Metastatic spread and cancer chemoresistance: genetic and epigenetic mechanisms

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Epigenetics

Metastatic spread is the most common cause of cancer-related death. Dissemination of cancer cells to other organs/tissues involves multiple steps, including cancer cells’ escape from the primary tumor, local invasion, intravasation, survival in the circulating system, extravasation and colonization of distant tissues. This biological process is rather inefficient, as most cancer cells never leave the primary tumor, and of those that intravasate and thrive as circulating cancer cells, the vast majority fail to colonize distant tissues. Epigenetic plasticity is emerging as one of the drivers of the metastatic cascade. DNA methylation is one of the epigenetic mechanisms that cells use to modulate gene expression. Hypermethylation of CpG islands in the gene promoter region can result in stable, yet reversible, gene silencing. Recent studies have demonstrated that methylation of CpG islands in the promoter of known tumor suppressor genes (BRCA1, MLH1, RASSF1A, TP73, SFRP1) occurs in cancer cells as an alternative mechanism to genetic copy loss or gene mutational inactivation.

We found that the promoter of the gene encoding the ubiquitin ligase FBXL7 is highly methylated in pancreatic and prostate cancers, correlating with decreased FBXL7 mRNA and protein levels. Low levels of FBXL7 mRNA are predictive of poor survival in patients with pancreatic and prostatic cancers. We also found that the FBXL7 protein targets the non-receptor tyrosine kinase c-SRC for proteasomal degradation. The DNA-demethylating agent decitabine recovered FBXL7 expression and restricted epithelial-to-mesenchymal transition and cancer cell invasion in a c-SRC-dependent manner. In vivo, FBXL7-depleted prostate cancer cells formed tumors with high metastatic burden, but co-silencing of c-SRC prevented metastases. Similarly, FBXL7−/− mouse pancreatic cancer cells displayed metastatic spread to distant organs, but this effect was abrogated by treatment with the c-SRC inhibitor dasatinib. Furthermore, decitabine treatment reduced metastases derived from prostatic and pancreatic cancer cells in a FBXL7-dependent manner. Taken together, these results suggest that c-SRC and DNA methylase inhibitors may represent an effective adjuvant and neoadjuvant therapeutic strategy aimed at
counteracting early metastatic dissemination in a subset of prostate and pancreatic cancers.

**Genetics**

Mitochondria are key intracellular signaling hub that play a pivotal role in several steps of cancer development and progression, including metabolic reprogramming, acquisition of invasive ability, and response to chemotherapeutic drugs. The majority of cancer cells harbors somatic mutations in the mitochondrial genome (mtDNA) and/or alterations in the mtDNA content, leading to mitochondrial dysfunction. “Dysfunctional” mitochondria can activate a mitochondria-to-nucleus signaling (retrograde signaling) that promotes rewiring of the bioenergetics and biosynthetic profile of cancer cells resulting in changes in transcription and/or activity of cancer-related genes and signaling pathways. We found that reduction of the mtDNA content in prostate cancer cells activates a retrograde signaling that results in reduction of the expression of the tumor suppressor BRCA2 and promotion of invasion and drug resistance.

We also demonstrated that loss of the tumor suppressor BRCA2 promotes resistance to anoikis, a crucial property of cancer cells that allows them to survive after intravasation in the circulating system. We found that loss of BRCA2 in castration-resistant prostate cancer cells increased the sensitivity to the chemotherapeutic drug 6-thioguanine and olaparib-induced apoptosis but did not affect cancer cell response to taxanes. BRCA2-proficient prostate cancer cells showed resistance to 6-thioguanine-, taxane- and olaparib-based treatment but were sensitive to 2-amino-6-bromopurine and 2,6–dithiopurine, two 6-thioguanine analogues. Taken together, these results provide a pre-clinical evidence for the use of 6-thioguanine in the treatment of BRCA2-deficient castration-resistant prostate cancers, and of certain 6-thioguanine analogues in the therapy of BRCA2-proficient prostate cancers.

**References**

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