Opinion

Decoding the blood peptidome as a new biomarker resource for cancer detection

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Proteases play important roles in all stages of cancer progression. Specific protease activities are known to degrade protein/peptide substrates to alter cancer cell behavior- including survival, growth, invasion, metastasis and death-through their actions to regulate growth factor activity, remodel the cancer microenvironment and affect other processes. Better understanding of specific protease actions to regulate of tumor behavior are complicated by the sheer number of proteases that could act in this process, as the human proteome contains at least 569 proteases and or protease homologues while the mouse and rat proteomes, respectively, contain at least 644 and 629 protease superfamily members. Within this complex systemic mixture of proteases, however, specific tumor-resident proteases (TRPs) are now increasingly regarded as informative biomarkers for staging cancer progression and evaluating therapeutic efficacy.[1] Current approaches to measure tumor-associated TRP expression or activity, however, require invasive biopsy that severely limits the utility of this information for tumor staging and treatment evaluation. Non-invasive methods to address this question would thus be of great potential use in approaches to improve early cancer detection and to monitor cancer progression and responses to treatment interventions.

Systemic markers of TRP activity may represent an alternate approach to evaluate TRP phenotypes and their correlation with cancer phenotypes. Several recent studies have established that serum peptide patterns correlate with cancer outcomes, and peptide profiles can be used to diagnose and evaluate the tumor stage of patients with certain types of cancer,[2] although most studies have not attempted to directly correlate tumor-associated peptide patterns with specific TRP activities. Our own results indicate that identifying the action of specific TRP activities is possible by analysis of the circulating peptide profile of tumor patients. Carboxypeptidase N (CPN)-associated peptide profiles in mouse and human blood samples correspond with those found in the interstitial fluid of mouse breast tumors or with CPN expression in normal breast tissue or breast tumor biopsies of women with various stage breast tumors.[3] We also found that in mice carrying ovarian tumors, serum levels of two complement C3f-derived peptides were primarily generated by tumor-resident matrix metalloproteases 9 (MMP-9) activity, which decreased in response to positive responses to therapeutic siRNA intervention.[4]

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Yaojun Li, Tony Y Hu
Department of Nanomedicine, Houston Methodist Research Institute, USA

Correspondence: Tony Y. Hu, 6670 Bertner Ave. R7-114, Houston, TX 77030, Fax +17134417834, Email yhu@houstonmethodist.org

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Based on importance of TRP activity during tumor development and progression, and recent results indicating the correlation of circulating peptide profiles with tumor stages and outcomes, we believe that systemic TRP peptide profiles have great potential as cancer biomarkers. Mass spectrometry (MS)-based diagnostic assays for cancer diagnosis, staging and treatment evaluation should be readily translatable to clinical use as MS diagnostics are already emerging as an important component of modern clinical laboratories.

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Conflict of interest

The author declares no conflict of interest.

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