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Commentary

Commentary on a "Strategy to Develop Clinical Peptide Biomarkers for More Accurate Evaluation of the Pathophysiological Status of Hypertensive Disorders of Pregnancy"

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) are serious complications of pregnancy. Many studies have sought to identify candidate disease biomarkers (DBMs) for use in clinical testing. Accumulating evidence suggests that many proteolytic peptides associated with individual health conditions are present in human body fluids, including peripheral blood. Here, the potential utility of peptidomic analysis for monitoring the pathogenesis of HDP is introduced and described. In particular, the importance of understanding the current technical limitations of the methods used to discover DBM in the blood is emphasized.

Keywords: Hypertensive disorders of pregnancy; Peptidomics; Disease biomarker

BACKGROUND

Pregnancy as a reproductive strategy is very unnatural, as many organisms have gone through sexual reproduction to become oviparous [1]. In humans, various mechanisms to maintain pregnancy exist between the uterus and placenta, which are at the forefront of the maternal-fetal interaction supporting a transplanted fetus for 266 days [1]. Hypertensive disorders of pregnancy (HDP) are among the most frequent and typical diseases in which this maintenance mechanism is impaired, and these disorders are life-threatening for the mother and child.

Documented at the time of Hippocrates (4th century B.C.), the pathogenesis of this syndrome is so complex that no essential treatment has been established since the mid-20th century (when it was known as "pregnancy toxicosis"). The English notation has not always been internationally standardized to date. The etiology of the syndrome is diverse. Despite a variety of basic and clinical studies, there is still no definitive method to predict the onset of this syndrome.

AN APPROACH TO MONITOR THE PATHOPHYSIOLOGICAL STATUS OF HDP, AN INTRACTABLE DISEASE OF UNKNOWN ETIOLOGY, USING PEPTIDOMICS

Various pathways are used to synthesize and metabolize proteins in living organisms. The process of cleavage of amino acid chains (polypeptides) by proteolytic enzymes is important. It has been hypothesized that the metabolic processes of these protein-derived peptide chains partly reflect various pathological conditions. Recent technological developments have helped identify various peptide fragments in tissues and body fluids. In particular, multiple peptide molecules have been reported to be present in blood, which is a commonly used clinical specimen [2]. These peptide metabolites appear to be altered in various pathological conditions, suggesting the usefulness of peptide fragments as pathological and disease markers (DBMs) [3,4].

Over the past decade, we have been experimenting with peptidomic approaches to search for DBMs that reflect the pathogenesis of HDP. We first attempted to identify candidate DBM peptides in peripheral blood samples from HDP patients by a comprehensive peptidomic analysis using one-step direct-transfer technology without depleting the major proteins in the blood, and identified 7 of the 23 peptides as fragments derived from kininogen-1 (three peptides), fibrinogen-α, complement component C4-A/B, α-2-HS-glycoprotein and inter-α-trypsin inhibitor heavy chain H4 [5,6].

Major proteins, such as albumin in serum, are barriers to blood peptidomics, but this is not an issue when using our method. Peptidomic analysis using mass spectrometry (MS) systems is very sensitive but costly. Therefore, this method has clinical

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significance for initial screening, but as a clinical test, a less expensive assay system, such as an immunological detection system using specific antibodies, needs to be developed. We developed immunodetection system for these DBM candidate peptides for validation experiments [7,8]. Moreover, quantitative MS studies of peptide fragments against which antibodies are difficult to produce have shown that peptidomic-based approaches may be useful for identifying DBMs predictive of HDP [9].

MS has been used since the beginning of the 21st century to identify and quantify various substances. There has been a great deal of technological innovation in this area, and MS has a very high sensitivity for detecting target molecules as stated above. However, high sensitivity is associated with sample preparation difficulties. Some problems remain in the application of peptidomic analyses in clinical laboratory medicine, particularly when analyzing serum samples.

Many of the conclusions and inferences drawn from these studies tend to be overestimated and exaggerated. Our method is no exception and is still in its infancy as an analytical technique; the benefits and concerns of using this method to elucidate the etiology of HDP, particularly the use of blood samples, have been described in detail in a recent review article [10].

CONCLUSION

The use of blood peptidomics to explore dynamic imbalances in vivo from a new perspective is an attractive concept for an important disease of unknown etiology, such as HDP. However, peptidomics is still in its infancy, and further research is needed to evaluate its usefulness in clinical medicine. More basic research needs to be performed on the application of peptidomics in clinical applications, including an investigation of the sample preparation conditions. The accumulation of reliable basic data, including the results of animal experiments, is essential for the sound and rational development of this technology in clinical applications.

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