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Hypoxia mediated epigenetic deregulation DNA mismatch repair and epithelial-mesenchymal transition pathways in prostate cancer

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Introduction: Intra-tumoral hypoxia plays a significant role in progression, metastasis and ultimate clinical outcome in various cancers. The response to hypoxia is primarily mediated by the hypoxia-inducible transcription factor (HIF) which orchestrates a wide variety of epigenetic events including deregulation of histone and DNA modifications as well as expression of non-coding RNAs. The present study chiefly focuses onto hypoxia-mediated epigenetic deregulation genes pertaining to certain cellular pathways namely DNA mis-match repair (MMR) and epithelial-mesenchymal transition (EMT) pathways in prostate cancer.

Materials & Method: Gene expression of molecules connected to MMR and EMT pathways were compared between biopsy specimens collected from prostate cancer and benign prostatic hyperplasia patients. The observation of gene expression assay was validated in PC3 cell line following hypoxic treatment. Promoter methylation status of MMR genes was interrogated by methylation-specific-PCR and bisulfite-sequencing. Interaction between microRNAs and MMR genes was verified by 3'UTR-based dual luciferase assays.

Results: HIF-1α exhibited elevated expression tumor tissue samples as well as in PC3 cells following hypoxic stress. Expression of DNA methyl-transferases and several micro-RNAs were detected to be significantly dysregulated in tumor tissues. Hsa-miR-155 & Hsa-miR-141 and Hsa-miR-155 & Hsa-miR-21 were demonstrated to bind to their putative seed sequences in hMLH1 and hMSH6 3'UTRs respectively, downregulating the respective genes in tumor specimens. A critical zone in the promoter region of hMLH1 gene was identified to be hypermethylated in prostate cancer patients in a tissue-specific manner. Aberrant expression of several EMT markers and related transcription factors were observed in tumor tissues. Hsa-miR-205 that was reported to function in counteracting EMT and to be under direct transcriptional repression by HIF-1 was also found to be down-regulated in cancer tissues. Mi-RNAs over-expressed in prostate cancer tissues were detected in the patients' serum samples at higher level.

Conclusion: The present study detects HIF1-α as a master transcriptional regulator whose over-expression in prostate cancer results in an imbalance of several epigenetic modulators including DNA methyl transferases, onco miRs and tumor suppressor miRs as well as certain EMT-related transcription factors.

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