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ANPEP: A potential regulator of tumor cell - macrophage metabolic interactions in prostate cancer of African American men

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African American men (AA) are more than twice as likely to die of prostate cancer (PCa) compared to European American men (EA). Among many contributing factors, unraveling the metabolic derangements in PCa of AA holds a promise in reducing health disparity. We recently discovered that aminopeptidase N (ANPEP, CD13) represents one of the differentially expressed genes in PCa of AA compared with EA. While ANPEP plays regulatory and/or modulatory functions in many immune and metabolic pathological conditions, its role in PCa remains unknown. We sought to investigate the metabolic functions of ANPEP in PCa development and exploit its role as a therapeutic vulnerability, particularly in AA men. Accordingly, we prospectively examined the differential gene expression of PCa from clinically matched AA and EA in the VANDAAM clinical trial. The VANDAAM study is a validation study of DecipherTM genomic testing in 240 men with localized PCa. Our findings indicate that ANPEP is the top differentially expressed gene between AA and EA men. To explore the molecular mechanisms of ANPEP in PCa in unbiased fashion, we combined computational and experimental approaches. Our preliminary computational analyses revealed that ANPEP correlates with signatures of cholesterol transport, estrogen and androgen receptor (AR) signaling. Based on our recent study demonstrating dominance of these signatures in macrophage-rich PCa, we reasoned that ANPEP expression may be driven in part by high macrophage infiltration in AA. Thus, we compared immune cell repertoire in patients with high ANPEP and low ANPEP by deconvoluting immune cell content using the in silico approach, CIBERSORT. These analyses illustrated that only AA patients with high ANPEP expression significantly accumulated high content of M1 inflammatory macrophages. Immune phenotyping of prostate tumors demonstrated that ANPEP indeed represents a marker of M1 inflammatory macrophages and tumor-associated macrophages. In conclusion, these findings suggest that ANPEP is a macrophage related protein in PCa with a potential role in cholesterol transport and / or androgen signaling. Future work will focus on the functional role of

ANPEP activity in the tumor immune microenvironment using Liquid chromatography-high resolution mass spectrometry (LC-HRMS) and explants derived from AA and EA prostate cancer patients.

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