Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbapap

Review

Mass spectrometry-based proteomic quest for diabetes biomarkers ☆

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ARTICLE INFO

Article history:
Received 15 August 2014
Received in revised form 6 November 2014
Accepted 10 December 2014
Available online xxxx

Keywords:
Biomarker
Diabetes
Mass spectrometry
Proteomics
Selected reaction monitoring
SWATH MS

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia, which affects hundreds of millions of individuals worldwide. Early diagnosis and complication prevention of DM are helpful for disease treatment. However, currently available DM diagnostic markers fail to achieve the goals. Identification of new diabetic biomarkers assisted by mass spectrometry (MS)-based proteomics may offer solution for the clinical challenges. Here, we review the current status of biomarker discovery in DM, and describe the pressure cycling technology (PCT)—Sequential Window Acquisition of all Theoretical fragment-ion (SWATH) workflow for sample-processing, biomarker discovery and validation, which may accelerate the current quest for DM biomarkers. This article is part of a Special Issue entitled: Medical Proteomics.

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1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia. Individuals suffering from DM are estimated to increase worldwide from 171 million in 2000 to 366 million in 2030 [1]. There are two main subgroups of DM, type 1 (T1DM) and type 2 diabetes mellitus (T2DM) [2]. T1DM results from selective autoimmune damage to insulin-producing β cells which lead to irreversible dysfunction of the cells [3]. T2DM presents two major defects—β-cell dysfunction and insulin resistance in peripheral tissues, resulting from various causes including glucose toxicity and lipotoxicity [4,5]. Chronic hyperglycemia of diabetes can cause long-term damages to different organs, especially eyes (diabetic retinopathy), kidney (diabetic nephropathy), and nerves (diabetic neuropathy) [6]. The prevalence of diabetic complications rises up to 98% for patients diagnosed with diabetes for 10 years or more and the complications severely affect patient's quality of life and can ultimately lead to death [6,7].

Although great advances have been achieved the field of diabetes research over the past decades, a multitude of clinical problems persist. The identification of new biomarkers for early diagnosis and prediction of complications, particularly those in easily accessible clinical samples, would be useful to improved clinic outcome. Herein, we review the current status of diabetic biomarker research and provide some insights into the limitations and possible solutions for biomarker discovery and validation.

2. Clinical challenges of diabetes

Diagnosis of diabetes regularly relies on the measurement of blood glucose and insulin/C-peptide levels. However, blood glucose often rises temporarily under certain conditions of stresses such as myocardial infarction, infections, and surgery [8]. The use of medications can affect glucose levels as well [9]. Additionally, all the tests are exclusively dependent on the precise threshold values used which makes these tests relatively difficult to interpret and somewhat arbitrary [6,9]. It is not rare that some DM patients, who do not fulfill formal diagnostic criteria, may be already in the disease progression with certain degree of insulin resistance or inadequate insulin secretion [10].

Prediction and early detection of diabetes have potential to delay or reverse the diabetic progress. The pre-diabetic condition of T2DM is determined according to the plasma glucose measurement. However, many individuals in a pre-diabetic condition may have already acquired certain symptoms, while some of these pre-diabetic individuals can also remain in pre-diabetic status without progressing to diabetes [10,11]. It is not possible to personalize treatment for T2DM patients simply based on glucose measurement. For T1DM, the appearance of one or more autoantibodies targeting β-cells is among the first detectable clues of

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http://dx.doi.org/10.1016/j.bbapap.2014.12.012
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immune related β-cell attack [12]. However, not all islet autoantibody-positive subjects progress to T1DM [13]. A more precise prediction for diabetes is thus highly desirable.

Diabetic patients are prone to develop renal, retinal, or neurological complications. Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) [14]. Early diagnosis and medical intervention (e.g. angiotensin-converting-enzyme inhibitor, ACEI) of this complication can prevent its development to CKD and uremia [15]. Microalbuminuria has been used as a biomarker for decades. However, debate emerges about the predictive value of microalbuminuria because 1) only a small percentage of patients with microalbuminuria develop to proteinuria and eventually diabetic nephropathy, 2) progressive renal dysfunction can already be present in some patients with normal urinary albumin levels, and 3) many other nephropathies can cause microalbuminuria in diabetic individuals [16]. These limitations may be attributed to the routine immunoassay-based albumin measurement, which can detect only the immunoreactive forms of albumin, whereas other forms of albumin remain undetectable. It is indispensable to identify some predictive markers which enable clinicians to evaluate the necessity of medical intervention, especially for patients in CKD phase but with normal urinary albumin.

Effective monitoring of glucose levels is required for diabetic patients to achieve greater glycemic control. The blood glucose can be measured using either home self-monitoring of blood glucose (SMBG) or continuous monitoring of blood glucose (CMBG) [17]. Although SMBG is effective, patient compliance is poor mainly due to the requirement of blood sampling. Only about a quarter of diabetic subjects who require close glucose monitoring checked their glucose regularly [18]. CMBG includes a glucose sensor placed under the skin, which measures plasma glucose every a few minutes. However, CMBG is only applied in hospitalized patients, leading to a few drawbacks including high cost and invasive surgery [17,18]. Non-invasive specimens (e.g., salivary and tears) and assessments may benefit patients for better glucose monitoring.

To overcome these and other clinical challenges associated with DM, new biomarkers are highly desirable. Theoretically, genetic alterations (DNA-based), differentially expressed transcripts (RNA-based), and differentially regulated proteins (protein-based) can all be used as biomarkers. Recent genome-wide association studies (GWAS) have reported many loci implicated in T2DM pathophysiology. Saxena et al. identified and confirmed three loci associated with T2DM by analyzing 386,731 common single-nucleotide polymorphisms (SNPs) in 1464 T2DM patients [19]. However, establishing a clear and direct causal relationship between common genetic variations and disease development is not trivial [20]. It is evident that RNA levels do not necessarily correlate with protein levels and that protein levels are difficult to predict from genomic patterns [21]. The protein patterns are highly dynamic and are tightly regulated by intra- and extra-cellular stimuli without any change at genetic level [22]. Proteins are the final products of the gene expression process and they are therefore thought to be more direct reflection of disease status than nucleic acid-based markers. Therefore, proteins offer high potential to serve as biomarkers for clinical application [23].

Currently, enormous efforts have been invested to protein-based biomarker research, triggering rapid progress on MS-based proteomics in recent years. Nowadays, proteomics has penetrated into various field of biomedical research, including the exploration of diabetic biomarkers from a variety of biospecimens. In this article we review the quest for DM biomarker from sample-processing to discovery and validation using MS-based proteomics.

3. Specimens in DM biomarker research

3.1. Biofluids samples

Easily accessible human body fluids such as plasma and urine are thought to contain tens of thousands of different proteins [24] and they have become the most widely used samples for diabetic biomarker studies. New technologies of sample collection and preparation allow us to explore biomarkers in non-invasively obtained samples other than blood and urine. Bencharit et al. proposed that salivary proteomes of patients with DM can vary along with changes in their HbA1C levels [25], which may be used for glucose monitoring and help patients to achieve greater control on their diabetes. Kim et al. identified some tear proteins differently expressed in diabetic patients with retinopathy compared to control subjects [26], a finding that might be useful as diagnostic biomarkers of diabetic retinopathy. Moreover, vitreous humor is a highly hydrated extracellular matrix of the eye and is in close contact with the retina. It therefore reflects the physiological and pathological conditions of the retina and replaces blood fluid as a new source of for diabetic retinopathy research [27].

However, these biofluids share some common limitations. Take plasma for example, proteins in one clinical sample can span across a large dynamic concentration range of up to 12 orders of magnitude, which increases the difficulty of detecting low-abundance proteins [24]. The presence of very high abundance proteins such as serum albumin (35–50 mg/ml) which mask the lower abundance plasma proteins presents major challenges for comprehensive plasma proteome analysis [24]. The plasma flows through all organs; therefore tissue derived proteins get highly diluted in the systemic circulation to a concentration range of ng/ml and below [24]. Based on the information of HUPO plasma proteome collaborative study [28] and currently used plasma biomarkers [29], it is evident that the concentration ranges of the two populations minimally overlap [30], suggesting that the proteomic strategies used lacked the sensitivity to reliably detect potential biomarker proteins in the lower concentration ranges. These considerations remind us to re-consider the value of these newly identified diabetic biomarkers from biofluids. The new diabetic biomarkers discovered by MS-based methods are in the range of μg/ml to mg/ml, i.e. Complement C3 [31], Apolipoprotein (Apo) A-I [32], Apo C-II [33], Apo E [34], C-reactive protein (CRP) [34], and transferrin [35]. In contrast, the concentrations of C-peptide and insulin (routinely clinical used biomarkers) in blood plasma of healthy individuals are around 0.9 ng/ml and 0.36 ng/ml (Fig. 1). The two plasma biomarkers are thus situated below the region which traditional proteomic technology can reliably detect proteins and the same applies to many other clinically used biomarkers known today.

To comprehensively analyze plasma and other body-fluid samples at the required concentration range, specific sample preparation strategies have been developed. First, fractionation methods prior to MS analysis are introduced to allow the identification of lower-abundance proteins in serum and plasma [36,37]. However, such techniques can be problematic. Although sample fractionation is effective in increasing the depth of coverage of identified proteins, it also increases the number of samples to be analyzed per sample, which is time and labor intensive and thus prohibits comparative measurements of larger patient groups. Additionally, a multi-step protein separation workflow will add another level of bioinformatic complexity towards the detection of disease related patterns. Another strategy to achieve higher sensitivity has been the selective removal of high-abundance proteins by selective immunodepletion. This method is now routinely used and several reagents depleting different numbers of proteins are commercially available and quite robust (Table 1). Brand et al. reported that removal of the six most abundant plasma proteins leads to an estimated five-fold enrichment of a potential biomarker [38]. A third approach focuses on the in-depth analysis of subproteomes, for example, the identification of N-linked glycopeptides in complex biological samples (glycosylation enrichment) [39]. With this method, Liu et al. reported that 273 unique N-linked glycopeptides can be identified in plasma sample and the quantification of plasma glycoproteins was in the low ng/ml concentration range [40].

Besides sample preparation strategies, new MS technology has to be developed to be more sensitive to identify and quantify minute amounts of proteins in plasma (this will be discussed below).

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Please cite this article as: S. Shao, et al., Mass spectrometry-based proteomic quest for diabetes biomarkers, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbapap.2014.12.012

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