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News & Views

The Human Diabetes Proteome Project (HDPP): The 2014 update

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ABSTRACT

Diabetes is an increasing worldwide problem leading to major associated health issues and increased health care costs. In 2012, 9.3% of the American population was affected by diabetes, according to the American Diabetes Association, with 1.7 million of new cases since during the year (www.diabetes.org). Proteome initiatives can provide a deeper understanding of the biology of this disease and help develop more effective treatments. The collaborative effort of the Human Diabetes Proteome Project (HDPP) brings together a wide variety of complementary resources to increase the existing knowledge about both type 1 and type 2 diabetes and their related complications. The goals are to identify proteins and protein isoforms associated with the pathology and to characterize underlying disease-related pathways and mechanisms. Moreover, a considerable effort is being made on data integration and network biology. Sharing these data with the scientific community will be an important part of the consortium. Here we report on: the content of the HDPP session held at the 12th HUPO meeting in Yokohama; recent achievements of the consortium; discussions of several HDPP workshops; as well as future HDPP directions as discussed at the 13th HUPO congress in Madrid, with a special attention given to the lists of prioritized, diabetes-related proteins and the proteomic means to study them.

Abbreviations: HUPO, Human Proteome Organization; HPP, human proteome project; B/D-HPP, biology/disease-human proteome project; C-HPP, chromosome-centric human proteome project; T1D, type 1 diabetes; T2D, type 2 diabetes; SRM, selected reaction monitoring.

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1. Introduction

The pathology of diabetes is an increasing concern in both industrialized and developing countries, and is therefore of major importance for the life science community. The Human Diabetes Proteome Project was created to gather worldwide experienced professionals in the field, aiming at joining the efforts to better understand the pathology and its associated complications. Meetings and workshops are organized throughout the year by the different partners, to promote sharing of scientific information concerning projects associated to the initiative. They are also used to discuss and decide on the group's objectives. The HUPO meeting in Yokohama (September, 2013), the HDPP workshop in Uppsala (April, 2014) and the HUPO meeting in Madrid (October, 2014) were the most recent occasions for the HDPP partner, as well as other scientists with particular interest in the field, to share their expertise and exchange their recent findings. We describe here the work accomplished by the partners during the year 2014, as well as the future directions intended by the consortium.

2. 4th HUPO diabetes workshop, Yokohama

Yokohama (Japan) hosted the 12th Human Proteome Organization (HUPO) annual world congress. HUPO congresses enable researchers involved in the Human Proteome Project (HPP) initiative to share their experiences, to network, and to advance their scientific research and collaborations. During the Biology/Disease Human Proteome Project (B/D-HPP) session led by Gilbert S. Omenn and Ruedi Aebersold, scope and objectives of the initiative were outlined: all B/D-HPP initiatives should follow the HPP requirements, in that they are based on three main pillars: the antibody pillar, the mass spectrometry (MS) pillar and the knowledge-based pillar [1–3]. Additionally, the importance of comprehensive network-based and systems-level approaches to decipher important disease-related mechanisms was emphasized.

The 4th Human Diabetes Proteome Project (HDPP) workshop at HUPO 2013 attracted about 90 attendees. The overall initiative was re-introduced and related themes were debated. Jean-Charles Sanchez, HDPP chair in 2013, presented the HDPP roadmap, website (www.hdpp.info), as well as the creation of the first "priority list" of proteins to be studied by the consortium (described in [4] "1000 diabetes-protein list").

HDPP aims at collecting various datasets from diverse origins, and at integrating them to perform network biology in order to maximize the conversion from data to knowledge. These resources include proteomic data from islets of Langerhans, beta-cells and blood; plus other tissues and fluids as described by Topf et al. [4]. Preferably, human samples will be analyzed, supplemented by data from other species, such as rat or mouse.

Several partners presented their projects at this workshop. These presentations included:

- An alternative to selected-reaction monitoring (SRM) for biomarker discovery in islets and subsequent quantification in plasma (Domitille Schvartz, Univ. Geneva, Switzerland).

The B/D-HPP aims also include the MS-based pillar, specifying the need for qualitative and quantitative measurements of the proteins of interest by mass spectrometry. The Translational Biomarker Group in Geneva developed an isobaric Tandem Mass Tag (TMT)-based method to identify and quantify proteins that are tissue-specific and also circulate in human blood, the latter being the most important biofluid for human biomarker discovery/validation. This method was applied to human islets and enabled the quantification of 729 human islet proteins in plasma, many of them having estimated plasma concentrations below 1 ng/ml (Human Plasma Proteome Database [5]; http://www.plasmaproteomedatabase.org/). Among these proteins, 449 are part of the 1′000-HDPP list, and 81 of them were detected for the first time in plasma (with reference to the human plasma database). This innovative approach presents a useful alternative to SRM for the detection, quantification and monitoring of proteins of interest in complex body fluids such as plasma.

- A systems omics perspective of diabetes (Michael Snyder, Stanford Univ., USA)

The Stanford group presented results of multi-omic longitudinal profiling (genomics, transcriptomics, proteomics, metabolomics, autoantibody profiles, metagenomics (i.e., microbiome) of a single individual over 3.5 years as well as plans to increase the study to a cohort of 60 individuals for three years. This longitudinal, $n = 1$ multi-omics approach revealed health trajectories and early deviations thereof.

- Beta-cell function in juvenile obesity and type 2 diabetes (Peter Bergsten, Uppsala Univ., Sweden).

Development of type 2 diabetes is connected to obesity. With growing numbers of overweight and obese children, the incidence of type 2 diabetes early in life is increasing dramatically. The progression towards overt type 2 diabetes reflects that the function of the insulin-producing beta-cell is impaired in those cases. The group in Uppsala is focused on defining mechanisms for this beta-cell impairment through the study of both isolated human islets at the cellular level and patient samples obtained from obese and normal weight children.

- Beta-cells and mitochondrial function (Martin Kussmann, Nestlé Institute of Health Sciences, Switzerland)

In the frame of the HPP MS pillar, the Nestlé Institute of Health Sciences in Lausanne has partnered with Thermo Fisher Scientific to advance technology and leverage this to the characterization and quantification of mitochondrial proteomes. Mitochondria were isolated from the rat livers. Ten-plex TMT was used for relative protein quantification between 18 experimental conditions. The samples were analyzed with reversed-phase liquid chromatography (RP-LC), coupled to either a hybrid linear ion trap-Orbitrap (LTQ-OT) Elite or an OT Fusion Tribrid mass spectrometer [6]. While both MS platforms roughly delivered the same proteome coverage, i.e., about 1′000 protein identifications (93% overlap), significant differences at the quantification level were obtained: using MS/MS/MS [7], the OT Fusion Tribrid usually provided larger and more discrete quantitative protein fold ratios with respect to the LTQ-OT Elite that employed MS/MS. More data points and less missing protein quantitative values were obtained with the OT Fusion Tribrid instrument.

3. From Yokohama to Madrid

3.1. From the 1000-HDPP to the 100-HDPP and the 25-HDPP

One of the prime requirements from HUPO and HPP for the B/D-HPP initiatives was to generate priority lists of biology/disease-relevant proteins and render them publicly available. This was achieved by the HDPP consortium during its first year of existence (2013), by creating the 1′000-HDPP protein list, containing to date 1′398 proteins considered to be of high interest in the field of diabetes, as well as their corresponding neXtProt, Human Protein Atlas and PeptideAtlas entries [8–10]. This list was published in the

first HDPP paper in 2013, and is also available from the HDPP web portal: http://www.hdpp.info/. Additionally, these proteins were marked in the PeptideAtlas with a specific mention of the "HDPP initiative". From the 1′000-HDPP, several sub-lists were created within the consortium: the 100-HDPP (Supplemental data), encompassing a selection of 100 proteins under consideration for biomarker development for diabetes and related conditions. This list is based on the literature and on expert recommendations. The 5th HDPP workshop in Uppsala in April 2014 was the occasion to generate an even more condensed list of 25 top-priority HDPP proteins, derived from the 100-HDPP, and representing the 25 top candidate biomarkers for diabetes-related conditions and their diagnostics in plasma. These proteins were selected based on collective expertise, discussions between the partners during the various workshops, and extended bibliographic research (Table 1).

Using Ingenuity Pathway Analysis (http://www.ingenuity.com), the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING [11]), and Protein Analysis Through Evolutionary Relationships (PANTHER) [12,13]; http://david.abcc.ncifcrf.gov/) analyses of the collected lists were made by the Univ. of Turku, providing an overview of the functional associations between these proteins. This 25-HDPP shortlist includes insulin; four insulin receptor proteins; and proteins involved in glucose and lipid homeostasis. The key pathways included type 2 diabetes, insulin signaling, adipocytokine signaling, as well as sugar and carbohydrate metabolism (Table 2). STRING provided a good visualization of the 25-HDPP (Fig. 1). To simplify the IPA analyses of the 25-HDPP, the 1000-HDPP was used as background; these analyses underlined the associations and importance of STAT3 (included in the 1000) in pathways related to immune response (Fig. 2). For the 100-HDPP, IPA presented some clear and distinct networks (Fig. 3). The network in Fig. 3**,** described as lipid metabolism, molecular transport, small molecule biochemistry, includes a number of the apolipoproteins (e.g., APOA1, APOA2, APOA etc.) and some interleukins (IL1 and IL2). In addition to NFκB, the peroxisome proliferator-activated receptors (PPARD, PPARG, PPARA), retinoic acid receptor (RXRA) and hepatocyte nuclear factors (HNF) occupy nodal positions. The Ingenuity canonical pathways of LXR/RXR activation and FXR/RXR activation were the most significant (analysis of the 100-HDPP, Table 3), indicating the participation of almost 20 proteins. Farnesoid X receptor (FXR) and liver X receptor (LXR) activation are both involved with cholesterol homeostasis. LXR, in particular is also involved with glucose and fatty acid homeostasis, whereas the primary role of FXR concerns suppression of cholesterol 7 alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis from cholesterol. Since insulin is a component of this pathway, the Ingenuity canonical pathways presented for the HDPP25 also included FXR/RXR activation. Additional details of the annotation and networks are provided as Supplemental data.

Table 1
The 25-HDPP. List of the top-25 proteins considered to be potential plasma biomarkers for diabetes-related disorders.

Name	Gene name	neXtProt
Adiponectin	ADIPOQ	NX_Q15848
Carboxypeptidase E	CPE	NX_P16870
Glucagon	GCG	NX_P01275
Glucagon receptor	GCGR	NX_P47871
Glucokinase	GCK	NX_P35557
Glucagon-like peptide 1 receptor	GLP1R	NX_P43220
Hexokinase-1	HK1	NX_P19367
Hexokinase-2	HK2	NX_P52789
Hexokinase-3	HK3	NX_P52790
Islet amyloid polypeptide	IAPP	NX_P10997
Insulin	INS	NX_P01308
Insulin receptor	INSR	NX_P06213
Insulin receptor substrate 1	IRS1	NX_P35568
Insulin receptor substrate 2	IRS2	NX_Q9Y4H2
Insulin receptor substrate 4	IRS4	NX_O14654
Leptin	LEP	NX_P41159
Leptin receptor	LEPR	NX_P48357
Apolipoprotein(a)	LPA	NX_P08519
Lipoprotein lipase	LPL	NX_P06858
Pro-neuropeptide Y	NPY	NX_P01303
Pancreatic prohormone	PPY	NX_P01298
Somatostatin	SST	NX_P61278
Mitochondrial uncoupling protein 1	UCP1	NX_P25874
Mitochondrial uncoupling protein 2	UCP2	NX_P55851
Mitochondrial uncoupling protein 3	UCP3	NX_P55916

3.2. The islet proteome database

3.2.1. Update on the database

Human islets are of central interest for type 1 and type 2 diabetes research, as they are a key functional unit for insulin production and secretion, and glucose homeostasis. Many efforts have already been made to characterize the human islet proteome and gain insight into the islet-related mechanisms involved in the development of diabetes [14,15]. We are building the largest human islet proteome database, constructed from two bottom-up proteomic studies. In the first study by Metz et al. the authors used two complementary proteolytic digestion protocols. They fractionated each sample with strong cation exchange, followed by RP-LC, and analyzed the peptides on a linear ion trap MS. MS/MS data analysis was done with SEQUEST, resulting in highly confident identification of 3′365 proteins with at least two unique peptides sequenced per protein (and 4′925 with one unique peptide) [16]. In the second study by Topf et al. digested peptides were fractionated by off-gel electrophoresis followed by RP-LC and analyzed by gas-phase fractionation MS. The authors identified 3′799 proteins with at least two unique peptides and a FDR $< 1\%$ (5′309 with one unique peptide) [4]. These two protein lists were combined into a set of 4′494 human islet proteins with two unique peptides sequenced per parent protein. In addition to their close similarity, the combination of the results from the two data sets significantly increased the overall number of entries in the reference database (Supplementary data). The islet proteins are equally distributed across all 24 human chromosomes, representing approximatively 30% of all protein coding genes for each chromosome, except for chromosome Y (Supplementary data).

In order to clarify whether this new islet proteome database contains yet unidentified proteins, we searched the neXtProt database for proteins in our database whose existence was not yet confirmed at the protein level. neXtProt, the knowledge-based pillar of HDPP, defines protein existence based on criteria established by UniProtKB/Swiss-Prot in 2007 [9]. Five levels of evidence have been defined: (1) evidence at protein level (e.g., identification by MS, detection by antibodies, sequence by Edman degradation, or tridimensional structure resolved); (2) evidence at transcript level (e.g., ESTs or full length mRNA); (3) inferred by homology (strong sequence similarity to known proteins in related species); (4) predicted and (5) uncertain (e.g., sequences that are likely the products of erroneous translations of pseudogenes). neXtProt applies the same criteria, but since it contains more MS data there is evidence for a larger number of proteins.

According to the neXtProt database, 34 of the proteins in our islet proteome database have to date only been identified at the transcript level. Table 4 describes these specific proteins and their chromosomal localization. This list will be spread into the scientific community, targeting especially C-HPP initiatives, through the HDPP website and the various congresses and workshops. This work thus bridges with the C-HPP initiatives to target their research of missing proteins across the various chromosomes [17].

Table 2
KEGG pathways associated with the 25-HDPP. The analysis was made using STRING, and a Bonferroni correction applied to the *p*-values calculated for the pathway enrichment.

KEGG_pathway	Protein count of 25	*p*-value (Bonferroni corrected)
hsa04930: Type II diabetes mellitus	9	1.0E-16
hsa04920: Adipocytokine signaling pathway	7	1.5E-10
hsa04910: Insulin signaling pathway	8	2.2E-10
hsa00524: Butirosin and neomycin biosynthesis	4	1.4E-09
hsa00052: Galactose metabolism	4	4.1E-06
hsa04960: Aldosterone-regulated sodium reabsorption	4	2.0E-05
hsa00520: Amino sugar and nucleotide sugar metabolism	4	4.8E-05
hsa00500: Starch and sucrose metabolism	4	5.7E-05
hsa00010: Glycolysis/gluconeogenesis	4	0.00013
hsa00051: Fructose and mannose metabolism	3	0.0018
hsa04973: Carbohydrate digestion and absorption	3	0.0024
hsa03320: PPAR signaling pathway	3	0.015
hsa04080: Neuroactive ligand-receptor interaction	4	0.048

3.3. Non-enzymatic glycation and aspirin-induced acetylation on blood

Another project implicated in the HDPP initiative concerns the characterization of specific post-translational modifications (PTMs) associated to diabetes. Diabetic complications have been proposed to occur through non-enzymatic modification of proteins by glucose, namely glycation, in various tissues, favoring, among others, the occurrence of atherosclerosis, renal failure, retinopathy, micro- and macro-angiopathy. Beside continuous advances in treatment of the deleterious effects of hyperglycemia, aspirin was shown to play a key role in the protection against the initial glycation process and, also, to be associated to a decrease in occurrence of cardiovascular events in high risk diabetic patients [18,19]. A mutual influence between aspirin-acetylation and protein glycation, was already proposed for human albumin [20] and for several other proteins as well, but few studies are currently available for complex samples with high dynamic ranges. For this purpose, in vitro analysis of protein extracts from blood fractionated plasma, erythrocytes (RBCs), leukocytes (WBCs) and platelets (PLTs) were carried out using high resolution tandem mass spectrometry coupled with a label-free approach, in order to provide (1) qualitative data through the identification of the preferential acetylation and glycation sites, and (2) quantitative information to evaluate the abundance of these PTMs. A total number of 40, 33, 73 and 44 unique acetylated proteins were identified in plasma, RBCs, PLTs and WBCs, respectively. On the other hand, a total number of 75, 60, 87 and 45 unique glycated proteins were identified in plasma, RBCs, PLTs and WBCs, respectively. These data are available on the HDPP website. Quantitative data were obtained for the majority of the identified proteins, and a significant effect in glycation and acetylation levels was observed for most of them including apolipoproteins, fibrinogen and complement factors in plasma; different hemoglobin subunits, carbonic anhydrase 1 and isoforms of peroxiredoxin in RBCs; interleukin α-1, protein S100 isoforms and

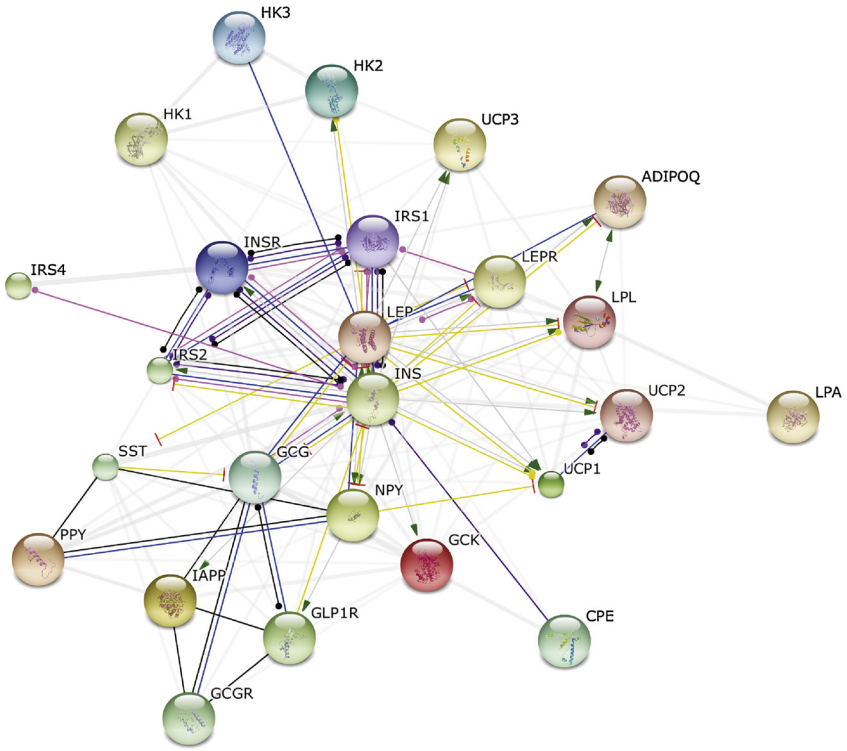

Fig. 1. STRING analysis of the 25-HDPP proteins. Nodes are either colored (if they are directly linked to the input or white (nodes of a higher iteration/depth)). Edges, i.e., predicted functional links, consist of up to eight lines: one colour for each type of evidence.

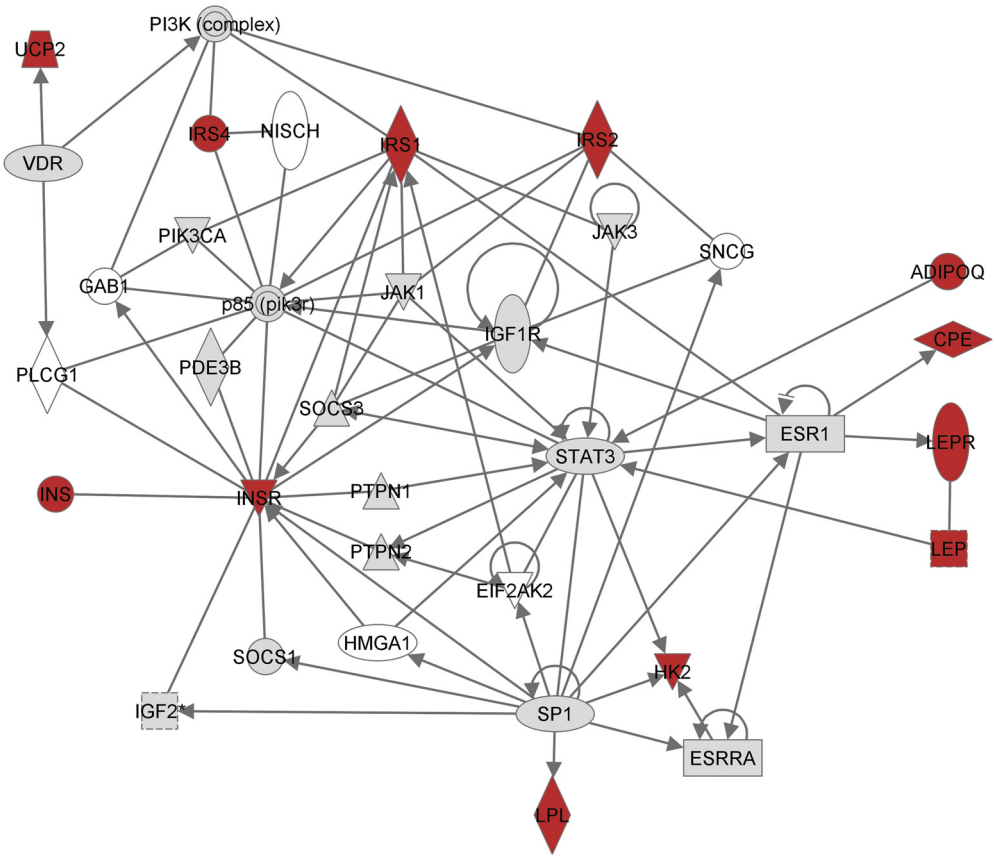

Fig. 2. Ingenuity pathway analysis of the HDPP proteins. Based on the 25-HDPP with a background of the 1000-HDPP (direct interactions only). The network identified is described as carbohydrate metabolism, endocrine system disorders and metabolic disease. Red shading represents proteins in the 25-HDPP, grey other proteins in the 1000-HDPP, and the uncoloured shapes are from proteins added by IPA.

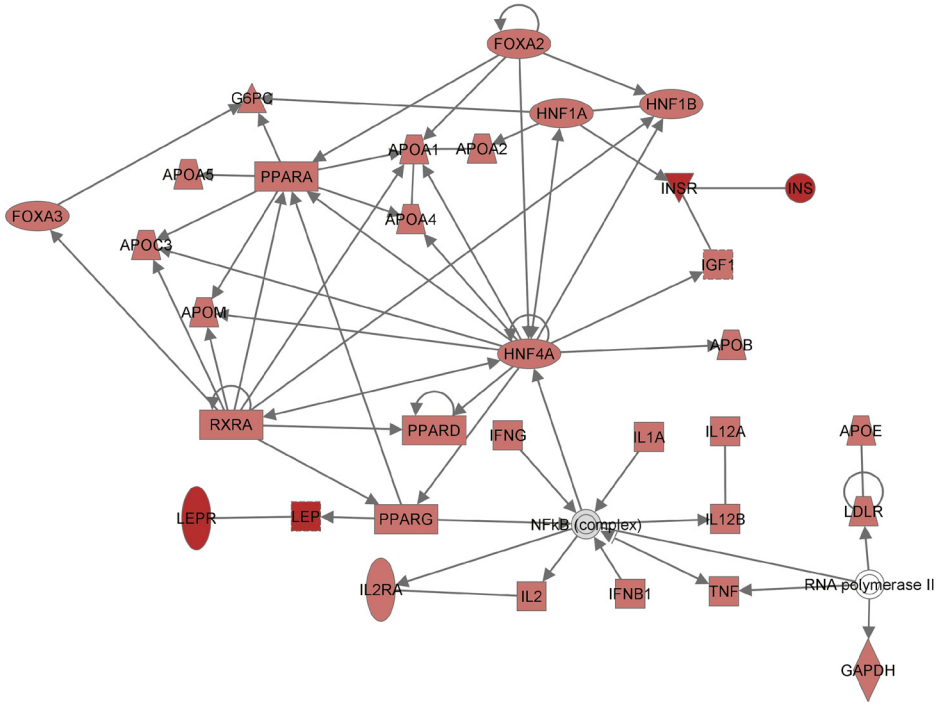

Fig. 3. Ingenuity pathway analysis of the HDPP proteins. Based on the 100-HDPP. The brighter red shading represents proteins in the 25-HDPP (e.g., LEPR & INS).

Table 3
The top Ingenuity canonical pathways associated with the 100-HDPP, giving an overview of the proteins associated with the LXR/RXR Activation and FXR/RXR Activation pathways. The pathways involving IL-12 signalling and other cytokines are also highly significant.

Ingenuity canonical pathways	*p*-value	Count	Molecules
FXR/RXR activation	1.26E-25	18	PPARG, PPARA, APOE, IL1A, APOB, HNF1A, IL18, APOA1, FASN, APOC3, FOXA2, INS, FBP1, IL1B, G6PC, RXRA, HNF4A, TNF, FOXA3
LXR/RXR activation	5.01E-24	19	APOE, IL1A, APOM, APOA4, APOB, LPA, APOA2, APOA5, IL6, RXRG, IL18, LDLR, APOA1, APOC3, FASN, LPL, IL1B, RXRA, TNF, APOD
IL-12 signaling and production in macrophages	1.00E-21	18	PPARG, IFNG, APOE, APOM, APOA4, APOB, LPA, IL12A, IL10, APOA2, IL18, APOA1, IL12B, APOC3, PIK3CB, RXRA, TNF, IL4, APOD
Role of cytokines in mediating communication between immune cells	2.00E-18	12	IFNG, IL18, IL1A, IL12A, IL12B, IL2, IL10, IFNB1, IL1B, IL6, IL13, TNF, IL4

myeloperoxidase in WBCs; integrin α-IIb, P-selectin and thymosin β-4 in PLTs (to cite few). These results strongly confirm the protective role of aspirin over protein glycation and in parallel highlight new interesting features through which glycation may influence aspirin-acetylation. In the near future we will use the same analytical method to compare the extent of protein glycation and aspirin-mediated acetylation in non-diabetic control subjects (HbA1c $\leq$ 6%) and in poorly controlled diabetic patients (HbA1c $\geq$ 8%), before and after aspirin treatment, in order to provide insights on the interplay exerted in vivo by aspirin and glucose at protein level and, at the same time, offer an alternative perspectives for the characterization of new potential markers

Table 4
List of 34 human islet proteins known in neXtProt only at the transcript level.

Chromosome	Uniprot	neXtProt	Band	First position	Last position
1 (China)	A6PVY3	NX_A6PVY3	q41	222910549	222924147
	Q5TZ20	NX_Q5TZ20	q44	248684916	248685964
	Q5VU65	NX_Q5VU65	q21.3	153965161	154127592
	Q6XR72	NX_Q6XR72	q41	219858769	220131989
2 (Switzerland)	Q9UBK7	NX_Q9UBK7	q13	114384806	114400973
	Q68DN1	NX_Q68DN1	p23.3	27799389	27805588
	Q6ZRH9	NX_Q6ZRH9	q31.1	175200604	175202151
4 (Taiwan)	O75795	NX_O75795	q13.2	69402902	69434245
	P78426	NX_P78426	q21.23	85413140	85419603
5 (Netherlands)	Q8NGU9	NX_Q8NGU9	q15	94955782	94957846
6 (Canada)	Q29865	NX_Q29865	p21.33	31228737	31232108
	Q8NA58	NX_Q8NA58	q25.3	160221298	160241736
7 (Australia)	Q96PB1	NX_Q96PB1	q21.3	94138531	94186331
	O43374	NX_O43374	q22.1	102220093	102257204
	Q96NL0	NX_Q96NL0	q21.12	87256864	87461611
	Q99680	NX_Q99680	q22.3	107110463	107116098
9 (Korea)	Q5TYW2	NX_Q5TYW2	q13	67926761	67969840
10 (USA)	O95231	NX_O95231	q26.3	135050908	135055433
	Q5W0B7	NX_Q5W0B7	p12.33	18041218	18089855
11 (Korea)	Q8NGF8	NX_Q8NGF8	p11.2	48238344	48239314
	Q96QZ0	NX_Q96QZ0	q24.2	124481386	124490252
	Q9Y2U2	NX_Q9Y2U2	q13.1	65360326	65363467
12 (India, Singapore, Taiwan, Thailand)	Q5BKT4	NX_Q5BKT4	p11.1	34175216	34182629
	Q9NQS5	NX_Q9NQS5	q13.13	54756229	54758271
15 (Brazil)	Q8NG48	NX_Q8NG48	q26.3	101099574	101143435
	Q8NCU7	NX_Q8NCU7	q22.2	62359176	62363116
	Q9UKL4	NX_Q9UKL4	q14	35043233	35047166
16 (Spain)	P17538	NX_P17538	q23.1	75252898	75258822
	P69849	NX_P69849	p13.11	16326352	16388668
17 (USA)	P05496	NX_P05496	q21.32	46970127	46973233
21 (Canada)	P58505	NX_P58505	q22.3	47720095	47743789
X (Japan)	O15391	NX_O15391	p22.12	21874105	21876845
	Q96DU9	NX_Q96DU9	q21.31	90689594	90693583
	Q9NY87	NX_Q9NY87	q27.2	140335596	140336629

of glycemic control, besides the commonly used glycated hemoglobin (HbA1c).

4. Madrid 2014 workshop

The international HDPP consortium is still growing and now encompasses 23 partners. The 13th HUPO congress in Madrid, Spain, was the opportunity for the key proteomic players in diabetes research to meet for their 6th HDPP workshop, which has been the follow up on the preceding HPP, C-HPP and B/D-HPP meetings. It was the place to discuss the 25-HDPP proteins list and its diffusion within the scientific community. This list was selected as the starting point of the first collaborative wet-lab project to be executed by the consortium, namely to develop MS and/or antibody-based assays to quantify these proteins systematically across human diabetes studies. The importance of working with panels of proteins was emphasized in the context of diabetes early diagnostic and follow-up.

In addition to protein "priority lists" created so far in the consortium, the workshop discussed future possibilities to provide added value by including metabolites, lipids, PTMs or other measurable biomolecules. Members of the consortium finally accentuated the importance of data sharing across the community, notably through scientific publications and the evolution of the HDPP website.

5. Conclusions

The Human Diabetes Proteome Project focuses on two main objectives: (i) to conduct comprehensive analysis of diabetes-associated molecular networks; and (ii) to identify diagnostic/prognostic proteins and isoforms associated with the pathology. For the past two years the consortium has collected and integrated datasets and is now rendering the related information accessible for researchers in the field. In parallel, priority lists were generated to highlight the proteins of key importance and relevance to diabetes research. According to the HPP guidelines, efforts will be made in the future to make MS and/or antibody-based assays available for the detection and quantification of these priority proteins as potential biomarkers for early disease diagnostics and/or or monitoring.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.trprot.2015.03.001.

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