P44 Epigenetic reprogramming and mitochondrial dynamics drive self-renewal and tumorigenic capability of prostate cancer stem cells: new prospects for treatment of prostate cancer

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Introduction & Objectives: Intratumoral heterogeneity and the emergence of treatment-resistant cancer stem cells (CSCs) limit the efficacy of current therapies. These processes are genetically defined and epigenetically regulated. Notably, mitochondria play important roles in preserving the CSC subpopulation. Mitochondria fission provides for the elimination of dysfunctional organelles and retention of functional mitochondria in the CSC progeny during asymmetric cell division. Here, we investigated the basis of mitochondrial-dependent regulation of prostate CSCs and identified targetable elements to interfere with these essential processes in CSCs.

Materials & Methods: Prostate cancer cell lines were cultured as 2D adherent monolayers and 3D tumor-spheres. Protein and gene expression were assessed by immunohistochemistry, western blot and RT-PCR. Gene knockdown was performed using shRNAs. Mitochondria were examined by confocal microscopy and Seahorse flux analyzer. Cell senescence and proliferation were assessed by flow cytometry and colorimetric assays. In vivo tumorigenicity was determined by subcutaneous implantation of tumor cells in nude mice.

Results: We found that mitochondrial fission factor (Mff), a key player in mitochondrial fission, was frequently upregulated in hormone-refractory metastatic prostate cancers compared to primary tumors and normal prostate. Mff was upregulated in CSC-enriched tumor-spheres compared to bulk tumor cells. Depletion of Mff caused inhibition of mitochondrial fission and accumulation of elongated and distorted mitochondria in tumor-sphere cells. This was associated with deterioration of mitochondrial function selectively in tumor-sphere cells with minimal impact in bulk tumor cells. Inhibition of mitochondrial fission led to impaired asymmetric division with induction of senescence and loss of self-renewal in prostate CSCs. Conversely, proliferation of bulk tumor cells in 2D cultures was minimally affected. Genetic inhibition of Drp1, the Mff ligand, produced similar effects. Furthermore, Mff-depleted tumor cells had reduced ability to form tumors in mice, which correlated with reduced content of stem-like tumor cells in the xenografts. We found that increased expression of Mff in prostate CSCs relied on BRD4-dependent transcriptional activation. Accordingly, genetic knockdown and pharmacological inhibition of BRD4 caused improper mitochondrial fission and segregation in tumor-sphere cells resulting in loss of proliferative and self-renewal capability in vitro and reduced tumorigenicity in mice.

Conclusions: Prostate CSCs rely on enhanced mitochondrial fission to avoid senescence and preserve indefinitely self-renewal and tumorigenic potential. This provides a selective vulnerability that can be exploited for developing CSC-directed therapies and innovative approaches for treatment of prostate cancer.