A personalized medicine approach to identifying dysregulated epigenetic enzymes in the development of castrate-resistant prostate cancer

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Recent advances in proteomic and chromatin immunoprecipitation tools have been crucial in studying cancer epigenetics. However, the ability to measure directly the enzyme activities of dysregulated histone-modifiers has lagged. Here, we developed and utilized a high-throughput peptide microarray assay to identify altered histone lysine (de)acetylation activity in prostate cancer (PCa) cells. The microarray-based activity assay revealed up-regulated histone acetyltransferase (HAT) activity against specific histone H3 sites in an androgen-independent (AI) PCa cell line compared to its androgen-dependent (AD) isogenic counterpart. Employing these microarrays for NAD+-dependent deacetylation assays revealed down-regulated Sirtuin activity in AI cells. Together these results suggest a concerted mechanism leading to hyperacetylation of specific histone acetyllysine (H3K9, H3K14, H3K18) signatures, which were consistent with increased levels of these marks on endogenous histones extracted from AD and AI cells. Auto-acetylation of p300 at K1499, a modification known to enhance HAT activity and to be a target of deacetylation by SIRT2, was highly elevated in the AI cells. Among the sirtuins, only SIRT2 and SIRT3 protein levels were reduced in AI cell lines and in the majority (8/12, 66%) of AI human xenograft cell lines compared to their AS progenitors. Interrogation of AI human tumor tissue arrays reveals markedly upregulated H3K19acetylation and downregulated SIRT2 expression consistent with p300 overactivity. Together, the results suggest that reduced SIRT2 deacetylation of K1499 on p300 is responsible, in part, for enhanced p300 activity during the progression to AI, and that hyperacetylation of H3K9, H3K14, H3K18 is the net result of increased p300 and decreased SIRT2 activities. This novel microarray approach provides a method to identify commonly dysregulated chromatin enzymes during progression to AI in individual patients providing a therapeutic strategy that can direct available drugs to target epigenetic enzymes.

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