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Review

The Human Diabetes Proteome Project (HDPP): From network biology to targets for therapies and prevention☆

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ABSTRACT

Type 2 diabetes is a worldwide disease reaching epidemic dimensions. The rapid progression of the disease urgently calls for both a broader and deeper understanding of its pathophysiology. In line with this statement, the Human Diabetes Proteome Project (HDPP) was officially launched at the 11th HUPO meeting in Boston, 2012. A special session was dedicated to this new initiative, gathering experts in the main topics related to diabetes and its associated complications. Key issues were debated with a focus on how deranged circulating glucose and free fatty acids induce dysfunction. It has been decided that HDPP will therefore focus on studying the early stages of diabetes that lead to abnormal glucose and lipid levels. The initiative will initially focused on islets of Langerhans, insulin-producing cell lines, and blood human samples from diabetes-related cohorts. In subsequent stages HDPP will investigate target tissues in which glucose and lipids could promote protein dysfunctions. Omics-rooted systems approaches enhanced by bioinformatics will be deployed to unravel effects of lipids and glucose triggering diabetes initiation and progression. A first milestone has been defined

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Glucose
Fatty acids

for the 12th HUPO meeting in Yokohama, 2013: the 1000 diabetes-associated protein (the 1000-HDPP) database, i.e. a freely available internet resource (www.HDPP.info) of more than 1000 proteins with links to their corresponding proteotypic peptides, affinity reagents and protein-specific biological/biomedical information.

Contents

1. Introduction

Epidemiological data from late 19th-century described diabetes mellitus (from the Greek "pass through" and Latin "sweet as honey") as a rather frequent disorder in man, in obese people above 50 years old, in cities and in western countries [1]. This classified diabetes as a disease of modern urban life. There are two main types of diabetes: (1) insulin-dependent diabetes mellitus (type 1 diabetes), which is an autoimmune disorder, and (2) non-insulin-dependent diabetes mellitus (type 2 diabetes), which is a complex multi-factorial disease. Type 2 diabetes (90% of the diabetic population) [2] affects nearly 150 million persons and is considered by WHO to reach soon epidemic proportions. Diabetes is a global public health problem with high costs and suffering primarily due to long term complications. The pathogenic process involves complex interactions between genetic and environmental factors. Type 2 diabetes is characterized by an abnormal glucose homeostasis leading to hyperglycemia. The glucose homeostasis deregulation is mainly due to a combination of insulin resistance and defects in insulin secretion. Many candidate genes have been reported to be associated with both defects, however none of them accounts for the majority of patients affected by type II diabetes. In addition, factors including diet, stress, exercise, aging and obesity seem to play a major role in the development of the disease. The long-term complications associated with diabetes lead to chronic degenerative complications. They have been classified as macro-vascular (atherosclerosis and subsequent classical consequences such as stroke and myocardial infarction) and micro-vascular complications (nephropathy, retinopathy and neuropathy). However, the relationship between the metabolic disorders and these complications is not clearly understood. For that reason, a better understanding of the early pathophysiological mechanisms causing multiple organ and cell type dysfunction is required to further development of more efficient treatments. Diabetes is a complex condition with genetic, environmental and lifestyle factors. Therefore, only a highly interdisciplinary international collaboration can deliver the multidimensional insights needed to unravel the dynamics of cellular pathways that are of key interest in diabetes and its associated complications.

We propose here to leverage a worldwide constellation of expertise into a Human Diabetes Proteome Project (HDPP) initiative to generate systems-level insights into diabetes-associated cellular changes by gathering multivariate data sets over time from specialized cells and organs of healthy and diabetes-affected individuals. Longitudinal systems biology

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data sets will be collected from human body fluids, organs and cells, as well as from cellular and animal model systems of the disease. The results generated by the consortium will be made available to the wider research community by means of public repositories and data integration platforms such as neXtProt [3].

The HDPP is not only expected to deliver comprehensive information on disease mechanisms but also to identify proteins and isoforms associated with diabetic pathogenesis and complications that are crucial for the development of better diagnostics, therapies and prevention strategies. The integration of HDPP into the overarching Human Proteome Project (HPP) [4] initiative opens favorable conditions for information exchange and collaboration across all the Chromosome and Biology/Disease HPP (C-HPP [5] and B/D-HPP [6]) initiatives.

2. Network biology of glucolipotoxicity

Diabetes occurs when insulin secretion is inadequate and can no longer maintain normoglycemia. Failure of the beta-cell secretory machinery has been suggested as a primary cause for the reduced insulin secretion but loss in beta-cell mass by a skewed ratio of apoptosis *versus* proliferation has also been suggested [7–9]. It has been demonstrated that a tight control of glycemia in T2DM improves insulin sensitivity and secretion, suggesting a toxic effect of elevated glucose levels on beta-cells and insulin target cells [10]. Indeed, prolonged exposure of beta-cells to high levels of glucose decreases insulin secretion [11]. Not only glucose but also fatty acids cause harmful actions depending on their concentration and exposure time [12]. Chronic high glucose and lipid exposures modify a number of biological pathways including the expression of glucose and lipid metabolic enzymes as well as transcription factors. Two concepts have thus emerged: glucotoxicity and lipotoxicity. The concept of glucolipotoxicity with the hypothesis that elevation of both glucose and fat synergize their toxicity on cells has also been proposed, where glucose-induced reduction in fat oxidation and promotion of lipid esterification in beta-cells could contribute [13,14]. This concept is potentially complementary to the fact that reactive oxygen species (ROS) and glycation of proteins are implicated in both glucotoxicity and lipotoxicity inducing cell apoptosis [15]. The goal of the HDPP initiative is to understand the complexity of cellular responses through the use of large-scale network biology-based approaches on various specialised cells and tissues. This network based approach will allow to dissect the regulatory mechanisms that underlie the detrimental effects of glucose and lipids, and potentially development of new therapeutic drugs protecting cells and organs from the toxicity of excess of these molecules.

3. The target disease: diabetes

Type 1 as well as type 2 diabetes are progressive diseases. Their progression is associated with numerous complications such as micro- and macrovascular disease, retinopathy, neuropathy, nephropathy and obesity. The HDPP consortium aims at increasing the overall knowledge about the diabetes-related pathology and associated phenomena. For this purpose, the HDPP consortium has prepared a 10-years plan allowing the different diabetes-associated problematics to be covered. During the first phase, partners intend to focus their work on islets of Langerhans, insulin-producing cell lines, and blood samples from diabetes-related cohorts as these are already accessible through various existing omics datasets. In a second phase, the work will be extended to hepatocytes, muscle tissue, neurons, adipose tissue, vascular endothelial cells, retina, kidney, plasma/serum, erythrocytes, peripheral blood mononuclear cell (PBMC), platelets, lacrimal fluid, and saliva. Cell line models that might be representative of the above tissues will also be studied in this phase. Moreover, even if human samples are of greatest interest, other species samples are available and have other advantages. For instance, datasets from rodent beta-cells are already available to be included in the HDPP initiative.

The HDPP plan includes working at different levels of knowledge. The aim is to gather datasets from proteomics, peptidomics, lipidomics, metabolomics, transcriptomics, epigenomics, but also modifications of interest in the field such as glycation, acetylation and palmitoylation. Mapping the diabetes related data on existing interaction networks will be the first step in data integration. This will lead to a better understanding of the pathways involved in diabetes. Furthermore, networks will be generated from each new dataset. On each resulting network, public available functional annotations, pathways and Gene Ontology terms will be mapped. This will lead to an extension of the existing networks but also help to focus on relevant nodes and edges within the network.

Our future generated datasets and those already available will be integrated in public repositories and databases to share them with the research community. NeXtProt [3] that integrates UniProtKB/Swiss-Prot [16,17] for provision of gold standard protein function is hereby the starting point. Moreover, high-throughput experimental datasets such as the one provided by the Human Protein Atlas [18] are our central resource for antibody-based catalogue and tissue microarrays. ProteomeXchange [19] and PeptideAtlas [20] will be used for exchanging and addressing the challenge of reanalysis and finally to access to the primary experimental mass spectrometry data.

The long-term goal of HDPP is to identify and understand the cellular pathways that are of central interest in diabetes and its associated complications. A better understanding of the decline in cellular function the occurs in diabetes is expected to reveal new target pathways and thereby help develop treatments to decelerate and even arrest the disease process by restoring normal cellular function. HDPP will develop and apply network biology to highlight mechanisms related to the biological effects of glucose and lipids. The HDPP project goals and deliverables are based on the three HPP pillars: (1) build and expand the diabetes proteome knowledge base, which we will implement using data integration techniques, (2) augment specific diabetes-relevant protein binding reagents, which will be realized by development of novel and cataloging of already available protein affinity reagents, and (3) enhance mass spectrometric tools for these proteins and peptides.

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4. Initiative structure

As one of the B/D-HPP initiatives, the HDPP will be structured to match HUPO requirements [3,6,21,22]. Working groups were created within the consortium in order to fulfill the various milestones established in the initiative. Additionally a management structure was created to lead the project.

4.1. *Working groups (WGs)*

Working groups were first set as presented in Table 1, but will evolve during 2013 as projects will be precisely defined.

4.2. *Management and structure*

The core of the decision making structure is composed of the Project Coordinator (PC) and Project Management Committee (PMC) (Fig. 2). The PMC will be composed of a representative of each working group and partner and of the PC. This structure insures the coordination and the management of the project with several decision levels including global strategy and assessment of HDPP. The aspects related with dissemination for an appropriate diffusion of the results of the projects are dealt by the PMC as well.

4.2.1. *Milestones*

The project has specific milestones that are set for monitoring progress. The milestones will also be a way to verifying that the HDPP activities in terms of obtained and expected results are in agreement with the B/D-HPP milestones.

4.2.2. *Information exchange*

Working documents, minutes of meetings, bibliography, data, publications and presentations given on behalf of HDPP will be available on the web-based platform (www.HDPP.info). The aim of the website is to serve as a communication platform for the partners of the HDPP project. The website is build using the Drupal content management system [23]. It is hosted by the University of Geneva and is available at www.HDPP.info to the public. The Drupal based system has been extended by an email contact form, user and mailing-list management and an internal area. Keeping security in mind, all confidential content is only accessible at the internal area of website after secured login. Fig. 1 shows the login form of the website.

The latest news on project status and upcoming events are published on a blog, which serves as front-page. In the future, the website will become the central resource of HDPP diabetes-related knowledge. All tools developed for the integration of omics data and their analyses will be made available on it.

Table 1 – Description of the HDPP Working Groups (WG).

Groups	Themes
WG1	Obesity related to diabetes
WG2	Neuropathies related to diabetes
WG3	Retinopathies related to diabetes
WG4	Nephropathies related to diabetes
WG5	Macro-vascular diseases (atherosclerosis)
WG6	Omics platforms
WG7	Post-translational modifications (glycation and palmitoylation)
WG8	Databases
WG9	Computational biology
WG10	HPP integration
WG11	Funding
WG12	Management and dissemination

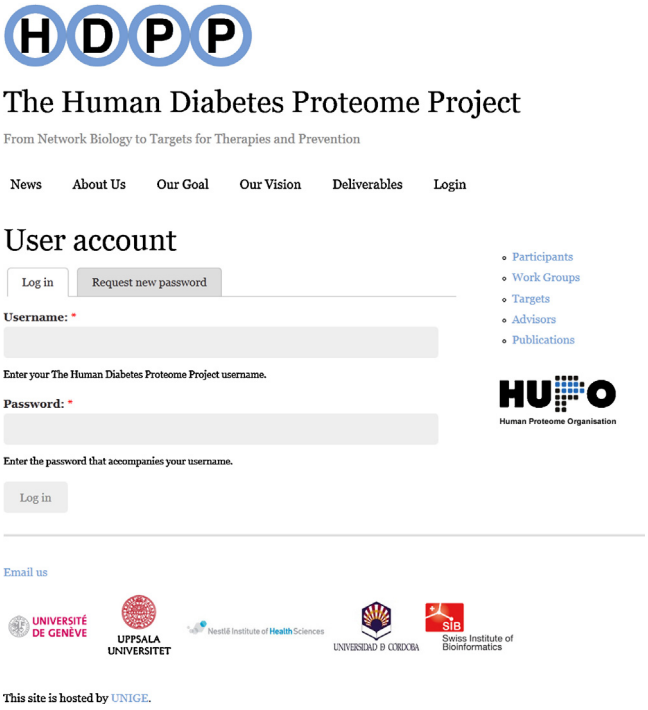

Fig. 1 – The login form of www.HDPP.info.

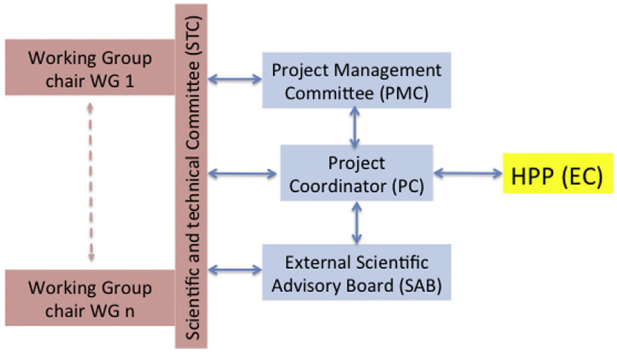

Fig. 2 – Structure of the HDPP initiative.

5. Deliverables and key research projects

The first short-term objective of the HDPP project is to gather knowledge on diabetes and related complications already acquired by the different partners. Data on human islets, rodent beta-cells, and blood glycation are already accessible from partners' research projects as described in this section. They will be grouped and further processed using

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bioinformatics tools to enhance current knowledge of key diabetes pathways. This first leveraged knowledge base will be further enhanced by integration of results from additional HDPP projects.

5.1. *The 1000 diabetes-related proteins: the 1000-HDPP*

The first deliverable for HDPP is to generate a list of proteins that are of central interest for the condition of diabetes. This list (supplementary data 1) was generated from the neXtProt database, by first searching this public domain with specific key words related to different subtypes of diabetes, and then by expert validation of the retrievals.

Supplementary material related to this article found, in the online version, at doi:10.1016/j.trprot.2013.03.002.

The actual list comprises 1379 proteins, and will further evolve and mature over time. Each entry contains: the protein and gene names; the neXtProt/UniProtKB accession number; the SRM/PeptideAtlas and Human Protein Atlas cross-references; a list of available protein binding reagents; the chromosome location; and the number of isoforms/variants/PTMs. This resource is already available on the HDPP website (www.HDPP.info).

5.2. *The human islet of Langerhans proteome database*

A proteomic analysis in the context of the Beta-JUDO project (see Section 5.5) allowed the identification of more than 5300 human islet-related proteins by Gas-Phase Fractionation mass spectrometry. The resulting dataset has been submitted to PRIDE (27518-27529) *via* ProteomeXchange (10.6019/PXD000050). Furthermore, this list was used by neXtProt to upgrade the protein existence level of some proteins. A brief overview of the identified proteins can be found in supplemental data 2. Each entry contains the same type of data than the 1000-HDPP list.

Supplementary material related to this article found, in the online version, at doi:10.1016/j.trprot.2013.03.002.

5.3. *The rodent beta-cell proteome database*

The rat insulin-secreting cell line INS-1 was established in 1992 [24]. It is probably the most widely used clonal cell model in beta-cell research. Several proteomics datasets on total cell [25] and sub-cellular fractions [26] have been obtained from this slowing growing rat insulinoma beta-cell with more than 2500 identified proteins. The list is in supplementary data 3. Each entry contains the UniProtKB accession number, the name and the gene name.

Supplementary material related to this article found, in the online version, at doi:10.1016/j.trprot.2013.03.002.

5.4. *The human blood glycated proteome database*

An analysis of glycated proteins in biological samples could give new insights into the characterization of the blood glycated proteome [27]. Therefore a qualitative/quantitative approach has been developed. Hyperglycaemia is a conditioning factor promoting the non-enzymatic glycation of proteins in those sites kinetically favored. The blood glycated proteome is dynamic and evolves qualitatively and quantitatively with unbalanced glucose concentration. For this reason, it is interesting to obtain profiles containing information of glycation sites as a function of hyperglycaemia level. The application of the analytical approach has revealed the identification of 35 glycated proteins in normoglycaemic plasma with detection of 113 glycation sites [27]. The list of glycated proteins is in supplementary data 4. Complementarily, human hemolysates with different levels of hyperglyacemia have also been analysed with the same approach revealing quantitative modifications of the glycation profile with the concentration of glycated haemoglobin [28]. The dynamic character of the blood glycated proteome under hyperglycaemia justifies using the same approach to different blood fractions in order to understand modifications occurring as a result of unbalanced glucose homeostasis.

Supplementary material related to this article found, in the online version, at doi:10.1016/j.trprot.2013.03.002.

5.5. *The Islet Human Diabetes Proteome Project (i-HDPP)*

The insulin-producing beta-cell is located in the pancreatic islets of Langerhans. In individuals with diabetes this cell type is either lost (type 1 diabetes mellitus, T1DM) or functionally impaired (type 2 diabetes mellitus, T2DM). The prevalence of especially T2DM in connection to obesity is rising [29]. To halt the increase in the number of individuals developing diabetes, gathering available information about which pathways are differentially activated in the islet under normal conditions as well as during development of diabetes is crucial.

Building an islet (i) resource by collecting available data sets generated from the islet organ and beta-cell lines of human and non-human origin will be central in the islet HDPP. Expression data sets obtained at different stages of the disease are of particular interest. An additional aim of the *i*-HDPP is to identify areas less investigated and stimulate and promote research efforts in such areas.

Establishing links between past, present and future research projects, where beta-cell pathway profiling is a component, and the *i*-HDPP resource is an important task of the initiative. An example of such interaction is the on-going FP7 project "Beta-cell function in juvenile diabetes and obesity" (Beta-JUDO). This project is investigating the role of the beta-cell in the development of obesity in young individuals. In one part of the project human islets are exposed to different conditions relevant for obesity development. This part of the work has already allowed the identification of 5300 human islet-related proteins by mass spectrometry (see Section 5.2). In the project, changes in human islet expression data sets are subsequently generated and analyzed by network biology strategies.

Dysfunction or loss of the insulin-producing beta-cell is the main factor in development of diabetes in both its forms. The number of individuals developing diabetes is escalating. Coordinating and making available existing and future islet

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beta-cell expression data sets may prove decisive in finding novel strategies to halt the destructive beta-cell process precipitating the disease.

5.6. *Dysfunction of insulin-producing cell lines induced by high glucose*

Given their role in insulin secretion and therefore in glucose regulation beta-cells are pivotal in diabetes pathologies. It is thus essential to increase our knowledge about beta-cell function and dysfunction to gain insight into the disease. In line with the HDPP, the aim of the project is to monitor proteomic and transcriptomic modulation of insulin-producing cell lines exposed to chronic high glucose levels, which is a hallmark of type 2 diabetes. Stable isotope labeling with amino acids in cell culture (SILAC) was applied to rat insulinoma INS-1E cell line grown either at intermediate or high glucose levels. Whole cell extract as well as insulin secretory granules (ISGs), mitochondria and nuclei were prepared. Proteins were separated on SDS-PAGE, digested with trypsin, and peptides were analyzed by LC-MS/MS. Proteins were identified and quantified with MaxQuant [30]. Transcriptomic data sets ($n = 12$) were generated under similar conditions using Illumina ratref-12 expression bead-chips. Validation of the protein localization and level of expression were performed by qRT-PCR, western blots and immunofluorescence. About 2500 proteins were identified in the sub-cellular INS-E fractions (see Section 5.3). Among them, 33 displayed an expression significantly affected by high glucose concentration. These proteins are mainly related to fatty acid metabolism, proliferation, and apoptosis such as Neuronal Pentraxin 1, NP1. Bioinformatic integrations of these different rodent datasets will contribute to the comprehension of glucose-induced effects on beta-cells, and is therefore of high interest for the HDPP project.

5.7. *Profiling analysis of human glycated proteins by isotopic labeling with ^{13}C-reducing sugars*

In the last years several efforts have been carried out to elucidate the connection between glucotoxicity effects under hyperglycemia and the wide spreading of systemic long-term complications that occur under diabetes mellitus. High glucose levels in the bloodstream (>11 mM) tend to enhance the kinetics of a non-enzymatic reaction involving sugar attachment to protein specific sites. This process, termed glycation, results in the impairment of proteins activity by the formation of adducts that affect recognition sites directly involved with the protein function or, at long-term, by formation of advanced glycation end products (AGEs) that alter the structure of proteins. Here, recent advances on the state-of-art of glycation analysis are presented with an approach relying on differential labeling of proteins with isotopically labeled glucose ([$^{13}C_6$]-glucose). An incubation step with [$^{13}C_6$]-glucose mimicking physiological conditions initiates this protocol to label chemoselectively only the sites, which are prone to glycation. Qualitative analyses are carried out by tandem mass spectrometry after Glu-C protein digestion and boronate affinity chromatography for enrichment of glycated peptides. Two orthogonal tandem mass spectrometry methods are used: HCD-MS2 and CID-MS3 with neutral loss scanning. Quantitative analyses are based on the relative ratio between MS1 precursor signals corresponding to endogenous glycated peptides (labeled with [$^{12}C_6$]-glucose) and *in vitro* glycated peptides ([$^{13}C_6$]-glucose). This experimental strategy enabled to characterize and quantify the native glycation state of proteins from human plasma and hemolysate (see Section 5.4). Apart from that, predictive analyses intended to evaluate qualitatively and quantitatively the effect of prolonged hyperglycaemia over the glycation profile can be planned. Further studies on the high-risk population of diabetic patients should provide new insights about the influence of glycation on molecular and functional networks related to hyperglycemia. For this reason, as described in Section 3, partners will initially focused on islets of Langerhans, insulin-producing cell lines, and blood human samples from diabetes-related cohorts. In subsequent stages the glycation approach will be applied to target tissues in which hyperglycaemia could promote dysfunctions such as hepatocytes, muscle tissue, neurons, adipose tissue, vascular endothelial cells, retina, kidney, erythrocytes, peripheral blood mononuclear cell (PBMC), platelets, lacrimal fluid, saliva and cell lines associated with the listed primary cells. A complementary phase could be the application of this methodology to animal models in those situations in which it could be required. This project will be an integral part of the new Human Diabetes Proteome Project (HDPP) initiative to generate systems-level knowledge into diabetes-associated cellular changes.

5.8. *Mitochondria and beta-cell function*

Insulin resistance alone does not result in T2DM because hypersecretion of insulin from beta-cells is able to maintain normal glucose homeostasis. However, subsequent decline of insulin secretion will lead to impaired glucose homeostasis and the development of the disease. Islets from diabetic human donors secrete much less insulin in response to glucose even when correcting for total insulin content [31]. These results suggest beta-cell dysfunction as an early event during diabetes progression prior to beta-cell loss.

The beta-cell acts as a fuel sensor. The uptake and metabolism of nutrients in beta-cells is linked to the formation of downstream signals stimulating insulin secretion. This process is known as metabolism-secretion coupling and is tightly linked to mitochondrial function [32]. Mitochondria are not only the site where nutrients are oxidized but the organelle also exports metabolites that are activators of insulin granule exocytosis. This is best studied for the ATP/ADP ratio, which increases as a result of mitochondrial activation. This rise induces the closure of the KATP channel, depolarization of the plasma membrane resulting in calcium influx, which stimulates insulin granule exocytosis.

Consistent with the central importance of mitochondria, inhibition of respiration blocks insulin secretion. Furthermore, mitochondrial dysfunction has been observed in islets from individuals with T2DM. Both insulin secretion and the ATP/ADP response to glucose were strongly impaired in islets from donors with T2DM [33]. These findings were supported by

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dramatic morphological abnormalities of mitochondrial ultrastructure in these islets.

We will study the molecular mechanism leading to mitochondrial abnormalities during T2DM disease progression. These studies will be initiated with mitochondria from INS-1E beta cells following nutrient oversupply. The changes in the mitochondrial proteome observed in this model system can then be tested in a more focused manner studying mitochondria of rodent or human islets. This analysis will be complemented by functional studies of beta-cell mitochondria at the single cell level, which are designed to elucidate the mechanisms leading to beta-cell dysfunction during T2DM progression.

5.9. *Cardiovascular diseases: focus on antiplatelet therapy*

Platelets play a key role in the pathogenesis and the ischemic complications of atherosclerosis, a major macro-vascular complication of diabetes [34]. Although antiplatelet drugs usually belong to the first line treatment in cardiovascular patients, its efficacy in preventing recurrence of ischemic events in those patients with diabetes is controversial. Aspirin is the most prescribed antiplatelet drug for the long term prevention of ischemic events [35]. Through acetylation of cyclooxygenase 1 (COX-1), aspirin abolishes platelet-derived thromboxane (Tx) A2 production and impairs platelet activation. However, despite appropriate antiplatelet therapy, vascular events recur in a significant proportion of patients, raising the possibility of biological "aspirin resistance" being implicated in these treatment failures [36]. Indeed, variability of the biological effect of aspirin has been described. The ability of platelets to generate TxA2 is best reflected by serum TxB2, a stable spontaneous breakdown product of TxA2. A prospective study on 700 consecutive aspirin-treated patients presenting for diagnostic cardiac catheterization showed that high TxB2 levels (present in 8% of the population) were independently associated with cardiovascular ischemic events during a 2-year follow-up (HR 2.4, 95% CI 1.1–5.5) [37]. Determinants of the variability of aspirin response are not well understood but diabetes and platelet turnover are consistently associated with increased residual platelet reactivity in these patients [38–40]. This finding is consistent with the lower, if any, cardiovascular protective effect of aspirin in diabetic patients [41]. The effect of both aspirin and glucotoxicity relies on protein derivatization. The discovery of the identity and function of the glycated blood proteins generated by chronic hyperglycemia and the impact of glycation on the acetylation potency of aspirin would thus be of a considerable help to further understand some of the underlying mechanisms implicated in protein dysfunction associated to glucotoxicity as well as the impaired protective effect of aspirin in diabetic patients. We will thus investigate the impact of chronic hyperglycemia on the blood glycated proteome (plasma, red blood cells, white blood cells and platelets) from type 2 diabetic patients compared to age and sex-matched non-diabetic controls. We will also evaluate the protein acetylation profile after *in vitro* and *in vivo* treatment with aspirin in those diabetic patients and controls. These experiments will help us to delineate the impact of protein glycation on the acetylation potency of aspirin as well as the putative prevention of aspirin in inhibiting protein glycation.

5.10. *Bioinformatics and network based biology*

This bioinformatics and network-biology (systems biology) will be supported through several layers of essential information, data and knowledge. Protein information required for analysis of datasets will be obtained from UniProtKB/Swiss-Prot, that contains high quality, manually curated functional data on all proteins of interest to the HDPP consortium. This data is complemented by additional information available in neXtProt, a human-specific knowledge resource that provides data provided by third party databases in addition to those available in UniProtKB/Swiss-Prot, including HPA [18] and Bgee [42], of high relevance to HUPO and HDPP. The bioinformatics group of HDPP will specifically support HDPP by including datasets provided by HUPO-projects and initiatives, including the data from the HDPP itself. In order to maximize the access to experimental datasets, the ProteomeXchange mechanism will be used as main channel for high quality datasets maintenance.

6. Collaborative vision and integration into the B/D-HPP program

Disease initiatives are translational in nature and only a worldwide international constellation of expertise can deliver the breadth and depth of translational knowledge, such as targeted by the HPP. The project will be multidisciplinary and executed based on a solid collaboration between universities, hospitals, institutes, large-scale enterprises, and – potentially – SMEs. The challenging objectives defined in the present diabetes application are not achievable by any one partner in isolation because of the complementary expertise only being accessible through the present consortium. All partners are experts in their respectively assigned work packages. The integration into the overarching HPP initiative will favor collaborations and exchange of information across all C-HPP and B/D-HPP initiatives. Results obtained by the consortium will be disseminated through ProteomeXchange and PRIDE into Human Proteome/Diabetes repositories. They will further be published in peer-reviewed journals and at international conferences and workshops. The results will be used in educational activities such as student courses, as well as M.Sc. and Ph.D. projects. An (External) Scientific Advisory Board (SAB) will be formed, which will include key players in the field of diabetes and network biology as well as members of other HPP initiatives.

7. Concluding remarks

The HDPP initiative has been started to combine and leverage a high level of uniquely complementary expertise in the field of diabetes and its associated complications. HDPP will execute several omics-rooted projects with systems biology character. The project was officially launched at the 11th HUPO meeting in Boston, USA. At the next (12th) HUPO meeting in

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Yokohama, Japan, HDPP will present first results related to the early deliverables and milestones.

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