Sci Ther 2019, Volume 11
DOI: 10.4172/1948-5956-C1-159

32nd Euro Congress on

Cancer Science & Therapy

March 07-08, 2019 | Barcelona, Spain

Aldehyde dehydrogenase 7A1 (ALDH7A1) contributes to the reduction of reactive oxygen species generation in colorectal tumor microenvironment

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Reactive oxygen species (ROS) are reported to increase cancer cell proliferation, survival and migration. Paradoxically, high concentrations can trigger apoptotic or necrotic cell death. Mounting evidence indicates that hypoxic cancer cells undergoing exposure to oxidative stress develop adaptive strategies to survive the hostile milieu. These are indeed antioxidant responses that may result in aggressiveness and resistance toward chemotherapy. Aldehyde dehydrogenase 7A1 (ALDH7A1) is a drug metabolizing enzyme that has protective role against hyperosmotic stress and oxidative stress. Increased expression was reported in different cancer types. However, its expression and role in tumor microenvironment has not been investigated. The aim of this study was to evaluate the impact of hypoxia on the expression of ALDH7A1 and to assess its effect on ROS generation. Colorectal cancer (CRC) cell lines (HT29 and DLD-1) were grown as monolayer and exposed to normoxic or hypoxic conditions (0.1% O2). Multicellular spheroids (MCS) were generated in spinner flasks. ALDH7A1 gene and protein expression was evaluated using qRT-PCR and western blot, respectively. Immunohistochemistry was done to assess the expression at different depths within MCS and correlate it with hypoxia using the hypoxic marker, pimonidazole. Knockdown studies were done using siRNA and ROS was measured using carboxy-H2DCFDA. The gene and protein analysis data showed that ALDH7A1 was significantly upregulated in both cell lines upon exposure to hypoxia. Cells residing in the hypoxic region of both MCS showed significant increase of ALDH7A1 compared to surface layer cells and monolayer cells. ROS generation was reduced in hypoxic cells in comparison to normoxic cells, while ALDH7A1 knockdown studies showed elevation in ROS level. Our data suggests that ALDH7A1 upregulation in CRC cells as a result of tumor hypoxia might be one of the adaptive and protective responses against oxidative stress. As a consequence, ALDH7A1 might act as a potential biomarker for aggressive cancer phenotypes and/or a target for therapeutic intervention in CRC tumor microenvironment.

Recent Publications

1. L Elsalem, A Fotopoulos, A Papathanasiou, S Allison, J Moreb, Z Cournia and K Pors (2016) Human aldehyde dehydrogenase 7A1 (ALDH7A1) expression affects cancer cell proliferation, migration and cell protection against oxidative stress. European Journal of Cancer 61(1):S103.
2. Victoria Vinader, Maria Sadiq, Mark Sutherland, Mengying Huang, Paul M Loadman, Lina Elsalem, Steven D Shnyder, Hongjuan Cui, Kamyar Afarinkia, Mark Searcey, Laurence H Pattersona and Klaus Pors (2015) Probing cytochrome P450-mediated activation with a truncated azinomycin analogue. Journal of Medicinal Chemistry Communications 6(1):187-191.
3. Sheldrake H M, Travica S, Johansson I, Loadman P M, Sutherland M, Elsalem L, Illingworth N, Cresswell A J, Reuillon T, Shnyder S D, Mkrtchian S, Searcey M, Ingelman-Sundberg M, Patterson L H and Pors K (2013) Re-engineering of the duocarmycin structural architecture enables bio-precursor development targeting CYP1A1 and CYP2W1 for biological activity. Journal of Medicinal Chemistry 56(15):6273–6277.

Biography

Lina Elsalem has obtained her PhD in Cancer Pharmacology in The Institute of Cancer Therapeutics at University of Bradford, UK. She is a young researcher and investigator in the field of Cancer Research. Currently, she is working on projects related to drug metabolizing enzymes in colorectal and bladder carcinoma as well as bacterial drug resistance in wound infections. She has presented more than 10 abstracts at prestigious national and international conferences. She is an Assistant Professor in the Department of Pharmacology, Faculty of Medicine at Jordan University of Science and Technology. Her research interests are focused in the role of hypoxia in the regulation of drug metabolizing enzymes in tumor microenvironment as well as drug resistance in solid tumors and bacterial infections.

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