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Pediatric endocrine and metabolic diseases and proteomics

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ABSTRACT

The principles of Predictive, Preventive and Personalized Medicine (PPPM) dictate the need to recognize individual susceptibility to disease in a timely fashion and to offer targeted preventive interventions and treatments. Proteomics is a state-of-the art technology- driven science aiming at expanding our understanding of the pathophysiologic mechanisms that underlie disease, but also at identifying accurate predictive, diagnostic and therapeutic biomarkers, that will eventually promote the implementation of PPPM. In this review, we summarize the wide spectrum of the applications of Mass Spectrometry-based proteomics in the various fields of Pediatric Endocrinology, including Inborn Errors of Metabolism, type 1 diabetes, Adrenal Disease, Metabolic Syndrome and Thyroid disease, ranging from neonatal screening to early recognition of specific at-risk populations for disease manifestations or complications in adult life and to monitoring of disease progression and response to treatment.

Significance: Proteomics is a state-of-the art technology- driven science aiming at expanding our understanding of the pathophysiologic mechanisms that underlie disease, but also at identifying accurate predictive, diagnostic and therapeutic biomarkers that will eventually lead to successful, targeted, patient-centric, individualized approach of each patient, as dictated by the principles of Predictive, Preventive and Personalized Medicine. In this review, we summarize the wide spectrum of the applications of Mass Spectrometry-based proteomics in the various fields of Pediatric Endocrinology, including Inborn Errors of Metabolism, type 1 diabetes, Adrenal Disease, Metabolic Syndrome and Thyroid disease, ranging from neonatal screening, accurate diagnosis, early recognition of specific at-risk populations for the prevention of disease manifestation or future complications.

1. Introduction

Predictive, preventive, personalized medicine (PPPM) is an emerging but quickly expanding concept in the provision of Health care services that aim to provide individualized risk assessment, preventive strategies and therapeutic options that are adapted to the needs of each patient and to the characteristics of the specific patient's disease, taking into account both genetic and environmental factors [1]. Within the context of PPPM, it is essential that we obtain a deeper knowledge of the mechanisms that underlie diseases, so as to be able to discern the subtle differences that render each patient unique and consequently offer him more prompt, cost effective interventions that treat or-ideally-completely interrupt the pathway from predisposition to disease [2]. To attain this target, the identification of reliable, clinically relevant biomarkers is of paramount importance. As defined by NIH, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions" [3]. Establishing validated biomarkers for disease risk, early and accurate disease diagnosis, staging and response to treatment (pharmacological or not) is one of the main pillars of a highly precise, personalized medicine. Proteomics is a technology-based science which studies the proteins, their post-translational modifications, their interactions, the changes in their levels, which result on account of specific diseases or from various

Abbreviations: 17OHPG, 17-Hydroxyprogesterone; Apo, Apolipoprotein; CAH, Congenital Adrenal Hyperplasia; CDG, Congenital Disorders of Glycosylation; DHEAS, Dehydroepiandrosterone Sulfate; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; ER, Endoplasmic Reticulum; GeLC-MS/MS, Gel electrophoresis Liquid Chromatography-tandem mass spectrometry; HLA, Human Leukocyte Antigen; PCOS, Polycystic Ovarian Syndrome; PPPM, Predictive, Preventive, Personalized Medicine; PTM, Post Translational Modification; T1D, type 1 diabetes mellitus; T2D, Type 2 Diabetes Mellitus; tTG, tissue Transglutaminase

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Table 1
Summary of main human proteomic and steroid biomarkers in pediatric endocrine and metabolic disorders.

Disease group	Specific disease	Tested tissue/body fluid (reference)	Biomarkers	Findings
Inborn errors of metabolism	Congenital disorders of glycosylation (CDG)	Serum/plasma [6,7]	Serum transferrin	Underglycosylation
		Plasma [7]	A1-antitrypsin	Underglycosylation
		Serum [8]	Immune response, coagulation mechanism and tissue protection against oxidative stress.	
		Plasma [9], serum [10]	Apolipoprotein C–III	Different N- and O- glycosylation patterns
	Organic acidemias			
	- Methylmalonic-acidemia	Fibroblasts, lymphocytes, liver [reviewed in [11]]	Energy metabolism, oxidative stress, cellular detoxification, cytoskeleton organization and assembly	
	Lysosomal diseases			
	- Niemann-Pick	Fibroblasts [15]	Protein maturation, energy metabolism, metabolism of reactive oxygen species, antioxidant activity, steroid metabolism, lipid localization, apoptosis (Torsin family 4 member A, 24-dehydrocholesterol reductase 4, calmegin precursor, superoxide dismutase 2, heat shock protein family B member 7, acid alpha glucosidase)	
	- Fabry disease	Serum [16]	α2-HS glycoprotein, vitamin D-binding protein, transferrin, Ig-α-2C chain, and α-2-antiplasmin	Downregulation
		Urine [17]	Immune response, inflammation, and energetic metabolism (Uromodulin, prostaglandin H2 d-isomerase and prosaposin)	Upregulation
		Plasma [18]		Gender specific biomarker panel
	Gaucher disease	Spleen/plasma [19]	Cathepsins	Upregulation
	Mucopolysaccharidoses	Urine [20]	Extracellular matrix organization (β-galactosidase, collagen type Iα, fatty-acid-binding-protein 5, nidogen-1, cartilage oligomeric matrix protein, insulin-like growth factor binding protein 7, cartilage oligomeric matrix protein, insulin-like growth factor binding protein 7, β-galactosidase, protein Heg1)	Upregulation
	Pompe, Fabry, Gaucher, Niemann Pick A/B, Krabbe, Mucopolysaccharidosis type 1	Dried blood spot [22]	β-glucocerebrosidase, acid sphingomyelinase, α-glucosidase, α-galactosidase, galactocerebrosidase, α-L-iduronidase;	
	Wilson's disease	Saiva [23]	pIgR peptides, α-defensins 2 and 4,S100A8, S100A9 and their oxidized forms	Upregulation
	Short-chain acyl-CoA dehydrogenase (SCAD)	Fibroblasts [25]	Fatty acid β-oxidation, amino acid metabolism, protein quality control system, energy reprogramming, cell survival and proliferation (Adenylate kinase 4, nucleoside diphosphate kinase A, aldehyde dehydrogenase family 4 member A1).	Upregulation
	Alkaptonuria	Chondrocytes [reviewed in [26]]	Protein oxidation	
Type 1 Diabetes	Markers of T1D/progression to disease	Serum [27]	Lipid metabolism and homeostasis (ApoA4, ApoC4, Complement Factor 3 and 4, clusterin, kininogen, transthyretin)	Downregulation
		Serum [28]	Lipid and cholesterol transport, acute inflammatory response, immune response (ApoC 4 and Apo C 2, mannose-binding protein C)	Downregulation
			(Complement factor H– related protein 5, Complement 9, profilin-1, afamin)	Upregulation
		Serum and plasma [30]	Alpha-2-Glycoprotein 1 (zinc), corticosteroid-binding globulin, lumican	Upregulation
			Clusterin and serotransferrin	Downregulation
		Serum [31]	Inflammation, oxidation, metabolic regulation, and autoimmunity	
			Adiponectin, insulin-like growth factor binding protein 2, serum amyloid protein A, C-reactive protein	Upregulation
			Myeloperoxidase,transforming growth factor beta	Downregulation
		Serum [32]	Innate immune responses, the activation cascade of complement, inflammatory responses, blood coagulation. (Platelet basic protein and C1 inhibitor)	
		Human pancreata [33]	Inflammatory response, inflammatory disease, cell death and survival, cell to cell signaling and interaction (Transforming growth factor B1, interleukin 1B, interleukin 8-precursor)	Upregulation
		Human beta cell [40]	Ubiquitin COOH-terminal hydrolase 1	Upregulation
	Markers of the exocrine pancreas			

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