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ORIGINAL ARTICLE

PHD-2 activation: a novel strategy to control HIF-1α and mitochondrial stress to modulate mammary gland pathophysiology in ER+ subtype

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Abstract

Estrogen receptor–positive mammary gland carcinoma and its involvement in regulation of overexpressed hypoxia-inducible factor-1α and fatty acid synthase level in hypoxia influenced cancer cells are the present molecular crosstalk of this entire study. To test the hypothesis, we have proceed our study through chemical activation of prolyl hydroxylase 2 which leads to inhibition of hypoxia-inducible factor-1α and fatty acid synthase in ER+MCF-7 cancer cell line and n-methyl-n-nitrosourea induced mammary gland carcinoma rat model. ER+MCF-7 cells were evident with array of nuclear changes when stained through acridine orange/ethidium bromide. Afterward, JC-1 staining of the cells was evident in mitochondrial depolarization. The cells were arrested in G2/M phase when analyzed with flow cytometry. The morphological analysis of rat mammary gland tissue revealed decrease in alveolar buds, restoration of histopathological features along with intra-arterial cushion. The western blotting and fold change expressions of the genes validating the anticancer efficacy of BBAPH-1 is mediated through mitochondria-mediated apoptosis pathway. BBAPH-1 also modulates the expression of prolyl hydroxylase-2 with significant curtailment of hypoxia-inducible factor-1α, fatty acid synthase expression, and their respective downstream markers. These finding suggest that the BBAP-1-mediated activation of prolyl hydroxylase-2 significantly decreased the level of hypoxia-inducible factor-1α and fatty acid synthase. BBAPH-1 also activates the mitochondria-mediated death apoptosis pathway.

Keywords 2-Oxoglutarate · N-methyl-n-nitrosourea · Prolyl hydroxylase-2 · Breast cancer · Hypoxia

Introduction

Metastasis can be defined as, when the cells grow abnormally and invade to the nearby tissues and develops malignancy (Hanahan and Weinberg 2011). Tumor hypoxia is an imbalanced condition between the rate and supply of cellular oxygen (Heddleston et al. 2010). Previous literature validates the overexpression of hypoxia-inducible factor-1 α (HIF-1α) in tumor cells. Cancer cells have altered metabolism in hypoxic condition, and for the fulfillment of energy, cancer cells target glycolysis and lipid biogenesis (Warburg effect) (Cairns et al. 2011). HIF-1α upregulates the process of glycolysis and lipogenesis (Munoz-Pinedo et al. 2012), and this change is essential for cancerous cells to meet their metabolic requirements (Menendez 2010). HIF-1α is also reported to participate in the biological process of angiogenesis (Reddy 2013).

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