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Circulating protein biomarkers are a promising avenue for predicting patient response to cancer immunotherapies

Cancer immunotherapy relies on activating or enhancing the antitumor immune response and has taken a central position in cancer treatment modalities[1]. While offering a generally safer and more efficacious alternative to standard chemotherapy and radiotherapy[1,2], not all patients respond to immunotherapy, and combination immunotherapies increase cost of treatment and heighten the risk for toxicity-related adverse events[3,4]. An understanding of the molecular factors that contribute to clinical outcomes could enable improved selection of subject cohorts; therefore, identifying predictive biomarkers of immunotherapy response has become a growing focus of immuno-oncology research[4,5].

While understanding the complex molecular and cellular factors occupying the tumor microenvironment (TME) can provide important insights into immunotherapy response, accessing the TME requires surgery[4,6]. With recent studies suggesting that systemic host immune factors can predict patient response to immunotherapy treatment[4,7], there is now a mounting interest in using blood-based biomarkers to study immunotherapy response non-invasively. Circulating protein biomarkers are of particular interest as many immunotherapy treatments directly target proteins. However, blood-based proteins have been historically more difficult to measure due to the low concentration of biomarkers relative to unrelated background proteins and the low throughput of traditional protein detection techniques such as mass spectrometry and ELISA assays[8].

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Blood-based protein biomarkers can reliably predict response to cancer immunotherapy regimens

Initial investigations exploring the use of blood-based proteins as biomarkers have identified several promising prognostic indicators in blood. For instance, high levels of C-reactive protein (CRP) in blood have been used to predict resistance to Interleukin 2 (IL-2) therapy for melanoma[9]. Elevated blood levels of CRP and vascular endothelial growth factor (VEGF) are also associated with decreased overall survival following treatment with ipilimumab, an antibody that blocks the activity of CTLA-4, a receptor found on T cells that inhibits their antitumor functions[10]

VEGF belongs to a family of signaling proteins called cytokines, and studies assessing cytokine blood levels hold relevance to emerging, novel forms of immunotherapies that involve the genetic manipulation of an individual's own immune cells followed by their transplantation to enhance antitumor activity, such as chimeric antigen receptor T cell (CAR-T) therapy. While studies involving CAR-T therapy have demonstrated cancer remission rates of up to 80%, many individuals do not respond, and some even present with fatal toxicities resulting from a cytokine release storm (CRS)[11]. A study by Teachey et al. demonstrated that high pre-treatment blood levels of another cytokine, IL-6, are strongly associated with the development of CRS following infusion with CAR-T cells[12].

In addition to cytokines and CRP, other blood-associated proteins have been proposed as predictive markers for treatment response. Specifically, high pre-treatment blood levels of the angiogenesis promoting protein ANGPT2 were associated with reduced response and overall survival in single-drug immunotherapy-treated individuals. Intriguingly however, combination treatments decreased blood concentrations of ANGPT2[13]. A single-protein biomarker will thus likely not be sufficient to assess the complexity of the tumor-immune system interaction. A mass-spectrometry-defined 209-protein signature from patients with metastatic melanoma was recently reported to stratify cohorts into "sensitive" and "resistant" to immunotherapy regimens[14], but few laboratories have the equipment or expertise to adopt such a test at scale.

Using the SomaScan® Assay for identification of cancer-associated biomarkers

The immune-oncology field would greatly benefit from technologies that enable the detection of multiple novel blood-based biomarkers simultaneously in order to shed light on causal disease pathways and stratify individuals into cohorts for clinical trial analysis. Mass spectrometry-based approaches are insufficient as they are biased towards detection of more abundant proteins and are currently not suitable for complex body fluids with low-abundance blood-based proteins[15]. The SomaScan Platform is ideally suited for this purpose as it uses DNA aptamers: short, modified oligonucleotides that bind to proteins with high affinity and selectivity, enabling the simultaneous detection of 7,000 proteins across a 10-log dynamic range from just 55 µl of blood.

The successful identification of cancer-associated blood-based protein signatures using the SomaScan Assay has already been demonstrated for non-small cell lung cancer (NSCLC) in four different studies, resulting in the development of a 12-protein panel that differentiates lung cancer samples from controls and early stage vs late stage NSCLC patients[16]. A follow-up study by the same authors eliminated biomarkers influenced by sample processing, yielding a 7-biomarker panel that performed consistently in

two independent blinded verification cohorts with an area under the curve (AUC) of 0.85[17].
More recently, the SomaScan Assay not only successfully validated transcriptomic approaches that identified upregulation of proteases prevalent in prostate cancer, but also identified two previously unassociated proteases that are found in high prevalence in commercially available human prostate tumor samples[18].

Future potential of the SomaScan Assay for investigating immunotherapy-associated biomarkers

Studies conducted so far using the SomaScan Assay have demonstrated proof-of-principle that cancer-associated blood-based protein biomarkers can be reliably identified for multiple cancer types. Future studies involving time course monitoring of protein concentration changes and the identification of protein signatures associated with immunotherapeutic treatment response could lead to the development of models for stratifying patients. This information could be used to develop diagnostic tests that inform decision-making regarding patient subsets or for translational research projects comparing single agent versus combinatorial treatment strategies. The SomaScan Assay thus has immense potential in pinpointing mechanism of action for immune oncology treatment modalities that could help identify new treatment strategies as well as predicting successful response.

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