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Sarcosine as a potential prostate cancer biomarker and therapeutic target

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Keywords

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Unlike many solid tumors which present as a single mass, prostate cancer is usually multifocal and more difficult to detect.[1] Additionally, prostate cancer symptoms do not typically present until the cancer has reached an advanced stage.[2] As a result, physicians have consistently relied on biomarkers as indicators of the presence and progression of cancer; an ideal biomarker would allow the physician to determine cancerous tissue from non-cancerous, and perhaps even metastatic cancer from localized.

In their letter to *Nature* (Volume 457, 12 February 2009), Sreekumar et al. screened 262 clinical samples for metabolites and defined sarcosine as a potential biomarker of interest.[3] Sarcosine is a derivative of the amino acid glycine, formed by the enzymes glycine N-methyl transferase (GNMT) or dimethylglycine dehydrogenase (DMGDH), and converted back into glycine via sarcosine dehydrogenase (SARDH).[3] As prostate cancer progresses towards metastatic disease, amino acid metabolism along nitrogen breakdown pathways increases.[3] As a result, they hypothesized that the prevalence of sarcosine increases with escalating severity of disease.[3] Its role in the progression of metastatic disease also prompted the investigation of sarcosine as a potential target of cancer therapy.

Forty-two tissue samples (16 benign, 12 clinically localized cancer, and 14 metastatic cancer) and 110 each of urine and plasma matched samples were assayed. A total of 1,126 metabolites were profiled, and of these only 176 (15.6%) were shared between all three (tissue, urine, and plasma) sample types. Levels of expression of these metabolites were then categorized based on whether the patient was biopsy-positive or biopsy-negative. Of the metabolites detected in plasma or in urine samples, few showed robust differences in expression levels between biopsy-positive and biopsy-negative individuals and false discovery rates were high (99% and 67%, in plasma and urine respectively).[3] Accordingly, researchers focused on tissue samples for metabolite discovery. An assessment of the 626 metabolites detected in tissue samples (23% false discovery rate) revealed 60 metabolites that were present in localized or metastatic cancer but absent in benign tissue, indicating that cancerous and benign tissue have relatively different

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metabolic profiles.[3] The 626 metabolites found in tissue samples were categorized based on the biopsy classification(s) in which they were found. The metabolites shared between benign and localized cancer tissues (n=547) were analyzed, and 37 of those had levels that were significantly different between the two groups. Similarly, the levels of 91 metabolites (out of 533 shared metabolites) could successfully distinguish between metastatic and localized cancerous tissue. Six metabolites, of which sarcosine was one, could both distinguish between benign and localized tissue and between metastatic and localized cancers. This paper focuses on sarcosine, and does not mention the other metabolites.

Sarcosine was further validated as a potential biomarker for early disease detection and as a predictor of aggressivity because it was undetectable in any of the benign tissue samples.[3] These data also show that levels of sarcosine were significantly higher in urine sediments and supernatants from biopsy-positive prostate cancer patients than they were in biopsy-negative controls. The non-invasive nature of this assay could make it significantly more appealing than a standard biopsy.

In prostate cancer, prostate specific antigen (PSA) has been shown to be a strong indicator of overall survival, risk of developing prostate cancer, and treatment success.[4] PSA is currently the gold standard for prostate cancer screening.[5] However, high PSA does not necessitate cancer, and even some men with cancer present with PSA levels lower than 4 ng/mL.[5] Because of this, there is considerable debate over what PSA level demands concern and if PSA should be used at all. Between 2–10 ng/mL PSA, it is difficult to separate patients with prostate cancer from those without.[3] When the samples studied here were restricted to those samples that fit this gray-area criterion, sarcosine was shown to delineate the two diagnostic classes more successfully than PSA.[3]

Additional studies of sarcosine revealed differences in expression between prostate cancer cell lines and benign prostate cell lines, as well as an association with the androgen receptor (AR) and ETS gene fusion regulation pathways.[3] Androgen signaling and the ETS family of gene fusions are significant factors in the development of prostate cancer[6], and Sreekumar et al. have shown through chromatin immunoprecipitation sequencing (ChiP-Seq) that AR and ERG bind to the promoter of GNMT, with ERG alone binding to the promoter of SARDH.[3] This shows that they are active in the sarcosine pathway and implicates sarcosine as a key player in prostate cancer progression.

In another study, Varambally et al. found that overexpression of histone-lysine N-methyltransferase (EZH2) in benign cells could lead to cell invasion and neoplastic progression.[7] Because sarcosine levels were also found to be associated with cell invasiveness, Sreekumar et al. studied the association of sarcosine with EZH2 and found that overexpression of EZH2 in benign cells increased sarcosine levels, while knockdown of EZH2 in cancerous cells decreased the amount of the metabolite. Indeed, merely adding sarcosine to benign prostate epithelial cells imparted an invasive phenotype, suggesting that sarcosine is directly related to the process of cancer invasion. Thus GNMT, SARDH, and DMGDH, all enzymes that regulate sarcosine levels, could be potential targets for modulation of prostate cancer invasion.[3] These data demonstrate that inhibitors of GNMT and DMGDH resulted in a reduction of cell invasion *in vitro*, while inhibitors of SARDH resulted in an increase in sarcosine levels and a concomitant increase in cell invasion *in vitro*.[3]

These data have shown that sarcosine is not only a novel and predictive biomarker but a key element of a potentially promising target pathway for the treatment and control of prostate cancer development.

Abbreviations

GNMT	glycine N-methyl transferase
DMGDH	dimethylglycine dehydrogenase
SARDH	sarcosine dehydrogenase
PSA	prostate specific antigen
AR	androgen receptor
ChiP-Seq	chromatin immunoprecipitation sequencing
EZH2	histone-lysine N-methyltransferase

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