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Case Report

Proteomics Profiling of Heterozygous and Homozygous Patients with ABCA1 Gene Mutation: A Tangier Disease Molecular Map

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Received: November 18, 2014; **Accepted:** February 04, 2015; **Published:** February 10, 2015

Abstract

Tangier Disease (TD) is a rare inherited disorder with approximately 100 worldwide identified cases. Alpha-lipoprotein deficiency is the main characteristic of this disease, associated with a virtual absence of High Density Lipoproteins (HDL) in blood. Additional symptoms are mild hypertriglyceridemia, neuropathy and enlarged, orange-colored tonsils. Genetically TD is caused by mutations in the ABCA1 gene, which prevent the release of cholesterol and phospholipids from cells, leading to the accumulation of lipids within cells and body tissues.

In this work a TD patient and his parental heterozygous were examined from a proteomics point of view. Plasma as well as proteome and secretome of circulating monocytes were analyzed.

Plasma proteins underlined in TD the imbalance of lipid trafficking and metabolism, associated with the stimulation of pro-inflammatory pathways. Proteome and secretome of monocytes highlighted an extensive down regulation of mitochondrial enzymes and vesicular trafficking agents along with a substantial cytoskeletal rearrangement, suggesting a reduced activation state of monocytes from TD homozygous patient.

This work is the first proteomics profiling of heterozygous and homozygous TD phenotypes and it suggests a TD case as a model to understand general mechanisms of lipid transport and metabolism and their linkage to inflammatory processes.

Keywords: Tangier disease; Protemics profiling; Monocyte proteomics; Rare disease

Case Presentation

Tangier Disease (TD) is an autosomal recessive genetic disorder, described for the first time in 1961 [1] and characterized by impaired HDL-mediated cholesterol efflux and abnormal intracellular lipid trafficking and turnover. TD patients accumulate cholesterol in body tissues; show a reduced level of HDL, disturbances of nerve functions, premature atherosclerosis and a high incidence of Coronary Artery Disease (CAD). TD is a rare genetic disorder, with less than 100 cases reported in the literature, and patients present both alleles of ABCA1 gene mutated; this gene encodes a member of the ATP-Binding Cassette (ABC) transporter family [2, 3]. Carriers of a single ABCA1 mutation (heterozygotes) display an intermediate phenotype with a 50% reduction in the ABCA1-mediated cell cholesterol efflux [4]. Despite the commitment of a unique documented gene, TD is characterized by high variability in phenotypic manifestations, either qualitatively or quantitatively, in terms of clinical severity and organ involvement. In brief there is not a direct correlation between the gene mutation and the numerous and various clinical features described in TD patients.

ABCA1 is the major responsible transporter for clearing cholesterol from macrophages and, since cholesterol accumulation in arterial macrophages is atherogenic, this pathway has a clear involvement in the progression and/or regression of cardiovascular diseases [5]. Due to its central role in the modulation of cholesterol homeostasis, ABCA1 is an attractive target for drug development, but the molecular actors of the ABCA1 lipid pathway are not completely revealed. Studies are needed to understand how lipids are translocated across the plasma membrane and to identify associated proteins that modulate this pathway. Proteomics studies would help to disclose intracellular and secreted factors involved in dysfunction of lipid trafficking and in its clinical manifestation suggesting new targets for therapeutic interventions that might modulate ABCA1 activity assisting the traffic of cholesterol from cells and tissues.

In this paper, proteomics analyses of monocytes and plasma of a TD patient compared with his heterozygous father are reported. The clinical characterization, proband's kindred and plasma lipoprotein profiles of these two cases have been already published in Sampietro et al. [6] and in Puntoni et al. [7] (a brief description is also presented in the Supplementary Information).

In brief, molecular factors and activation pathways directly responsible of the pathological phenotype are highlighted and the TD case has been suggested as model to obtain insights in possible mechanisms responsible for lipid dysfunctions and eventually, as a consequence, for atherosclerosis initiation.

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Citation: Ucciferri N, Rocchiccioli S, Puntoni M, Bigazzi F, Cecchettini A, Citti L and Sampietro T. Proteomics Profiling of Heterozygous and Homozygous Patients with ABCA1 Gene Mutation: A Tangier Disease Molecular Map. A Proteomics. 2015;2(1): 1007.

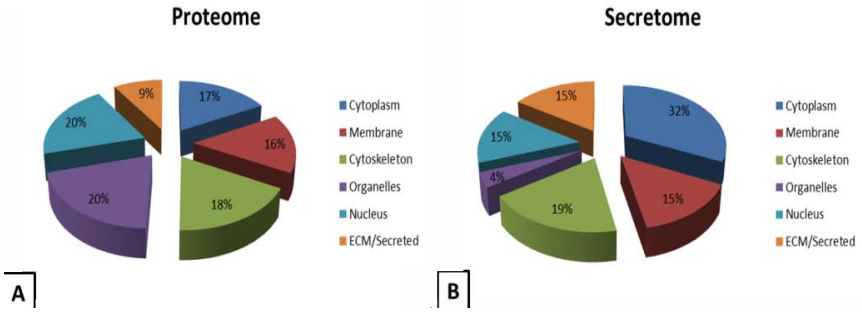

Figure 1: Monocyte proteome (A) and secretome (B). Identified proteins were classified according to their localization.

Proteomics Profiling

TD homozygous proteomics profile was compared with his parental heterozygous (for the ABCA1 mutation). This choice was suggested by the fact that genetic background is akin and both patients are subjected to the same clinical treatments for cardiovascular disease, even if the heterozygous is mildly affected. In this way it was possible to approximate differences in the proteomics profiles due mostly to the different expression of the pathology so as to extrapolate factors involved in dyslipidemia as a main cause of early onset of atherosclerosis.

Using a shot-gun proteomics strategy (for details see Supplementary Information), we were able to identify 197 proteins in depleted plasma samples of both patients (Table S1).

46 plasma proteins (Table 1) were found differentially expressed between TD patient and his heterozygous father. In particular 22 proteins resulted down-regulated and 24 up-regulated in homozygous with respect to heterozygous. Among the down-regulated in the homozygous, 13 different apolipoproteins were particularly interesting. In addition, also Paraoxonase 1 has been found down-regulated in homozygous patient plasma. This enzyme has been suggested to be involved in the protection against oxidative modification of lipoproteins and consequently against pivotal events leading to atheroma formation [8,9].These results, although preliminary, confirm that plasma proteomics can evidence the imbalance of lipid trafficking and metabolism in TD, suggesting a distinctive characteristic fingerprint, provided with a panel of correlated elements. Among the differentially expressed proteins some are linked to inflammation, such as Orosomucoid 1 and 2 and Kininogen 1. Kininogen 1 has been found over expressed in plasma of homozygous patient and it seems to be a key mediator of inflammation [10]. On the other hand, Orosomucoid 1 and 2 resulted down-expressed in homozygous plasma and, besides being involved in pro-inflammatory responses [11,12], they also exert a possible role as lipid carrier in blood circulation [13,14]. Moreover and of note, 4 differentially expressed proteins are related to different growth factor pathways: Vasorin may act as inhibitor of TGF-beta signaling [15], Insulin like Growth Factor Binding Protein 4 (IGFBP4) and Insulin-like Growth Factor-Binding Protein Complex Acid Labile Subunits (IGFALS) are key elements of the IGF pathway and Hepatocyte Growth Factor Activator (HGFA) that seems to play role in inflammatory processes [16]. In conclusion, plasma proteome of TD patient proves a general dysregulation of lipid trafficking and metabolism, associated with the stimulation of growth factor and inflammatory pathways.

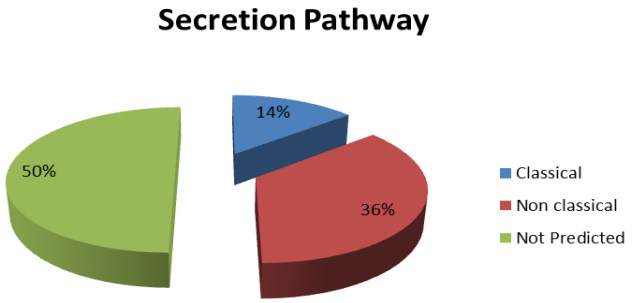

Figure 2: Monocyte secreted proteins classified according to the intracellular pathways (classically or non classically secreted) as predicted by SecretomeP Server.

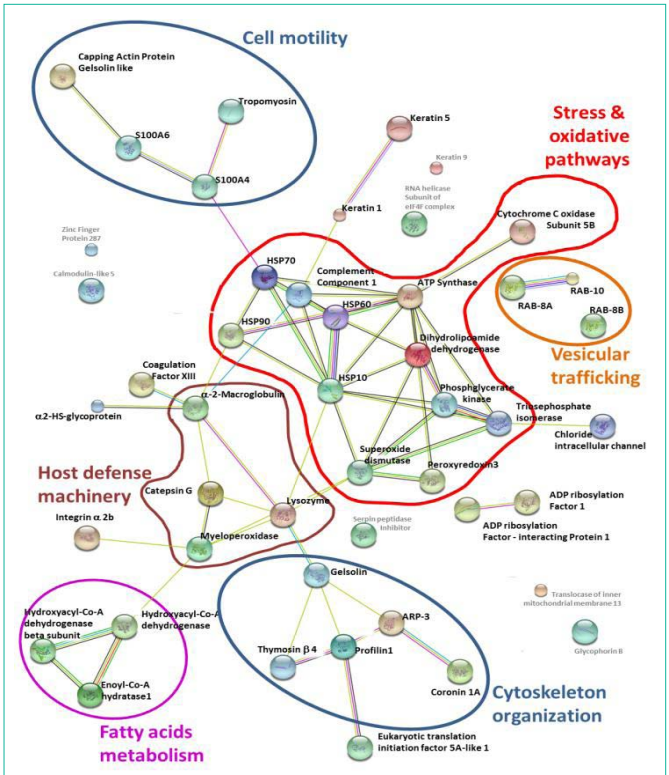

Figure 3: Interaction network of differentially expressed proteins in monocyte proteome. Top scoring and significant proteins were submitted to String database and resulted image was adapted.

Table 1: Differentially expressed proteins in plasma samples.

Accession	Peak Name	Protein names	Homo vs Hetero	p-value	Log (Fold Change)
Q04756	HGFA_HUMAN	Hepatocyte growth factor activator	DOWN	4.55E-05	0.847184
P02647	APOA1_HUMAN	Apolipoprotein A-I	DOWN	0.00017	0.771506
P02654	APOC1_HUMAN	Apolipoprotein C-I	DOWN	0.00054	0.726025
P00738	HPT_HUMAN	Haptoglobin-relatedprotein	DOWN	0.00072	0.350024
P00915	CAH1_HUMAN	Carbonicanhydrase 1	DOWN	0.00186	0.847092
P02652	APOA2_HUMAN	Apolipoprotein A-II	DOWN	0.00255	0.695098
P27169	PON1_HUMAN	Serum paraoxonase/arylesterase 1 (PON 1)	DOWN	0.00291	0.483498
P02042	HBD_HUMAN	Hemoglobinsubunit delta (Delta-globin)	DOWN	0.00394	0.362336
P00739	HPTR_HUMAN	Haptoglobin (Zonulin)	DOWN	0.00401	0.513322
O75636	FCN3_HUMAN	Ficolin-3 (Collagen/fibrinogen domain-containing lectin 3 p35)	DOWN	0.00597	0.330745
P00746	CFAD_HUMAN	Complement factor D (Adipsin)	DOWN	0.00684	0.503916
O95445	APOM_HUMAN	Apolipoprotein M	DOWN	0.00827	1.142308
P19652	A1AG2_HUMAN	Alpha-1-acid glycoprotein 2 (Orosomucoid-2)	DOWN	0.01005	0.435858
P22792	CPN2_HUMAN	Carboxypeptidase N subunit 2	DOWN	0.01067	0.552475
P35542	SAA4_HUMAN	Serum amyloid A-4 protein	DOWN	0.01249	0.63467
O14791	APOL1_HUMAN	Apolipoprotein L1	DOWN	0.01259	0.567598
P00488	F13A_HUMAN	Coagulation factor XIII A chain	DOWN	0.01438	0.720657
Q6UXB8	PI16_HUMAN	Peptidase inhibitor 16	DOWN	0.01584	1.509586
P02775	CXCL7_HUMAN	Platelet basic protein (PBP)	DOWN	0.02249	0.664629
P05090	APOD_HUMAN	Apolipoprotein D	DOWN	0.02422	0.332828
P02656	APOC3_HUMAN	Apolipoprotein C-III	DOWN	0.02636	0.844092
P80108	PHLD_HUMAN	Phosphatidylinositol-glycan-specific phospholipase D	DOWN	0.02891	0.720058
O43866	CD5L_HUMAN	CD5 antigen-like (IgM-associated peptide)	UP	4.06E-05	-0.6351
P01871	IGHM_HUMAN	Ig mu chain C region	UP	0.00013	-0.52174
P02768	ALBU_HUMAN	Serumalbumin	UP	0.0014	-0.50844
P06331	HV209_HUMAN	Ig heavy chain V-II region ARH-77	UP	0.00152	-0.60634
P04208	LV106_HUMAN	Ig lambda chain V-I region WAH	UP	0.00274	-0.87145
P01834	IGKC_HUMAN	Ig kappa chain C region	UP	0.00321	-0.35637
P35858	ALS_HUMAN	Insulin-like growth factor-binding protein complex acid labile subunit (ALS)	UP	0.00506	-0.37728
P01042	KNG1_HUMAN	Kininogen-1 (Alpha-2-thiol proteinase inhibitor)	UP	0.00524	-0.32611
P04430	KV122_HUMAN	Ig kappa chain V-I region BAN	UP	0.00608	-0.61736
P01591	IGJ_HUMAN	Immunoglobulin J chain	UP	0.00997	-1.05921
P01743	HV102_HUMAN	Ig heavy chain V-I region HG3	UP	0.01589	-0.81718
P06316	LV107_HUMAN	Ig lambda chain V-I region BL2	UP	0.01694	-2.00561
P04220	MUCB_HUMAN	Ig mu heavy chain disease protein (BOT)	UP	0.01833	-0.36182
P01876	IGHA1_HUMAN	Ig alpha-1 chain C region	UP	0.01903	-0.30019
P04433	KV309_HUMAN	Ig kappa chain V-III region VG (Fragment)	UP	0.02037	-0.62005
P01880	IGHD_HUMAN	Ig delta chain C region	UP	0.02129	-0.64278
P01859	IGHG2_HUMAN	Ig gamma-2 chain C region	UP	0.02168	-0.64733
P01861	IGHG4_HUMAN	Ig gamma-4 chain C region	UP	0.02441	-0.66096
P18428	LBP_HUMAN	Lipopolysaccharide-bindingprotein	UP	0.02811	-0.69375
P13645	K1C10_HUMAN	Keratin, type I cytoskeletal 10	UP	0.02953	-0.64284
P01857	IGHG1_HUMAN	Ig gamma-1 chain C region	UP	0.03532	-0.37459
P01717	LV403_HUMAN	Ig lambda chain V-IV region Hil	UP	0.03595	-1.08395
P03952	KLKB1_HUMAN	Plasma kallikrein	UP	0.03806	-0.59386
O00187	MASP2_HUMAN	Mannan-binding lectin serine protease 2	UP	0.04597	-1.06298

Although ABCA1 is expressed in many tissues, the accumulation of cholesterol in TD interests mostly macrophages [17]. An early event in atherogenesis is the recruitment of monocytes from the peripheral blood vessel intima as a consequence of high amounts of lipids and high levels of protein oxidation. Monocytes transmigrate into the vessel wall and differentiate into macrophages. Macrophages are well known to exert an important role in atheroprotection/atheroformation, removing excess of cholesterol from tissues. Reverse Cholesterol Transport (RCT) is a pathway responsible of the transport of accumulated cholesterol from the vessel wall to the liver for excretion, this process preventing inflammation and atherosclerosis [18]. Many studies indicate that the inflammatory process impairs RCT [19]. ABCA1 is the major cholesterol efflux system in macrophages, it plays a crucial role in the modulation of inflammatory response [20] and in mice its knockout increases inflammatory cell infiltration [21]. Monocytes are the circulatory

Table 2: Differentially expressed proteins in monocyte proteome samples.

Accession	Peak Name	Protein name	Homo vs Hetero	p-value	Log (Fold Change)
P08311	CATG_HUMAN	Cathepsin G	DOWN	0.00509	-0.81137
O00299	CLIC1_HUMAN	Chlorideintracellularchannelprotein 1	DOWN	0.00429	-0.98615
P06703	S10A6_HUMAN	Protein S100-A6	DOWN	0.03129	-0.71595
Q92930	RAB8B_HUMAN	Ras-related protein Rab-8B	DOWN	0.00329	-1.00065
P61006	RAB8A_HUMAN	Ras-related protein Rab-8A	DOWN	0.02228	-1.4238
P61026	RAB10_HUMAN	Ras-relatedprotein Rab-10	DOWN	0.00993	-0.81693
P11142	HSP7C_HUMAN	Heat shock cognate 71 kDa protein	DOWN	0.0011	-0.61458
P06396	GELS_HUMAN	Gelsolin	DOWN	0.00136	-0.64524
P06753	TPM3_HUMAN	Tropomyosin alpha-3 chain	DOWN	0.03406	-0.55569
P31146	COR1A_HUMAN	Coronin-1A	DOWN	0.01454	-0.54048
P14625	ENPL_HUMAN	Endoplasmin	DOWN	0.00317	-0.63045
P84077	ARF1_HUMAN	ADP-ribosylationfactor 1	DOWN	0.00311	-0.87542
P05164	PERM_HUMAN	Myeloperoxidase	DOWN	0.00178	-0.81517
P08575	PTPRC_HUMAN	Receptor-type tyrosine-protein phosphatase C	DOWN	0.03603	-0.96159
P04179	SODM_HUMAN	Superoxidedismutase [Mn], mitochondrial	DOWN	0.02356	-1.86513
P09622	DLDH_HUMAN	Dihydrolipoyldehydrogenase, mitochondrial	DOWN	0.00493	-1.1493
P10606	COX5B_HUMAN	Cytochrome c oxidasesubunit 5B, mitochondrial	DOWN	0.00089	-1.5417
P10809	CH60_HUMAN	60 kDa heat shock protein, mitochondrial	DOWN	0.00071	-1.05006
P61604	CH10_HUMAN	10 kDa heat shock protein, mitochondrial	DOWN	0.00384	-1.08989
Q16836	HCDH_HUMAN	Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial	DOWN	0.02882	-1.51385
P06576	ATPB_HUMAN	ATP synthase subunit beta, mitochondrial	DOWN	0.02171	-0.65835
P30048	PRDX3_HUMAN	Thioredoxin-dependent peroxide reductase, mitochondrial	DOWN	0.02955	-1.02142
Q13011	ECH1_HUMAN	Delta(3,5)-Delta(2,4)-dienoyl-CoAisomerase, mitochondrial	DOWN	0.0026	-1.13024
P55084	ECHB_HUMAN	Trifunctional enzyme subunit beta, mitochondrial	DOWN	0.00162	-1.0893
Q07021	C1QBP_HUMAN	Complement component 1 Q subcomponent-binding protein, mitochondrial	DOWN	0.01677	-1.11609
Q14240	IF4A2_HUMAN	Eukaryotic initiation factor 4A-II	DOWN	0.02237	-1.11038
P63241	IF5A1_HUMAN	Eukaryotic translation initiation factor 5A-1	DOWN	0.03193	-0.85348
P05154	IPSP_HUMAN	Plasma serine proteaseinhibitor	DOWN	0.02319	-1.1857
P01023	A2MG_HUMAN	Alpha-2-macroglobulin	DOWN	0.01839	-0.85005
P02765	FETUA_HUMAN	Alpha-2-HS-glycoprotein	DOWN	0.00435	-1.34102
P61626	LYSC_HUMAN	Lysozyme C	DOWN	0.01812	-1.54991
P04264	K2C1_HUMAN	Keratin, type II cytoskeletal 1	UP	0.00435	0.773886
P60174	TPIS_HUMAN	Triosephosphateisomerase	UP	0.04817	0.537814
P00558	PGK1_HUMAN	Phosphoglyceratekinase 1	UP	0.00521	0.614203
P40121	CAPG_HUMAN	Macrophage-cappingprotein	UP	0.03962	0.815598
P00488	F13A_HUMAN	Coagulation factor XIII A chain	UP	0.0026	0.830138
P13647	K2C5_HUMAN	Keratin, type II cytoskeletal 5	UP	0.031	0.954622
Q9NZT1	CALL5_HUMAN	Calmodulin-likeprotein 5	UP	0.01543	0.843285
P07737	PROF1_HUMAN	Profilin-1	UP	0.0115	0.177598
P35527	K1C9_HUMAN	Keratin, type I cytoskeletal 9	UP	0.00304	1.021316
P62328	TYB4_HUMAN	Thymosin beta-4	UP	0.00614	1.665154
P61158	ARP3_HUMAN	Actin-relatedprotein 3	UP	0.011	0.967938
P08514	ITA2B_HUMAN	Integrinalpha-IIb	UP	0.03896	1.792178
P26447	S10A4_HUMAN	Protein S100-A4	UP	0.0369	2.142443
Q9HBT7	ZN287_HUMAN	Zinc finger protein 287	UP	0.02335	1.781582

precursors of macrophages and play a central role under several pathophysiological conditions, particularly when inflammatory reactions are involved. For these reasons we were interested in analyzing the proteome and the secretome of monocytes from a TD patient and to compare these profiles with those of the heterozygous father.

Monocyte proteome analysis identified 198 proteins while 128 proteins were found in secretome. Proteins are reported in (Supplementary Data Table S2 and Table S3 respectively). They were classified based on their localization (Figure 1) using Uniprot database (www.uniprot.com), while the secretome proteins were also subdivided, according to the secretion pathway (Figure 2), in classically or non classically secreted, as predicted by the SecretomeP 2.0 Server (http://www.cbs.dtu.dk/services/SecretomeP/).

Monocyte whole proteome analysis brought to the identification of 198 proteins, of which, so much as 47 resulted differentially

Table 3: Differentially expressed proteins in monocyte secretome samples.

Accession	Peak Name	Protein Name	Homo vs Hetero	p-value	Log (Fold Change)
P61160	ARP2_HUMAN	Actin-relatedprotein 2	DOWN	0.00059	-0.73265
P31146	COR1A_HUMAN	Coronin-1A	DOWN	0.02114	-0.39996
Q9Y490	TLN1_HUMAN	Talin-1	DOWN	0.02877	-0.32292
P00558	PGK1_HUMAN	Phosphoglyceratekinase 1	DOWN	0.02932	-0.41883
P07996	TSP1_HUMAN	Thrombospondin-1	DOWN	0.04812	-0.65607
P07437	TBB5_HUMAN	Tubulin beta chain	DOWN	0.04965	-0.35121
P62937	PPIA_HUMAN	Peptidyl-prolylcis-trans isomerase A	UP	0.00154	0.465786
O15145	ARPC3_HUMAN	Actin-relatedprotein 3	UP	0.0023	0.687822
P60842	IF4A1_HUMAN	Eukaryotic initiation factor 4A-I	UP	0.00544	0.403022
P60660	MYL6_HUMAN	Myosin light polypeptide 6	UP	0.00622	0.860975
Q01518	CAP1_HUMAN	Adenylylcyclase-associatedprotein 1	UP	0.01958	0.294693
Q9NY33	DPP3_HUMAN	Dipeptidylpeptidase 3	UP	0.02472	0.360369
P32119	PRDX2_HUMAN	Peroxiredoxin-2	UP	0.02762	0.540569
P50395	GDIB_HUMAN	Rab GDP dissociation inhibitor beta	UP	0.02791	0.965144
P61978	HNRPK_HUMAN	Heterogeneousnuclearribonucleoprotein K	UP	0.03703	0.474348
P08670	VIME_HUMAN	Vimentin	UP	0.04041	0.285031

expressed (Table 2). Four principal functional groups may be underlined: a)- cytoskeleton organization (Coronin 1, Profilin 1, Tropomyosin 3, S100A6, Gelsolin, Thymosin beta4, Actin-related protein 3 and Macrophage-capping protein), b)- mitochondrial functions(Superoxide dismutase, Cytochrome C oxidase, ATP synthase beta, Thioredoxin-dependent peroxide reductase, Heat shock cognate 71 protein, Heat shock 60 kDa protein, Heat shock 10 kDa protein, Dihydroprolyl dehydrogenase, Hydroxyacyl-coenzyme A dehydrogenase, Trifunctional enzyme subunit beta, Complement component 1 Q subcomponent-binding protein), c)- vesicular trafficking regulation (RAS-related protein Rab-8B, RAS-related protein Rab-8A, RAS-related protein Rab-10, ADP-ribosylation factor 1) and d)-defense activities (Myeloperoxidase, Cathepsin G, Lysozyme C, Plasma serine protease inhibitor, Alpha-2-macroglobulin). It is interesting to note that all groups are somehow related to monocyte-macrophage transition since differentiation is triggered by mitochondrial functions, induces a dramatic rearrangement of cytoskeleton due to increasing motility and enhances vesicular trafficking for more intense intra- and intercellular interactions, these including also defense strategies.

Indeed, mitochondrial functions produce Reactive Oxygen Species (ROS), which are recognized triggers of monocyte activation [22]. Normally, the diffusion of ROS and damaged mitochondrial contents into the cytosol is prevented by autophagy. During autophagy cytosolic constituents are enclosed within a double-layered lipid vesicle addressed to fuse with lysosomes for degradation and recycling of the internal contents. Impaired autophagy may interfere with mitochondrial turnover [23].

In brief, the extensive down regulation of mitochondrial enzymes and vesicular trafficking agents along with cytoskeletal and defense proteins in monocyte proteome (Figure 3) suggest a reduced activation ability of monocytes from TD homozygous patient.

As expected, a lower number of proteins were identified in the secretome (128) and of these only 16 resulted differentially released within 24 h (Table 3). The majority (8 out of 16) are actin binding or related factors, underlining a reassessment of monocyte cytoskeleton.

Conclusion

In conclusion, it was possible to obtain a preliminary plasma fingerprint and a monocyte molecular map of Tangier disease. This study could be preparatory for deeper and more specific analyses that could help to understand general mechanisms of lipid transport and metabolism and their linkage to inflammatory processes.

Limitation of this work is the difficulty to establish if the results obtained with a TD patient can be extrapolated to other TD patients, due to the infrequence of this genetic disorder. Nevertheless, this case can be exploited as model for the study of general, common mechanisms in cell biology.

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A Proteomics - Volume 2 Issue 1 - 2015
ISSN : 2471-0164 | www.austinpublishinggroup.com
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Citation: Ucciferri N, Rocchiccioli S, Puntoni M, Bigazzi F, Cecchettini A, Citti L and Sampietro T. Proteomics Profiling of Heterozygous and Homozygous Patients with ABCA1 Gene Mutation: A Tangier Disease Molecular Map. A Proteomics. 2015;2(1): 1007.