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Invited critical review

Salivary proteomics in biomedical research

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ABSTRACT

Proteins that are important indicators of physiological or pathological states, can provide information for the identification of early and differential markers for disease. Saliva, contains an abundance of proteins, offers an easy, inexpensive, safe, and non-invasive approach for disease detection, and possesses a high potential to revolutionize the diagnostics. Discovery of salivary biomarkers could be used to scrutinize health and disease surveillance. The impact of human saliva proteome analysis in the search for clinically relevant disease biomarkers will be realized through advances made using proteomic technologies. The advancements of emerging proteomic techniques have benefited biomarker research to the point where saliva is now recognized as an excellent diagnostic medium for the detection of disease. This review presents an overview of the value of saliva as a credible diagnostic tool and we aim to summarize the proteomic technologies currently used for global analysis of saliva proteins and to elaborate on the application of saliva proteomics to the discovery of disease biomarkers, and discuss some of the critical challenges and perspectives in this field.

Contents

1. Introduction

Diseases are often discovered in an advanced stage because of the lack of specific symptoms and the diagnostic difficulties. An early molecular diagnosis is therefore of vital importance in order to increase the survival rate. Currently lack of an easy-to-use and inexpensive sampling method and lack of an accurate, and portable platform to facilitate early disease detection are the major limitations that have seriously hampered the development of clinical diagnostics [1]. A good diagnostic method should have the characteristics of high sensitivity, specificity, and functionality, and meet the requirements of high throughput, portability, and low cost for subsequent clinical application [2]. In most cases, the earlier the disease is diagnosed, the more likely it is to be successfully cured or well controlled, may dramatically reduce the severity of its impact on the patient's life, or prevent and/or delay subsequent complications [3]. Today, the improved efficiency and accuracy of proteomic technologies in biomarker discovery are turning salivary diagnostics into a clinical reality [4,5].

Human saliva is secreted from three pairs of major salivary glands namely parotid gland, submandibular gland and sublingual gland lying at the vicinity of oral cavity, and numerous minor salivary glands lying beneath the oral mucosa [6]. It contains a large array of proteins, many of which can be informative for the detection of diseases. Saliva is an attractive diagnostic fluid because it has several key advantages for disease diagnosis and prognosis, for example low invasiveness, minimum cost, and easy sample collection and processing [7]. As a clinically informative, it is useful for novel approaches to

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prognosis, clinical diagnosis, and monitoring and management of patients. Comprehensive analysis of human saliva proteome may contribute to the understanding of pathophysiology and provides a foundation for the recognition of potential biomarkers of human disease [8–10]. Saliva proteomic analysis shows great potential as a useful diagnostic tool and can facilitate monitoring of both disease progression and therapeutic treatments. These advantages have ensured the widespread use of saliva proteomics as a diagnostic tool in clinical practice, which will have an enormous impact.

Most clinical chemistry tests available today rely on old technologies, and these tests are neither sensitive nor specific for any particular disease and traditional markers only increase significantly after substantial disease injury [11]. Therefore, more sensitive markers of disease are eagerly needed, particularly, for the early detection of disease. Proteomics offers potential advantages that do not classically diagnose approaches, based on the following discovery of a suite clinically relevant biomarker that is simultaneously affected by the disease [12]. Recently, salivary proteomics has demonstrated a great potential for biomarker discovery and validation for various diseases [13]. Future of this field will depend on further validation of disease specific biomarkers, the assay that is quantitative, specific, rapid, reliable, sensitive, robust, and cost effective for broad implementation in diagnostic programs. In this review, the progress and prospects of salivary proteomics and its implications in diseases will be reviewed. In addition, we aim to summarize the proteomic technologies currently used for global identification and quantification of saliva fluid proteins, and elaborate the putative biomarkers discovered for a variety of human diseases.

2. Properties of saliva as a diagnostic fluid

Saliva is an important and necessary body fluid, contains a large array of proteins, many of which may be associated with the disease phenotype and can be very informative for human disease detection [14]. In general, whole saliva is most frequently studied because its collection is easy, noninvasive and rapid to obtain without the need for specialized equipment. Human saliva harbors proteins of clinical relevance and about 30% of blood proteins are also present in saliva [15]. It highlights that saliva can be used for clinical applications just as urine or blood. If successfully discovered and validated, these informative proteins may serve as biomarkers, leading to the use of non-invasive biofluid for detecting and monitoring the diseases.

Discovery of salivary biomarkers, and the ongoing development of diagnostic technologies have addressed its diagnostic value for clinical applications. Human saliva proteomics have proven to be a novel approach in the search for protein biomarkers for detection of diseases [16]. Moreover, the comprehensive analysis and identification of salivary proteins in whole saliva is a necessary pre-requisite to identify disease biomarkers and a powerful tool to better understand physiology. Currently, salivary proteome analysis represents an important field both for diagnosis and monitoring of various diseases and could be considered a novel approach to prevention of various pathological conditions [17]. Achievements of high-throughput approaches allow for disease-specific salivary biomarker discovery and establishment of rapid, multiplex, and miniaturized analytical assays [18]. As a diagnostic specimen in the clinic, saliva has many advantages in terms of collection, storage, shipping, and voluminous sampling; all of these processes can be carried out very economically compared with serum or urine. Saliva is also easier to handle during diagnostic procedures than blood because it does not clot, thus reducing the number of manipulations required. These advantages and developments have dramatically advanced saliva-based diagnostics. Therefore, the analysis of salivary proteomes emerges into a field of high interest with the future goal to maintain and improve livestock productivity and welfare.

3. Saliva diagnostics

People are aware of the importance of regular health check-ups; however, most diseases are not diagnosed until morbid symptoms become apparent in the late phase. To overcome this challenge, medical researchers are devoted to finding disease biomarkers that reveal a hidden lethal threat before the disease becomes complicated. For the patients, the noninvasive collection approach could dramatically reduce anxiety and discomfort, and increase their willingness to undergo health inspections [19–21]. For clinical applications such as monitoring disease status, onset, progression, and treatment outcome, there are three necessary prerequisites to materialize this goal: specific biomarkers associated with a health or disease state; a non-invasive approach to detect and monitor the biomarkers; and the technologies to discriminate the biomarkers [22,23]. Fortunately, saliva is a readily accessible and informative biofluid, making it ideal for the early detection of a wide range of diseases. Whole saliva is most frequently used for diagnosis of various human diseases since it is readily collected and contains serum constituents while gland-specific saliva is useful for investigating pathology of major salivary glands. One of the main advantages of saliva as a diagnostic tool is that sample collection is easy and noninvasive, thus dramatically diminishing discomfort associated with blood collection and privacy issues associated with urine collection [24]. This makes saliva a potentially valuable fluid for the diagnosis of various diseases.

Saliva diagnostics recently has there been a growing appreciation that saliva can reflect virtually the entire spectrum of disease states [25,26]. Saliva fluid being the 'mirror of body' is a perfect medium to be explored for health and disease surveillance. Recently, a growing number of proof-of-principle assays have been established using saliva to monitor diseases or bodily conditions such as infection, immune responses to viral infections, systemic levels of drugs, and the detection of illicit drug use [27,28]. A large number of medically valuable analytes in saliva are gradually unveiled and some of them represent biomarkers for different diseases including cancer, autoimmune diseases, viral diseases, bacterial diseases, cardiovascular diseases, and HIV [29]. These developments have extended the range of saliva-based diagnostics from the simple oral cavity to the personalized medicine applications. A major barrier to using saliva as a diagnostic fluid has been the fact that many informative analytes are generally present in lower amounts in saliva than in serum. Thus, saliva based diagnostics may offer a robust alternative for clinicians to use in the near future to make clinical decisions and predict post treatment outcomes.

Diagnostic markers for a number of diseases have been identified among salivary proteins, taking advantage of saliva as an easy-to-obtain biological fluid. There is an increasingly growing interest world-wide for the proteomics of saliva, since they provide a non-invasive source of unprecedently rich information [30]. The need remains to identify relevant disease associated salivary biomarkers for use in the pathological studies for diagnostic and therapeutic purposes. Salivary proteomic analysis represents an interesting and important field, both for the diagnosis and for the treatment of various diseases and could be considered a new approach to the prevention of diseases and various pathological conditions.

4. Salivary proteomics

Analysis of the key proteins in body fluids has become an important role to monitor the state of biological organisms and is a widely used diagnostic tool for disease. Proteomics provides potential advantages that classical diagnostic approaches do not, based on the following discovery of a suite of clinically relevant biomarkers that are simultaneously affected by the disease. Saliva has been increasingly recognized as an acceptable alternative to blood for use in diagnostic tests because salivary testing is safe, low cost, and non-invasive [31–33]. Global analysis of human salivary proteome is important