Heme Oxygenase -1 (HO-1) in the forefront of a multi-molecular network that governs cell-cell contacts and filopodia-inducedzippering in prostate cancer

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Background: Prostate Cancer (PCa) cells display abnormal expression of cytoskeletal proteins resulting in an augmented capacity to resist chemotherapy and colonize distant organs. We have previously shown that heme-oxygenase 1 (HO-1) is implicated in cell morphology regulation in PCa. Heme oxygenase 1 (HO-1) is the rate-limiting enzyme in heme degradation. HO-1 is a stress response protein and a critical mediator of cellular homeostasis. Although HO-1 role in cancer has been controversial, we have previously shown that its pharmacologic or genetic up-regulation is associated to a less aggressive phenotype in PCa. HO-1 inhibits cell proliferation, migration and invasion, it impairs tumor growth and angiogenesis in vivo and down-regulates the expression of target genes associated with inflammation. We have also demonstrated that HO-1 is implicated in the modulation of cellular adhesion in PCa, up-regulating E-cadherin and β-catenin expression, and relocating them to the cell membrane, favoring a more adhesive phenotype. However, it is yet unclear which are the HO-1 interactors and how it regulates cytoskeleton organization in PCa.

Methods: We undertook an in-depth mass spectrometry-based proteomics study to build the HO-1 interactome in PCa. We also took advantage of confocal microscopy to quantify and compare filopodia structures at the leading edge of PCa cells. Further we obtained RNA-sequencing (RNA-Seq) profiles of cells over-expressing HO-1 pharmacologically (hemin, 80 μM, 24h) and genetically (PC3HO-1).

Results: Through a multi “omics” approach we define the HO-1 interactome in PCa, identifying HO-1 molecular partners associated with the integrity of the cellular cytoskeleton. The bioinformatics screening for these cytoskeletal-related partners reveal that they are highly misregulated in prostate adenocarcinoma compared to normal prostate tissue. Under HO-1 induction, PCa cells present reduced frequency in migration events, trajectory and cell velocity and, a significant higher proportion of filopodia-like protrusions favoring zippering among neighboring cells. Moreover forced-expression of HO-1 was also capable of altering cell protrusions in transwell co-culture systems of PCa cells with MC3T3 cells (pre-osteoblastic cell line). Accordingly, these effects were reversed under siHO. Transcriptomics profiling evidenced significant modulation of key markers related to cell adhesion and cell-cell communication under HO-1 induction. The integration from our omics-based research provides a four molecular pathway foundation (ANXA2/HMGAl/POU3F1; NFRSF13/GSN; TMOD3/RAI14/VWF; PLAT/PLAU) behind HO-1 regulation of tumor cytoskeletal cell compartments.

Conclusion: The data presented here promise to move us closer to unravel the molecular framework underpinning HO-1 involvement in the modulation of cytoskeleton pathways, pushing towards a less aggressive phenotype in PCa.

Conflict of Interest: none

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