3. 心血管疾患の発現差異プロテオミクス解析

我々の研究室では、心血管疾患の病態の分子レベルでの解明を目指し、プロテオミクス解析を基盤とした研究を進めている。患者の腹部・胸部大動脈瘤や石灰化大動脈弁の手術時に切除された試料の一部や、患者術前・術後血清の一部を用いて、isobaric tag for absolute and relative quantitation （iTRAQ）試薬による標識とその後の Nano LC 装置による分離とマトリックス支援レーザー脱離イオン化飛行時間型タンデム質量分析計（MALDI-TOF/TOF MS/MS）による解析により、病変組織において正常組織と比べ発現変動を示す蛋白質の包括的なプロテオミクス解析を行っている。このような解析により、疾患特異的な病態バイオマーカー蛋白質の同定を目指している。

図 1. 正常組織と比べての石灰化大動脈弁組織における発現減少蛋白質

Unused[a]	% Cov[b]	Peptides[c] (95%)	Reproducibility[d]	Uniprot number	Gene symbol	Protein name	iTRAQ ratio Average ± SE	Molecular function
79.5	25.9	39	8	P22105	TNXB	Tenascin-X	0.37 ± 0.03	extracellular matrix
6.4	17.7	4	7	P55083	MFAP4	Microfibril-associated glycoprotein 4	0.39 ± 0.07	extracellular matrix
12.0	28.9	6	8	P20774	OGN	Mimecan	0.43 ± 0.05	extracellular matrix
31.3	53.5	19	8	P07585	DCN	Decorin	0.47 ± 0.06	extracellular matrix
15.7	31.4	8	8	Q06828	FMOD	Fibromodulin	0.49 ± 0.10	extracellular matrix
69.0	68.7	51	8	P08670	VIM	Vimentin	0.50 ± 0.08	structural protein
39.4	37.3	21	8	P12109	COL6A1	Collagen alpha-1(VI) chain	0.50 ± 0.06	extracellular matrix
18.4	5.5	11	8	P13611	VCAN	Versican core protein	0.51 ± 0.05	extracellular matrix
79.6	70.4	55	8	P08123	COL1A2	Collagen alpha-2(I) chain	0.52 ± 0.08	extracellular matrix
27.1	42.6	13	7	P02545	LMNA	Lamin-A/C	0.53 ± 0.09	structural protein
123.5	36.6	66	8	P12111	COL6A3	Collagen alpha-3(VI) chain	0.53 ± 0.05	extracellular matrix
31.7	39.6	21	8	P12110	COL6A2	Collagen alpha-2(VI) chain	0.54 ± 0.07	extracellular matrix
6.0	11.8	3	8	Q9UBX5	FBLN5	Fibulin-5	0.55 ± 0.07	extracellular matrix
18.1	22.9	10	8	P49747	COMP	Cartilage oligomeric matrix protein	0.55 ± 0.12	extracellular matrix
13.4	19.3	8	8	Q15582	TGFBI	Transforming growth factor-beta-induced protein ig-h3	0.56 ± 0.12	extracellular matrix
106.1	65.8	91	8	P02452	COL1A1	Collagen alpha-1(I) chain	0.58 ± 0.08	extracellular matrix
12.8	54.7	8	8	Q07507	DPT	Dermatopontin	0.60 ± 0.07	extracellular matrix
16.3	17.6	10	8	P19827	ITIH1	Inter-alpha-trypsin inhibitor heavy chain H1	0.61 ± 0.06	protease inhibitor
10.0	12.0	5	8	P23142	FBLN1	Fibulin-1	0.61 ± 0.09	extracellular matrix
73.8	19.8	42	8	P35555	FBN1	Fibrillin-1	0.62 ± 0.14	extracellular matrix
4.0	5.8	2	6	Q14767	LTBP2	Latent-transforming growth factor beta-binding protein 2	0.62 ± 0.05	signaling molecule
20.0	36.9	10	7	P07437	TUBB	Tubulin beta chain	0.62 ± 0.11	cytoskeletal protein
14.9	25.4	7	7	P04083	ANXA1	Annexin A1	0.62 ± 0.11	transfer/carrier protein
26.9	50.9	21	8	P51884	LUM	Lumican	0.64 ± 0.10	extracellular matrix
4.1	19.5	3	7	P04792	HSPB1	Heat shock protein beta-1	0.65 ± 0.09	structural protein
4.0	16.4	2	8	P22352	GPX3	Glutathione peroxidase 3	0.67 ± 0.09	peroxidase
33.2	57.2	16	8	P07355	ANXA2	Annexin A2	0.68 ± 0.12	transfer/carrier protein
9.4	8.5	5	7	Q92954	PRG4	Proteoglycan 4	0.68 ± 0.07	extracellular matrix
27.8	62.6	15	7	P00738	HP	Haptoglobin	0.69 ± 0.13	hemoglobin binding
9.7	48.5	5	7	P62805	HIST1H4A	Histone H4	0.71 ± 0.16	nucleic acid binding

（*Connect. Tissue Res.* **53**, 460-468, 2012 より引用）

図 2. 腹部大動脈瘤患者術前血清と比べての術後血清における発現変動蛋白質

Unused ProtScore[a]	%Coverage[b]	Peptides[c] (95%)	Uniplot number	Gene Symbol	Protein name	iTRAQ ratio[d] Average ± SE (postsurgical *vs.* presurgical)	*p* value[e] (patient *vs.* control)	Molecular function
Increased proteins								
37.7	86.9	28	P02735	SAA1	Serum amyloid A protein	8.09 ± 3.60	-[f]	acute phase reactant
48.8	56.5	37	P01011	SERPINA3	Alpha-1-antichymotrypsin	1.88 ± 0.12	0.0006	protease inhibitor
53.1	67.7	56	P02763	ORM1	Alpha-1-acid glycoprotein 1	1.85 ± 0.21	0.0250	transporter
26.2	54.5	14	P02750	LRG1	Leucine-rich alpha-2-glycoprotein	1.85 ± 0.15	0.0032	unknown
26.5	40.1	13	P02748	C9	Complement component C9	1.36 ± 0.09	0.0135	complement
116.9	80.9	139	P01009	SERPINA1	Alpha-1-antitrypsin	1.32 ± 0.06	0.0081	protease inhibitor
Decreased proteins								
26.1	30.4	12	P06396	GSN	Gelsolin	0.55 ± 0.03	0.0000	actin scavenger
37.3	54.2	29	P02765	AHSG	Alpha-2-HS-glycoprotein	0.61 ± 0.05	0.0002	extracellular matrix
18.5	74.0	17	P02652	APOA2	Apolipoprotein A-II	0.64 ± 0.05	0.0214	transporter
14.1	60.7	9	P02753	RBP4	Retinol-binding protein 4	0.65 ± 0.05	0.0005	transfer/carrier protein
20.9	36.3	10	P29622	SERPINA4	Kallistatin	0.68 ± 0.06	0.0196	protease inhibitor
10.0	25.1	6	P27169	PON1	Serum paraoxonase/arylesterase 1	0.69 ± 0.06	0.0010	hydrolase
89.6	89.9	110	P02647	APOA1	Apolipoprotein A-I	0.70 ± 0.04	0.0238	transporter
149.6	49.4	90	P02751	FN1	Fibronectin	0.72 ± 0.06	0.0330	extracellular matrix
163.9	82.5	176	P02787	TF	Serotransferrin	0.73 ± 0.04	0.0004	transfer/carrier protein
36.9	50.3	20	P04196	HRG	Histidine-rich glycoprotein	0.73 ± 0.03	0.0005	adapter protein
234.7	81.7	207	P01023	A2M	Alpha-2-macroglobulin	0.75 ± 0.04	0.0036	signaling molecule
44.3	35.7	26	P19823	ITIH2	Inter-alpha-trypsin inhibitor heavy chain H2	0.77 ± 0.06	0.0024	protease inhibitor

（*Proteome Sci.* **11**, article 27, 13 pages, 2013 より引用）