ANPEP regulates one-carbon metabolism in prostate cancer

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Background:
Prostate cancer (PCa) contributed to 34,700 cancer-related fatalities within the United States in last year alone. Notably, African American men (AAM) experience disproportionately higher rates of both PCa incidence and mortality compared to their European American counterparts (EAM). The current work investigates some of the biological factors which contribute to these disparities,

Methods
We carried out a genomic expression analysis of PCa stratified by ancestry using retrospective and prospective clinical cohorts. We then used molecular experiments and metabolomics to define characterize the functions of key candidates.

Results
We identified aminopeptidase N (ANPEP, APN, CD13), as the most differentially expressed gene in both self-identified and ancestry derived AAM compared with EAM. Previous studies demonstrated that the aminopeptidase ANPEP cleaves N termini of numerous hormones, cytokines, and chemokines involved in oncogenic signaling, cancer relapse and Inflammation. Specifically, ANPEP trims peptides with an N-terminal L-alanine and (L-cysteinylglycine)-S-conjugates while releasing alanine and glycine, respectively. While the role of ANPEP in cytokine activation is well studied, the contribution of ANPEP to amino acids homeostasis remains unknown. We demonstrate that expression of ANPEP predominantly correlates with various amino acid transporters. By employing untargeted metabolomics, we subsequently revealed a significant enrichment of one-carbon metabolism in cells that overexpress ANPEP. The one-carbon metabolism connects a series of metabolic pathways including the methionine cycle which in turn regulates methylation of various cellular substrates. We then performed genome-wide methylation profiling demonstrates that ANPEP overexpression is associated with elevated methylation of DNA. Because elevated methylation of DNA which is a determinant of therapeutic efficacy in prostate cancer, future studies will assess whether ANPEP regulation of methylation capacity impacts therapeutic efficacy and disease progression. To clinically validate our findings, we them carried out a fluxomic approach in ex vivo human tumor slice culture from 20 patients of prostate cancer. These studies demonstrate that PCa from AAM exhibit higher demand for methionine and cystine highlighting dominance of one-carbon metabolism.

Conclusion, we discovered a new function of ANPEP in regulating one-carbon metabolism in prostate cancer.

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Conflicts of Interest Disclosure Statement
Nothing to disclose.