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Commentary Open Access

N1,N12-Diacetylspermine as a Blood Based Lung Cancer Biomarker

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Commentary

It is becoming well recognized that metabolic perturbations are inherent hallmarks of tumorigenesis [1,2]. Metabolites represent the functional products of cellular processes, which are highly responsive to both pathological and environmental stimuli. As such, metabolites are the closest representation of an individual's current physiological state. Therefore, exploration of metabolic alterations in the context of disease pathophysiology, most notably cancer, holds great promise and considerable clinical value. This field of research has benefited from technological advances in mass spectrometry and ultraviolet-visible spectroscopic analyses that have enabled comprehensive metabolomic analyses of diverse arrays of metabolites, polyphenols and lipids in a variety of biological matrices with substantial robustness and sensitivity [3-9]. As a result, interest in the application of metabolomics to identify key metabolic differences related to pathological conditions has expanded. Indeed, metabolomics has been explored to gain insights into the pathophysiology of cancer, develop methods predictive of disease onset, and reveal new biomarkers relevant to disease diagnosis and prognosis [4-6] [10-12].

The application of metabolomics to the discovery of blood-based biomarker in cancer has substantial potential clinical relevance. Recently, we have identified the polyamine end-product N1, N12-diacetylspermine (DAS) as a novel pre-diagnostic serum biomarker for non-small cell lung cancer (NSCLC) [6]. In this study, DAS alone yielded an AUC of 0.610 and AUC 0.710 for sera collected 6 to 12 months and 0 to 6 months before onset of symptoms and diagnosis, respectively, in the discovery set. These findings were subsequently confirmed in an independent and blinded validation set [6]. Single markers are unlikely to exhibit sufficient performance to be fully informative of disease status. Therefore in our study we examined the performance of DAS in combination with another marker Pro-SFTPB, which we previously validated as a blood based marker for NSCLC [13]. The combination of DAS and Pro-SFTPB resulted in improved performance compared to either alone (Overall AUCs of 0.732, 0.650 and 0.699 in the validation set for Pro-SFTPB + DAS, DAS only and Pro-SFTPB only, respectively) [6]. This study highlights the potential contributions of metabolomics to the discovery of biomarkers that inform about disease risk before the onset of symptoms and, importantly, illustrates the value of DAS as a complementary non-invasive biomarker.

Recent findings by others have further demonstrated the potential of DAS. Takahashi et al. found that urinary DAS was an prognostic marker for NSCLC (hazard ratio of 4.652 [95% CI, 2.092-10.35]), particularly in squamous cell carcinoma [10]. Additionally, urinary DAS and N1,N8-diacetylspermidine have shown promise as diagnostic markers for breast and colorectal cancers [14].

While the latter findings implicate that DAS is not specific to lung cancer, it does highlight conserved metabolic dysregulation of polyamine biosynthesis, which is strongly associated with tumorigenesis [15,16]. However, one caveat that must always be considered is whether serum or urinary DAS differs between malignant and benign tumors. This is particularly relevant in lung cancer as screening methodologies have been largely hindered by high false positive rates, a consequence of the low prevalence of malignant solitary pulmonary nodules (SPNs) and high incidence of benign SPNs [17]. Thus, a clear delineation between malignant, benign, and control must be demonstrated, a matter being actively addressed. Furthermore, whether the biomarker of interest is directly originating from the tumor or is a reflection of a systemic inflammatory/immune response is an important aspect. Such knowledge is critical to assessment of the specificity of the marker. For instance, we have previously identified other circulating metabolites, independent from DAS, which distinguish subjects with NSCLC relative to control including reductions in the immune-regulatory metabolite tryptophan and elevations in maltose and glutamate [11].

Serum glutamate has exhibited good performance in discriminating early stage (IA/IB) NSCLC adenocarcinoma from control with an accuracy of 61.3% and 74.4% in the discovery and validation test sets, respectively [4]. Multiplex assays of 4 serum-based metabolite classifiers consisting of xylose, glutamate, aspartate and one unknown [Bin_225393] yielded accuracies of 66.9% and 72.7% in the discovery and test sets, respectively [4]. While these results are very encouraging, their performance may not be purely a reflection of cancer, given that metabolites such glutamate are also elevated in other pathologies and co-morbidities, such as diabetes [18,19]. Thus, in the case of glutamate, its value as a lung cancer-specific serum biomarker may hold very limited value when screening the general population. However, if the subject is already at high-risk of developing lung cancer and/or is suspected of having lung cancer then serum glutamate levels may be beneficial in aiding diagnosis.

Aside from its value as a biomarker, the biological significance of dysregulated metabolites, such as DAS remains to be determined and cannot be inferred from blood assays with respect to the source of the alteration. Assessment of metabolic alterations in cells and tissues would provide additional insights. Yet, even tissue-level metabolite information can be compromised by the inability to resolve directional fluxes without the use of stable-isotope tracers, sophisticated computational algorithms [20] and the ability to cover a comprehensive metabolic space. Under these constraints, the integration of multiple '-omic' methodologies (e.g. proteomics, genomics, transcriptomics) represents the strongest approach and provides a more accurate picture of the biology that may otherwise be missed or misconstrued by metabolomics only [21]. To the same extent, the influence that dysregulated metabolites have on the surrounding tumor microenvironment, particularly immune modulation, is equally intriguing. This is exemplified by metabolites such as tryptophan

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and its related catabolites that have garnered attention due to their immunosuppressive and pro-tumor growth functions [22-23].

In conclusion, the application of metabolomics to cancer blood-based biomarker discovery holds considerable potential. DAS serves as a promising pre-diagnostic marker for NSCLC that can complement other existing markers, such as Pro-SFTPB. The expansion of DAS to other cancers and cancer sub-types and whether or not it distinguishes between benign and malignant tumors remains to be determined. Coupling findings to the tumor microenvironment through integrative '-omic' approaches and basic research methodologies will be highly beneficial to derive biologically and clinically meaningful insights.

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