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Predictive biomarkers for type 2 of diabetes mellitus: Bridging the gap between systems research and personalized medicine

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ABSTRACT

The global incidence of metabolic disorders like type 2 diabetes mellitus (DM2) has assumed epidemic proportions, leading to adverse health and socio-economic impacts. It is therefore of critical importance the early diagnosis of DM2 patients and the detection of those at increased risk of disease. In this respect, Precision Medicine (PM) is an emerging approach that includes practices, tests, decisions and treatments adapted to the characteristics of each patient. With regard to DM2, PM manages a wealth of "omics" data (genomic, metabolic, proteomic, environmental, clinical and paraclinical) to increase the number of clinically validated biomarkers in order to identify patients in early stage even before the prediabetic phase.

Significance: In this paper, we discuss the epidemic dimension of metabolic disorders like type 2 diabetes mellitus (DM2) and the urgent demand for novel biomarkers to reduce the incidence or even delay the onset of DM2. Recent research data produced by "multi-omics" technologies (genomics/epigenomics, transcriptomics, proteomics and metabolomics), suggest that many potential biomarkers might be helpful in the prediction and early diagnosis of DM2. Predictive, Preventive and Personalized Medicine (PPPM) manages and integrates these data to apply personalized, preventive, and therapeutic approaches. This is significant because there is an emerging need for establishing channels for communication and personalized consultation between systems research and precision medicine, as the medicine of the future.

The increase of the incidence of obesity is abrupt, so it can be considered as a global epidemic with indirect effects on morbidity and mortality [1]. Likewise, the incidence of diseases like type 2 diabetes mellitus and coronary disease, which usually accompany obesity, is increasing [2]. Patients suffering from type 2 diabetes mellitus reached 347 millions in 2008 [1] from 153 millions in 1980 [3]. Several characteristics like old age, male sex, race and low socio-economic status have been recognized as risk factors [4]. Genetic predisposition is incontrovertible, especially when it comes from mother's side, but it is not the sole determinant [4]. DM2 is a metabolic disorder characterized by hyperglycemia due to the combination of decreased insulin secretion and increased tissue resistance to insulin action [4,5]. All the above, lead to both insufficient metabolism of glucose and low grade chronic inflammation of the adipose tissue [1,5]. The etiology of type 2 diabetes mellitus and obesity is multifactorial [1]. The interaction between genetic mutations, lifestyle and environmental factors determines the likelihood of this type of disease [1,5] (Fig. 1). The complications of the disease affect morbidity and mortality and have a negative impact on life expectancy [6,7]. A large body of data produced by '-omics' technologies, such as genomics/epigenomics, transcriptomics, proteomics and metabolomics, suggests that many potential biomarkers might be helpful in the prediction and early diagnosis of DM2 [8].

Age, sex, family history, lifestyle related factors (e.g. disturbed dietary patterns, lack of exercise, smoking, stress) [9,10] and anthropometric data (e.g. waist circumference, the Body Mass Index, BMI) form non-laboratory based clinical risk assessment of diabetes [11,12]. Commonly used biomarkers for the early diagnosis and monitoring of DM2 are glycosylated hemoglobin (HbA1c), fasting plasma glucose (FGP) levels and the oral glucose tolerance test (OGTT) [12,13]. In other studies, a correlation was found between salivary biomarkers (α2-macroglobulin, melatonin, α-hydroxybutyrate, glucose) and HbA1c [14,15]. Additionally, the DM2 risk stratification could use cardiovascular biomarkers, such as high sensitivity troponin (hs-trop) and B-natriuretic peptide (BNP) that appear to play an important role in the pathophysiological process of this metabolic disorder [11]. It is well known that polymorphisms in particular genes (e.g. PPARG, KCNJ11, TCF7L2, CDKAL1, HHEX, SLC30A8, IGF2BP2, CDKN2A) are associated with increased risk of developing DM2, and genotype scores based on

Abbreviations: DM, diabetes mellitus; PM, Precision Medicine; PPPM, Predictive, Preventive and Personalized Medicine

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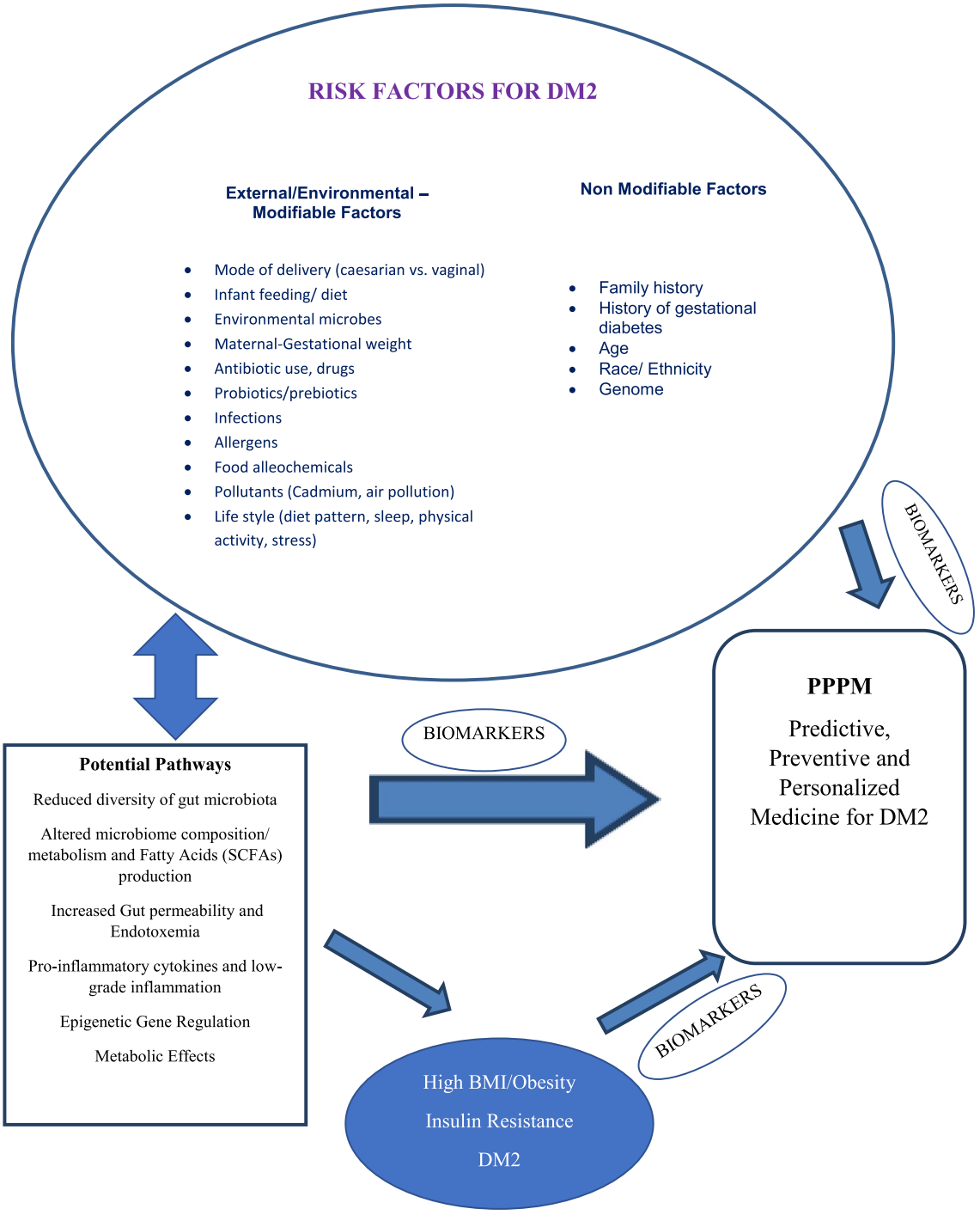

Fig. 1. Modifiable and non-modifiable risk factors for DM2 interact with gut microbiota and via multiple pathways induce insulin resistance and the onset of DM2. Potential predictive biomarkers could be identified using multilevel data from omics-driven technologies (genomic, proteomic, and metabolomics). These tools may enhance improved prediction, prevention, and treatment of T2D, in the settings of Predictive, Preventive and Personalized Medicine (PPPM).

allelic combinations are added to common and phenotypic risk factors [16–18]. At the epigenetic level, circulating miRNAs, e.g. miR-126, are an early detection tool for people at increased risk of illness [19,20]. Other potential predictors of DM2 are Branched Chain Amino Acids (BCAAs), such as valine, leucine and isoleucine, aromatic amino acids such as AA-phenylalanine, tyrosine, glycine, α-butyric acid, phosphatidylcholine, lysophosphatidylcholine, 10- and 12-(Z, E)-hydroxy-octadecadienoic acids, 2-aminoadipic acid, sex hormone binding globuline (HSBG), fatty acid binding protein (AFABP), cathepsin S, high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), total cholesterol, VLDL, LDL, HDL, vitamin D3 and its receptors, insulin, leptin, adiponectin, tissue plasminogen activator (t-PA), visaphin, resistin, betaphrotin, hepatic enzymes, such as Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), copeptin and pro-neurotensin [21–24]. It is impressive that in metabolomics research increased levels of metabolites such as the BCAAs have been found up to 13.7 years ahead of clinical expression in prediabetes and in DM2 [21,25].

A novel biomarker combination that includes measurements of alpha-hydroxybutyric acid (AHBA), linoleonyl-glycero-phosphor-choline (LGPC), and oleic acid in a fasting blood sample, is used to detect insulin resistance in high risk individuals, years before appearance of