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Letter to the Editor

Proteomic analysis of pericardial effusions in hematopoietic stem cell transplant recipients

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Running head: Proteomics of pericardial effusions after HSCT

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Hematopoietic stem cell transplant (HSCT) is an established treatment for malignant and non-malignant disorders in children and young adults. Pericardial effusion (PEF) is a potentially life-threatening complication of HSCT that occurs in up to 19% of pediatric patients and is associated with increased mortality due to cardiac tamponade[1-3]. In our clinical practice, most clinically significant PEFs occur in conjunction with transplant-associated thrombotic microangiopathy (TA-TMA), though the exact mechanism remains unclear[4]. Other potential risk factors for developing PEF after HSCT include myeloablative conditioning, graft-vs-host-disease (GVHD), GVHD prophylaxis, EBV viremia, and abnormal pre-transplant cardiac function testing[2-7]. Knowledge of PEF mechanisms would guide the use of novel targeted therapies and, combined with diligent screening, may prevent the need for pericardial drain placement in some patients. Our objective was to characterize potential mechanistic pathways in the proteome of pericardial fluid from pediatric HSCT recipients with PEFs.

We obtained permission from our Institutional Review Board to retrospectively review the clinical course of seven patients with TA-TMA and PEF with pericardial fluid samples stored in our biorepository. Transplantation demographics, details of TA-TMA diagnosis and management, and details of PEF management and clinical course were collected. Pericardial fluid from these seven HSCT recipients and four control autopsy pericardial fluid samples from available pediatric patients who died from non-cardiac causes were analyzed using an aptamer-based proteomics (SomaScan® 11K Assay) platform. Due to IRB restrictions, we were unable to ascertain any other cause of death details in the non-HSCT controls. TA-TMA was prospectively diagnosed using laboratory and clinical diagnostic criteria previously published by Jodele et al[8].

Patient demographics, transplant-related characteristics and the clinical courses of the seven patients with PEF are described in Table 1. All patients were diagnosed with TA-TMA, and the diagnosis was made at a median time of 21 days (range 2 to 66 days) from HSCT. Cardiac assessments revealed

predominantly sinus rhythm in pre-transplant ECG results, with one instance of sinus tachycardia. Pre-transplant echocardiogram findings included dilated aortic root, mildly thickened mitral valve, and a patent foramen ovale. Pericardial fluid sample collection with drain placement occurred between 4 to 224 days after HSCT following diagnosis by echocardiography. Eculizumab was given to all patients for TA-TMA directed therapy. Six patients required placement of a pericardial drain and 2 of those 6 required placements of a second drain due to fluid re-accumulation. No PEF was classified as malignant on clinical pathology review.

We wanted to characterize potential mechanistic pathways in the proteome of pericardial fluid from HSCT recipients with PEFs. Analysis of gene expression and pathway activation revealed significant findings when comparing the post-HSCT PEF cases with normal pericardial fluid collected at autopsy for non-cardiac deaths. A total of 1,271 differentially expressed proteins (DEPs) were identified with a p-value ≤ 0.05. The volcano plot in Figure 1 illustrates the $\log_2$ fold change against the $-\log_{10}$ p-value, highlighting several genes with notable expression changes, including CFHR5, SAA1, LEPROT, APOB, FTMT, TNFRSF25, HSD3B2, M1AP and LUM, suggesting potential involvement in the underlying biological processes leading to PEF. Twenty-seven proteins met more stringent differential expression criteria with an adjusted p-value (p_{adj}) ≤ 0.05 (Figure 1). A list of the first one-hundred DEPs is shown in Supplementary Table 1.

Differentially expressed proteins were then entered in Qiagen Ingenuity Pathway Analysis (IPA) software using a p-value cutoff of 0.05 and absolute log fold change cutoff of 0.75 (n=785 proteins). Enriched pathways are shown in Figure 2A using an absolute Z-score cutoff of 1.5. The top enriched pathway by p-value was regulation of insulin-like growth factor transport and uptake by insulin-like growth factor binding proteins (p=2.2e-14, Z-score=4.3; IGFBPs). IGFBPs have been previously described as diagnostic markers in malignant pleural and [9] effusions, though interestingly none of the

effusions in our study were malignant[10]. IGFBPs have a recognized role in cell senescence which has been described in endothelial disorders and kidney disease[11,12]. Sensescence occurs following tissue injury and associated inflammation, therefore the IGFBP enrichment observed may support endothelial and/or leukocyte senescence as a contributing factor to PEF biology in HSCT recipients.

Other highly enriched pathways were related to inflammation, including the pathogen-induced cytokine storm signaling pathway, IL-17 signaling, IL-17A signaling in airway cells, IL-17A signaling in fibroblasts, acute phase response signaling, and complement and coagulation cascades. IPA also generates leading upstream regulators of differentially expressed proteins and identified complement factor 5 (C5, p=3.2e-10, Z-score=3.3), complement C5a receptor 1 (C5AR1, p=1.1e-5, Z-score=3.3), IL6 (p=5.9e-16, Z-score=3.1) and IL17RA (p=1.6e-7, Z-score=2.9) as leading activated upstream regulators. Complement-related upstream regulator protein networks are shown in Figure 2B/C. The observed protein, pathway and upstream regulator changes highlight a novel and complex interplay of IL17 and complement-related pathways in HSCT recipient PEFs. Complement factors are known to affect the IL-17 axis, which makes it plausible that these complement and IL17 findings are both true and potentially related[13].

Clinically, we have previously reported that PEF after HSCT frequently occurs in the setting of TA-TMA[14]. Based on this, we focused our analysis on pathways relevant to TA-TMA, specifically complement and coagulation cascades, and identified IL-17 as a potential upstream mediator. This is biologically plausible, as IL-17 is known to promote endothelial activation, enhance vascular permeability, and prime the endothelium for pro-thrombotic states-hallmarks of TA-TMA. IL-17 also promotes endothelial cell senescence, which creates a mechanistic link to IGFBPs dicussed above[15]. Additionally, IL-17 has been shown to upregulate C3 expression and drive terminal complement activation in both endothelial and epithelial cells, supporting its role in complement-mediated

endothelial injury[13]. Consistent with this, we found that CFHR5, was one of the strongest differentially expressed proteins in our experiment. This finding aligns with the broader enrichment of complement and coagulation pathways observed in Figure 2, further implicating IL-17 driven complement dysregulation in the pathogenesis of PEF after HSCT. CFHR5 functions to protect the body from complement-mediated injury and mutations in this gene have been linked to CFHR5 nephropathy as well as TA-TMA[16,17]. The observed increase in CFHR5 may represent a host protective response to overactive complement activation in TA-TMA. Alternatively, this could indicate an underlying functional polymorphism in *CFHR5* that may predispose these patients to TA-TMA and even PEFs. Our prior study of complement gene polymorphisms in TA-TMA identified 4 TA-TMA patients with *CFHR5* polymorphisms which was the second most commonly mutated gene observed[18]. The association between IL-17, IGFBPs, complement proteins and PEFs therefore merits further study.

The data presented in this report are important for clinicians managing pediatric HSCT recipients, as PEF is a known complication with significant morbidity. All HSCT recipients in this study were diagnosed with TA-TMA and treated with a C5 inhibitor, therefore the effect of this therapy on PEFs after HSCT is not testable in our study cohort. However, complement pathway enrichment was still strong in the pericardial fluid proteome despite C5 inhibition. Our novel observations involving IL-17 and IGFBP pathways therefore merit further mechanistic study as potential targets of pharmacologic intervention outside of the complement system. IL-17 and IGFBP pathways may represent a unique mechanism of inflammation in the pericardial space of HSCT recipients that is linked to complement system activation. We acknowledge there are limitations to this study including the small sample size and use of normal pericardial fluid and not PEF from non-HSCT subjects as controls. While this limits the ability to differentiate the mechanism of HSCT PEFs from non-HSCT PEFs, we were still able to identify differentially expression proteins and enriched pathways in HSCT PEFs. Pericardial fluid specimens from HSCT recipients without effusions were understandably not available.

In conclusion, rapidly growing PEFs can quickly lead to life-threatening complications and the need for invasive procedures. Our study is the first to shed light on the mechanisms of PEFs in HSCT recipients and identified targetable pathways and proteins for future study and validation.

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Table 1. Patient demographics and transplant characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Male	Male	Female	Male	Female	Male	Male
Race	White	Black	White	Asian	White	White	White
Age at HSCT (years)	10.1	34.6	0.30	3.76	27.9	0.32	1.9
Primary diagnosis	ATRT	AML	Hurler syndrome	Fanconi anemia	AML	Hurler syndrome	AML
Donor type	Autologous	Unrelated	Unrelated	Related	Unrelated	Unrelated	Unrelated
Stem cell source	PBSC	PBSC	Cord	Bone marrow	PBSC	Cord	Cord
Degree of match	Auto	8/10	10/10	5/10	10/10	8/10	8/10
Conditioning regimen	Carb/TT	Bu/Cy	Bu/Cy	Cy/Flu/TBI	Clof/Mel/TT	Bu/Cy	Bu/Cy
GVHD prophylaxis	None	TCRαβ+/CD19+ Depleted	CSA/MMF	CSA/MMF/PTCY	ABA/CSA/MTX	CSA/MMF	CSA/MMF
Day 100 acute GVHD score	NA	4	0	0	2	1	1
Chronic GVHD	NA	No	No	No	Yes	No	Yes
TA-TMA onset (day from HSCT)	66	2	21	20	50	40	20
TA-TMA risk category	High	High	Moderate	High	High	High	High
Pre-transplant ECG results	Sinus rhythm	Sinus rhythm	Sinus rhythm	Sinus tachycardia	Sinus rhythm	Sinus rhythm	Sinus rhythm
Pre-transplant echocardiogram results	Normal	Dilated aortic root	Mildly thickened mitral vavle with mild prolapse; mild to moderate regurgitation	Normal	Normal	Mildly dilated aortic root, patent foramen ovale (left to right shunting)	Mildly dilated left atrium
Day of initial PEF diagnosis from HSCT	67	-23	3	16	207	84	74
Pericardiocentesis (day from HSCT)	67	4	81	29	224	88	104
Post-transplant initial PEF size description on echo	Large	Trivial to small	Trivial	Moderate	None visualized by echo, seen during autopsy	Large	Small to moderate
Presence of tamponade physiology on echo prior to pericardiocentesis	Yes	Yes	No	Yes	No	Yes	No
Medical interventions used for PEF and TA-TMA	Eculizumab	Eculizumab	Eculizumab	Eculizumab	Eculizumab	Eculizumab, methylprednisolone	Eculizumab
Complications related to PEF	Required 2 drains due to re-accumulation of fluid after first drain removed	None	Required 2 drains due to re-accumulation of fluid after first drain removed	None	None	None	None
Total length of time pericardial drain(s) in place (days)	8	2	32	12	NA	4	2
Cause of death	Alive	Multi-organ failure due to bacterial infection, TA-TMA	Alive	Multi-organ failure due to adenovirus infection	Cardiorespiratory failure	Alive	Primary disease relapse

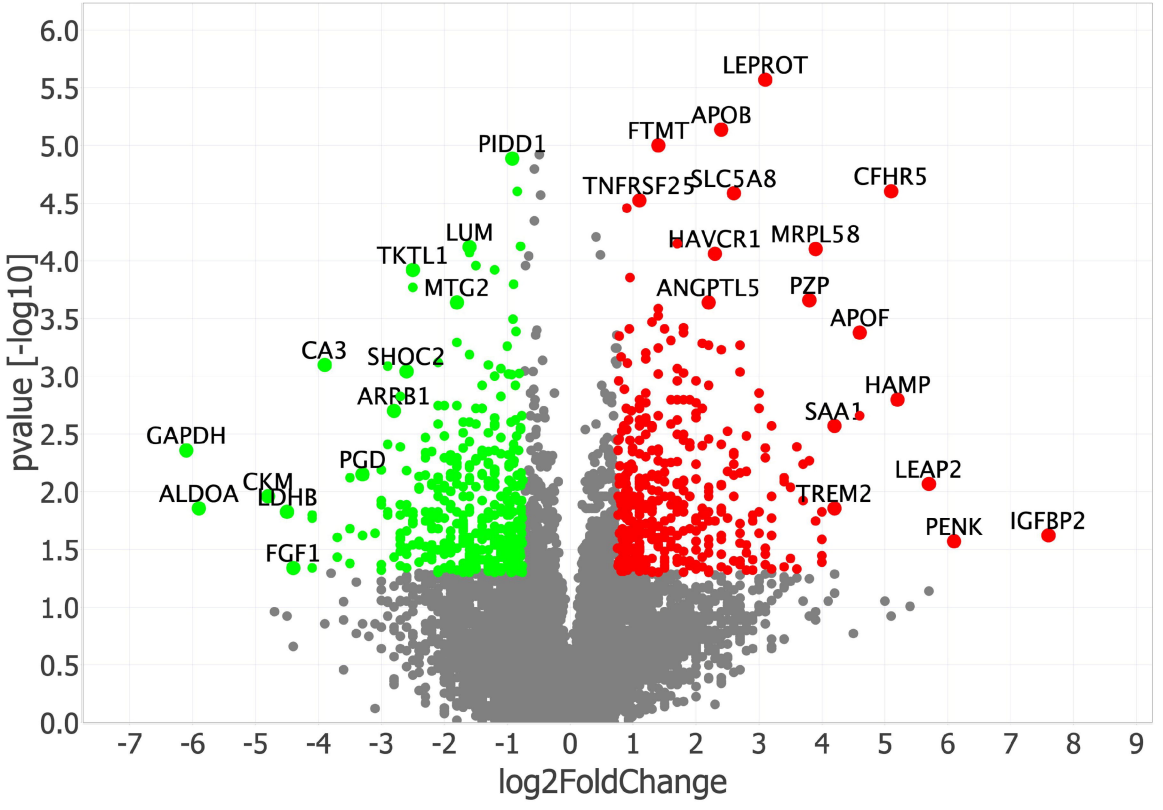
		and GVHD					

ATRT: atypical teratoid rhabdoid tumor; AML: acute myeloid leukemia; PBSC: peripheral blood stem cell; Carb/TT: Carboplatin/Thiotepa; Bu/Cy: Busulfan/Cyclophosphamide; Cy/Flu/TBI: Cyclophosphamide/Fludarabine/Total body irradiation; Clof/Mel/TT: Clofarabine/Melphalan/Thiotepa; GVHD: graft-vs-host disease; NA: not applicable; CSA/MMF: cyclosporine/mycophenolate mofetil; ABA/CSA/MTX: abatacept/cyclosporine/methotrexate; TA-TMA: transplant-associated thrombotic microangiopathy; GVHD: graft-vs-host-disease; HSCT: hematopoietic stem cell transplant; PEF: pericardial effusion; ECG: electrocardiogram

FIGURE LEGENDS

Figure 1. Volcano plot of differentially expressed proteins (DEPs) in pericardial fluid from HSCT recipients with pericardial effusions (PEFs). This volcano plot displays the $\log_2$ fold change (x-axis) versus $-\log_{10}$ p-value (y-axis) for all proteins analyzed. A total of 1,271 proteins were differentially expressed with $p \leq 0.05$. Red and green dots indicate significantly upregulated and downregulated proteins, respectively. Several proteins demonstrated marked differential expression highlighting potential mechanistic pathways. A subset of 27 DEPs met stricter criteria with adjusted p-values (padj) ≤ 0.05.

Figure 2. Pathway enrichment and upstream regulator analysis of differentially expressed proteins in pericardial fluid from HSCT recipients with pericardial effusions (PEFs). (A) Top enriched canonical pathways identified by Ingenuity Pathway Analysis from 785 proteins with $p \leq 0.05$ and absolute $\log_2$ fold change ≥ 0.75. Pathways are ranked by –log(p-value), and activity is predicted by z-score (orange: activated, blue: inhibited). The most significantly enriched pathway was "Regulation of IGF transport and uptake by IGFBPs," followed by several inflammation-related pathways including IL-17 signaling, cytokine storm signaling, acute phase response, and complement cascade. (B–C) Predicted upstream regulator networks derived from IPA. Complement factors and cytokines were identified as leading upstream regulators, including C5, C5AR1, IL6, and IL17RA. Network visualizations show predicted regulatory relationships and directionality of protein expression changes. These findings suggest a central role for complement and IL-17 pathways in the pathogenesis of PEF following HSCT.

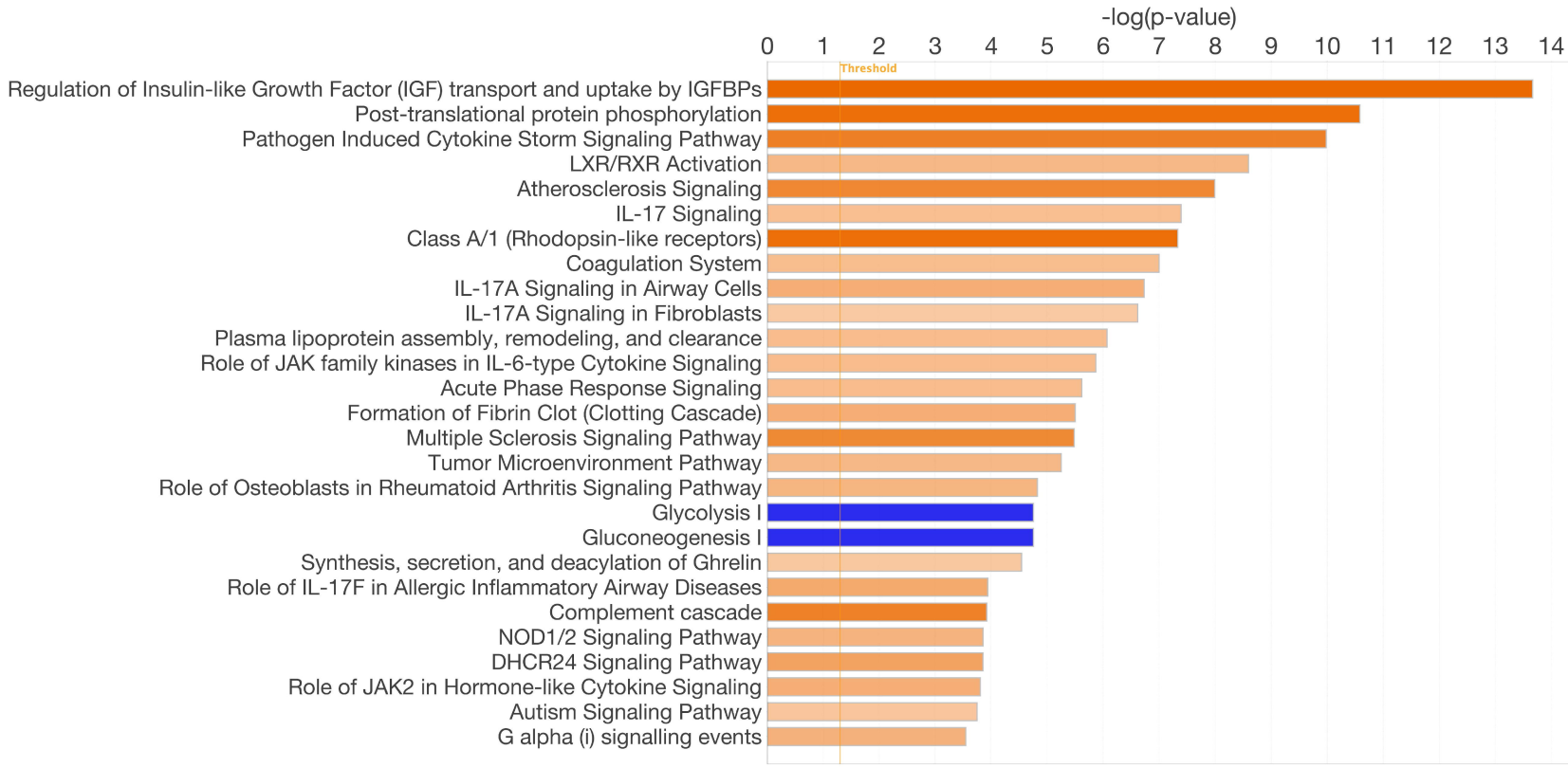


Symbol	Log Ratio	p-value	q-value
LEPROT	3.1	2.7E-06	0.029
APOB	2.4	7.3E-06	0.03
FTMT	1.4	0.00001	0.03
SHC2	-0.49	0.000012	0.03
PIDD1	-0.92	0.000013	0.03
CD2BP2	-0.57	0.000016	0.03
CFHR5	5.1	0.000025	0.03
NEUROD1	-0.84	0.000025	0.03
SLC5A8	2.6	0.000026	0.03
ST6GALNAC4	-0.47	0.000027	0.03
TNFRSF25	1.1	0.00003	0.03
APBB3	0.9	0.000035	0.032
HEXIM1	-0.57	0.000045	0.038
ARHGAP29	0.41	0.000062	0.046
HSD3B2	1.7	0.000071	0.046
BRD1	-0.79	0.000075	0.046
LUM	-1.6	0.000076	0.046
MRPL58	3.9	0.000079	0.046
M1AP	-1.6	0.000085	0.046
HAVCR1	2.3	0.000087	0.046
IL10RA	0.48	0.000089	0.046
SYT17	-0.66	0.000091	0.046
RIPK3	-1.5	0.00011	0.05
RNF157	-0.71	0.00011	0.05
RABIF	-1.2	0.00012	0.05
PPBP	-2.4	0.00012	0.05
TKTL1	-2.5	0.00012	0.05

A

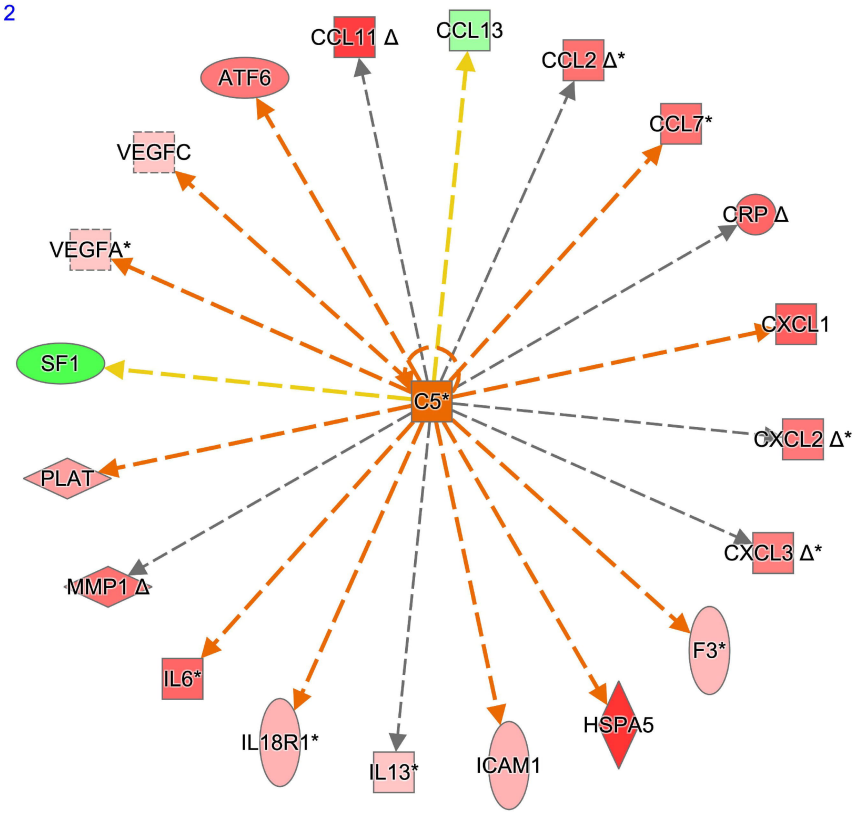
Analysis: PeriProteomics_p05_lfc075_1024-09-23 09:23 AM

positive z-score z-score = 0 negative z-score no activity pattern available



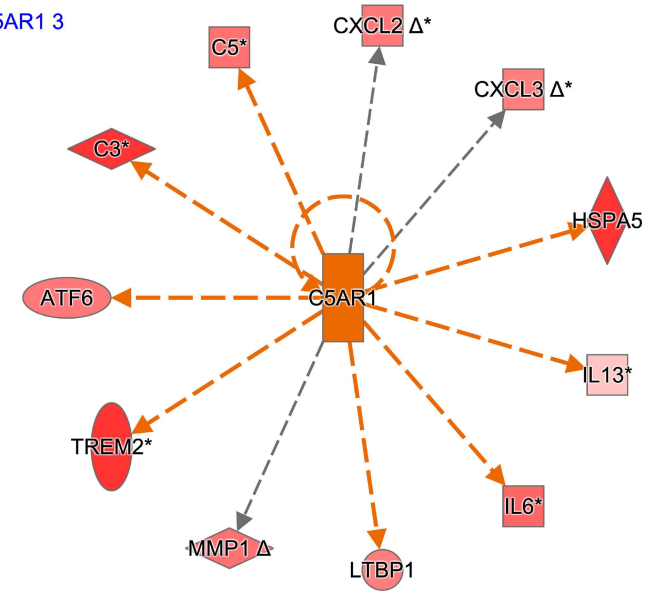
B

C5 2



C

C5AR1 3



Supplementary Table 1. Differential Enrichment analysis of first 100 proteins

Expr Log Ratio	Expr p-value	Expr False Discovery Rate (q-value)	ID	Flags	Symbol	Entrez Gene Name	Location	Type(s)
3.1	2.7E-06	0.029	LEPROT		LEPROT	leptin receptor overlapping transcript	Plasma Membrane	other
2.4	7.3E-06	0.03	APOB		APOB	apolipoprotein B	Extracellular Space	transporter
1.4	0.00001	0.03	FTMT		FTMT	ferritin mitochondrial	Cytoplasm	enzyme
-0.49	0.000012	0.03	SHC2		SHC2	SHC adaptor protein 2	Cytoplasm	other
-0.92	0.000013	0.03	PIDD1		PIDD1	p53-induced death domain protein 1	Cytoplasm	peptidase
-0.57	0.000016	0.03	CD2BP2		CD2BP2	CD2 cytoplasmic tail binding protein 2	Cytoplasm	other
5.1	0.000025	0.03	CFHR5	D	CFHR5	complement factor H related 5	Extracellular Space	other
-0.84	0.000025	0.03	NEUROD1		NEUROD1	neuronal differentiation 1	Nucleus	transcription regulator
2.6	0.000026	0.03	SLC5A8		SLC5A8	solute carrier family 5 member 8	Plasma Membrane	transporter
-0.47	0.000027	0.03	ST6GALNAC4		ST6GALNAC4	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	Cytoplasm	enzyme

1.1	0.00003	0.03	TNFRSF25	D	TNFRSF25	TNF receptor superfamily member 25	Plasma Membrane	transmembrane receptor
0.9	0.000035	0.032	APBB3	D	APBB3	amyloid beta precursor protein binding family B member 3	Cytoplasm	other
-0.57	0.000045	0.038	HEXIM1	D	HEXIM1	HEXIM P-TEFb complex subunit 1	Nucleus	transcription regulator
0.41	0.000062	0.046	ARHGAP29		ARHGAP29	Rho GTPase activating protein 29	Cytoplasm	other
1.7	0.000071	0.046	HSD3B2		HSD3B2	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2	Cytoplasm	enzyme
-0.79	0.000075	0.046	BRD1		BRD1	bromodomain containing 1	Nucleus	transcription regulator
-1.6	0.000076	0.046	LUM		LUM	lumican	Extracellular Space	other
3.9	0.000079	0.046	MRPL58	D	MRPL58	mitochondrial ribosomal protein L58	Cytoplasm	enzyme
-1.6	0.000085	0.046	M1AP		M1AP	meiosis 1 associated protein	Cytoplasm	other
2.3	0.000087	0.046	HAVCR1		HAVCR1	hepatitis A virus cellular receptor 1	Plasma Membrane	other

0.48	0.000089	0.046	IL10RA	D	IL10RA	interleukin 10 receptor subunit alpha	Plasma Membrane	transmembrane receptor
-0.66	0.000091	0.046	SYT17		SYT17	synaptotagmin 17	Plasma Membrane	other
-1.5	0.00011	0.05	RIPK3		RIPK3	receptor interacting serine/threonine kinase 3	Plasma Membrane	kinase
-0.71	0.00011	0.05	RNF157		RNF157	ring finger protein 157	Cytoplasm	enzyme
-1.2	0.00012	0.05	RABIF		RABIF	RAB interacting factor	Other	transporter
-2.4	0.00012	0.05	PPBP	D	PPBP	pro-platelet basic protein	Extracellular Space	cytokine
-2.5	0.00012	0.05	TKTL1		TKTL1	transketolase like 1	Cytoplasm	enzyme
0.95	0.00014	0.056	CALB1		CALB1	calbindin 1	Cytoplasm	other
-0.9	0.00016	0.062	TRAF3IP1		TRAF3IP1	TRAF3 interacting protein 1	Cytoplasm	other
-2.5	0.00017	0.064	PPBP	D	PPBP	pro-platelet basic protein	Extracellular Space	cytokine
3.8	0.00022	0.077	PZP		PZP	PZP alpha-2-macroglobulin like	Extracellular Space	other
2.2	0.00023	0.077	ANGPTL5		ANGPTL5	angiopoietin like 5	Extracellular Space	other
-1.8	0.00023	0.077	MTG2		MTG2	mitochondrial ribosome associated GTPase 2	Cytoplasm	enzyme

1.4	0.00026	0.085	ULBP2	D	ULBP2	UL16 binding protein 2	Plasma Membrane	transmembrane receptor
-2.3	0.00029	0.092	PPBP	D	PPBP	pro-platelet basic protein	Extracellular Space	cytokine
1.4	0.0003	0.092	POLA1		POLA1	DNA polymerase alpha 1, catalytic subunit	Nucleus	enzyme
-0.91	0.00032	0.096	NXF2		NXF2/NXF2B	nuclear RNA export factor 2	Nucleus	transporter
1.3	0.00034	0.1	TLR8		TLR8	toll like receptor 8	Plasma Membrane	transmembrane receptor
1.8	0.00038	0.1	NOG	D	NOG	noggin	Extracellular Space	growth factor
0.94	0.00039	0.1	PSMB3		PSMB3	proteasome 20S subunit beta 3	Cytoplasm	peptidase
1.5	0.00039	0.1	FBN1		FBN1	fibrillin 1	Extracellular Space	other
-0.53	0.0004	0.1	ERCC6L2		ERCC6L2	ERCC excision repair 6 like 2	Nucleus	enzyme
-0.86	0.00041	0.1	FAM78B		FAM78B	family with sequence similarity 78 member B	Other	other
4.6	0.00042	0.1	APOF		APOF	apolipoprotein F	Extracellular Space	other
1.8	0.00042	0.1	ENTPD1	D	ENTPD1	ectonucleoside triphosphate diphosphohydrolase 1	Plasma Membrane	enzyme

0.74	0.00044	0.1	CDC25A		CDC25A	cell division cycle 25A	Nucleus	phosphatase
-0.55	0.00044	0.1	PARN		PARN	poly(A)-specific ribonuclease	Nucleus	enzyme
0.78	0.00045	0.1	CHI3L2		CHI3L2	chitinase 3 like 2	Extracellular Space	enzyme
1.1	0.00046	0.1	NOG	D	NOG	noggin	Extracellular Space	growth factor
1.6	0.00049	0.11	ETV2		ETV2	ETS variant transcription factor 2	Nucleus	transcription regulator
-1.8	0.00051	0.11	PDCD10		PDCD10	programmed cell death 10	Cytoplasm	other
2.1	0.00052	0.11	KISS1		KISS1	KiSS-1 metastasis suppressor	Cytoplasm	other
2.2	0.00054	0.11	AATK		AATK	apoptosis associated tyrosine kinase	Cytoplasm	kinase
2.7	0.00054	0.11	PLXDC1		PLXDC1	plexin domain containing 1	Plasma Membrane	other
-1	0.00055	0.11	CRYBB2		CRYBB2	crystallin beta B2	Other	other
1.4	0.00057	0.11	FBXL4	D	FBXL4	F-box and leucine rich repeat protein 4	Nucleus	other
0.72	0.00057	0.11	SPCS1		SPCS1	signal peptidase complex subunit 1	Cytoplasm	peptidase
0.74	0.00057	0.11	WBP2NL		WBP2NL	WBP2 N-terminal like	Cytoplasm	other

2.4	0.00059	0.11	TXNDC12	D	TXNDC12	thioredoxin domain containing 12	Cytoplasm	enzyme
1.2	0.00063	0.12	A1BG		A1BG	alpha-1-B glycoprotein	Extracellular Space	other
-0.83	0.00064	0.12	KLK3	D	KLK3	kallikrein related peptidase 3	Extracellular Space	peptidase
-1.6	0.00065	0.12	PPP3CA	D	PPP3CA	protein phosphatase 3 catalytic subunit alpha	Cytoplasm	phosphatase
0.81	0.00068	0.12	TCP11		TCP11	t-complex 11	Cytoplasm	other
1.2	0.00071	0.12	PSD2		PSD2	pleckstrin and Sec7 domain containing 2	Plasma Membrane	other
-0.44	0.00073	0.12	GUCY2C		GUCY2C	guanylate cyclase 2C	Plasma Membrane	kinase
0.72	0.00074	0.12	NAALADL1		NAALADL1	N-acetylated alpha-linked acidic dipeptidase like 1	Plasma Membrane	peptidase
-2.1	0.00076	0.12	PTOV1		PTOV1	PTOV1 extended AT-hook containing adaptor protein	Nucleus	other
0.91	0.00077	0.12	IL17RC		IL17RC	interleukin 17 receptor C	Plasma Membrane	transmembrane receptor
0.74	0.00078	0.12	EDA2R		EDA2R	ectodysplasin A2 receptor	Plasma Membrane	transmembrane receptor

-1.3	0.0008	0.13	KLF15		KLF15	KLF transcription factor 15	Nucleus	transcription regulator
-3.9	0.0008	0.13	CA3		CA3	carbonic anhydrase 3	Cytoplasm	enzyme
-2.9	0.00082	0.13	MAPK10		MAPK10	mitogen-activated protein kinase 10	Cytoplasm	kinase
-1.1	0.00086	0.13	PHAX		PHAX	phosphorylated adaptor for RNA export	Cytoplasm	other
1.7	0.00086	0.13	BNC1		BNC1	basonuclin zinc finger protein 1	Nucleus	transcription regulator
-0.72	0.0009	0.13	PLAA		PLAA	phospholipase A2 activating protein	Cytoplasm	other
-0.59	0.00091	0.13	PTP4A3		PTP4A3	protein tyrosine phosphatase 4A3	Plasma Membrane	phosphatase
-2.6	0.00091	0.13	SHOC2		SHOC2	SHOC2 leucine rich repeat scaffold protein	Cytoplasm	other
2.7	0.00092	0.13	CSN3		CSN3	casein kappa	Extracellular Space	other
1.8	0.00094	0.13	P2RX4		P2RX4	purinergic receptor P2X 4	Plasma Membrane	ion channel
-0.81	0.00095	0.13	CCL20		CCL20	C-C motif chemokine ligand 20	Extracellular Space	cytokine
-0.98	0.00096	0.13	RASSF5		RASSF5	Ras association domain family member 5	Plasma Membrane	other

1.4	0.00096	0.13	CANT1		CANT1	calcium activated nucleotidase 1	Extracellular Space	enzyme
-0.93	0.00097	0.13	UNC5CL		UNC5CL	unc-5 family C-terminal like	Cytoplasm	peptidase
-1.2	0.001	0.13	MSANTD2		MSANTD2	Myb/SANT DNA binding domain containing 2	Other	other
0.77	0.0011	0.14	FARS2		FARS2	phenylalanyl-tRNA synthetase 2, mitochondrial	Cytoplasm	enzyme
2	0.0011	0.14	CXCL3	D	CXCL3	C-X-C motif chemokine ligand 3	Extracellular Space	cytokine
1.7	0.0011	0.14	CASTOR1		CASTOR1	cytosolic arginine sensor for mTORC1 subunit 1	Cytoplasm	other
-1.4	0.0012	0.15	CAND1		CAND1	cullin associated and neddylation dissociated 1	Cytoplasm	transcription regulator
2.2	0.0012	0.15	LTA4H		LTA4H	leukotriene A4 hydrolase	Cytoplasm	enzyme
0.5	0.0012	0.15	TCP11L2		TCP11L2	t-complex 11 like 2	Cytoplasm	other
-0.87	0.0012	0.15	BCAR3	D	BCAR3	BCAR3 adaptor protein, NSP family member	Cytoplasm	other
0.86	0.0013	0.15	PCDHB2		PCDHB2	protocadherin beta 2	Plasma Membrane	other

-0.58	0.0013	0.15	HOXA9		HOXA9	homeobox A9	Nucleus	transcription regulator
-0.25	0.0014	0.16	TFEC		TFEC	transcription factor EC	Nucleus	transcription regulator
-0.63	0.0014	0.16	ARHGAP17		ARHGAP17	Rho GTPase activating protein 17	Cytoplasm	other
1.2	0.0014	0.16	PRKAB1		PRKAB1	protein kinase AMP-activated non-catalytic subunit beta 1	Nucleus	kinase
0.55	0.0014	0.16	UPK3A		UPK3A	uroplakin 3A	Cytoplasm	other
3	0.0014	0.16	SURF1		SURF1	SURF1 cytochrome c oxidase assembly factor	Cytoplasm	enzyme

The first 100 differentially expressed proteins are shown, with columns indicating log ratio, *p*-value, q-value, gene symbol, and annotation. The full dataset (>10,000 entries) is available upon request.