Nanoporous Substrates-Enabled, Functional Mechanism-Based Method for the Early Diagnosis in Cancer Diseases

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Circulating peptides have been recognized as useful signatures that can be traced to cancer-specific metabolic or post-translational modification events at early-stage tumor progression. However, efforts to identify serological peptide biomarkers have met with limited success, hindering understanding of the biological process of cancer development and our ability to detect it early with any real accuracy. It is known that serum peptides can provide accurate class discrimination between patients and healthy controls. Yet, it remains unclear whether this complex peptidome may provide a robust correlate of certain biological events occurring in the entire organism. To address these technical and conceptual challenges, we have established "Nanotrap" to effectively fractionate blood peptides with little to no sample processing. By coupling this technique to advanced mass spectrometry, we can bypass the limitation of current proteomic technologies, by "amplifying" the amount of small peptides extracted from blood samples, without using immunoaffinity agents. The spectra for these species would otherwise be clouded by larger and more abundant serum proteins. Such an enrichment, performed on a high-throughput platform, enables the elimination of confounding factors to signal-to-noise optimization, and instead allows us to focus on analyzing true disease signatures. More importantly, our studies do not solely focus on the discovery and validation of novel biomarkers. We are the first to demonstrate a link between the activity of Carboxypeptidase N (CPN) for breast cancer and prolyl-4-hydroxylase (P4H) for pancreatic cancer within tumor sites and the cleavage patterns of their catalytic substrates or their post-translational modification product in blood. Our cutting-edge nanotechnologies coupled with advanced mass spectrometry and customized biostatistical analysis facilitated the functional mechanism-driven peptide biomarker studies for revealing the early events associated with the signature mutations or pathways in tumor progression, leading to abnormal biological responses in tumor cells or its microenvironment prior to noticeable physiological symptoms.