Table S1. Clinical and demographic data of patients analyzed in this study by combined bile and urine proteome analysis for CCA diagnosis.

Patient group	**Malignant biliary stricture case groups**		**Benign biliary stricture control groups**			
	CCA	**CCA on top of PSC**	**PSC**	**BBD**		
Patients, n	33	19	57	19		
Type of biliary disease (n)						
Choledocholithiasis				10		
Chronic pancreatitis				3		
SSC				3		
CBD dilatation				3		
Clinical and demographic parameters (normal values)					**P for malignant to benign group differences***	**AUC for CCA diagnosis**
Age, years, mean/range	63/35-85	46/22-68	43/21-83	60/35-84	0.0004	0.68
Female/male, n/n	11/22	4/15	13/44	8/11	1.00	n.d.
Alkaline phosphatase (35 – 104 U/L), mean/range	395/61-1023	342/128-670	300/47-1475	251/51-1173	0.001	0.68
γ-Glutamyltransferase (< 39 U/L), mean/range	521/10-2212	379/83-937	352/15-3638	304/30-1340	0.002	0.67
Bilirubin (< 17 µmol/L), mean/range	131/4-502	112/5-506	48/4-260	30/5-126	0.006	0.65
Leucocyte count (4-10/nL), mean/range	8.5/3.6-20.8	8.5/0.8-18.0	7.3/1.0-20.0	6.4/2.3-10.9	0.15	0.58
C-reactive protein (< 8 mg/L), mean/range	45/1-184	33/3-215	14/1-91	28/1-190	0.002	0.67
Alanine aminotransferase (< 35 U/L), mean/range	96/14-551	205/27-716	90/15-548	56/16-205	0.031	0.62
Aspartate aminotransferase (< 32 U/L), mean/range	90/18-333	169/23-767	77/6-378	52/24-110	0.004	0.66
Carbohydrate antigen 19-9 (< 27 kU/L), mean/range	3562/1-81243	785/1-3955	56/1-293	146/1-543	<0.0001	0.75
Number of detected peptides						
in urine, mean/range	1901/750-3462	2113/1033-3800	2036/946-3036	1859/1270-2940	0.69	0.52
in bile, mean/range	1562/320-4158	1827/423-4488	1653/327-4165	2018/491-3458	0.42	0.54
Classification factors by proteome analysis						
Bile proteome analysis (BPA)	0.59/-1.24-2.28	0.14/-1.74-1.65	-0.36/-1.49-1.16	0.05/-1.12-1.40	<0.0001	0.79
Urine proteome analysis (UPA)	-0.11/-2.41-2.74	0.22/-0.82-3.19	-1.49/-3.13-1.09	-1.48/-2.64-0.27	<0.0001	0.90
Combined BPA and UPA	2.40/-3.14-10.29	2.44/-3.73-13.05	-2.98/-9.16-4.69	-2.38/-6.08-0.94	<0.0001	0.92

*Two-tailed probability for continuous data and significance level by Fisher exact test for categorical data.

Abbreviations: AUC, area under the curve; BBD, benign biliary disease; CBD, common bile duct; CCA, cholangiocarcinoma; n.d., not determined; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis.

Table S2. Observed and *in silico* predicted protease associations to the N- and C-terminal amino acid sequence motifs of the bile and urine peptides included in the bile and urinary proteomic models for CCA diagnosis. Confirmed cleavage site associations are based on the MEROPS peptide database, whereas *in silico* protease prediction was done by the software tool Proteasix.

Evidence level*	Biofluid	CCA peptide marker sequence	Parental protein	Protease cleavage at the peptide's N-terminal end†	Peptide sequence including flanking cleavage motifs	Protease cleavage at the peptide's C-terminal end†
Observed	Bile	173-FYAPELLFFAK-183	Serum albumin	MEP1B (M12.004)[1]	RHPY.**FYAPELLFFAK**	
		2-VHLTPEEKSAVTA-14	Hemoglobin subunit β	unknown peptidase[2]	M.**VHLTPEEKSAVTA**.LWGK	CAPN1 (C02.001)[3] /CTSD (A01.009)[4]
		28-SVTEQGAELSNEER-41	14-3-3 protein ζ/δ	CTSL (C01.032)[5] / CTSK (C01.036)[5] / CTSS (C01.034)[5] / CTSV (C01.009)[5] / PRSS1 (S01.151)[6]	ACMK.**SVTEQGAELSNEER**.NLLS	PRSS1 (S01.151)[6]
	Urine	26-DFDDFNLED-34	CD99 antigen-like protein 2	unknown peptidase[2]	RGSG.**DFDDFNLED**	
		97-DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPGIVG-132	CD99 antigen	MEP1B (M12.004)[7]	ADLA.**DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPGIVG**	
Predicted	Bile	27-AEALERmFL-35	Hemoglobin subunit α	ADAMTS4 (M12.221)	GEYG.**AEALERmFL**.SFPT	CMA1 (S01.140) / KLK4 (S01.251)
		173-FYAPELLFFAK-183	Serum albumin	CMA1 (S01.140)	RHPY.**FYAPELLFFAK**	
		179-DLAGRDLTDYLm-190	Actin, cytoplasmic 1	CMA1 (S01.140) / ADAMTS4 (M12.221) / KLK4 (S01.251)	ILRL.**DLAGRDLTDYLm**	
		28-SVTEQGAELSNEER-41	14-3-3 protein ζ/δ		**SVTEQGAELSNEER**.NLLS	ADAMTS4 (M12.221)
		381-ILLTDGDPTVGETNPR-396	Inter-α-trypsin inhibitor heavy chain H4		**ILLTDGDPTVGETNPR**.SIQN	KLK4 (S01.251)
		43-FESFGDLSTPDAVmGNPK-60	Hemoglobin subunit β	CMA1 (S01.140)	TQRF.**FESFGDLSTPDAVmGNPK**	
	Urine	589-SGSVIDQSR-597	Uromodulin	ADAMTS4 (M12.221) / KLK6 (S01.236)	TRFR.**SGSVIDQSR**.VLNL	CASP1 (C14.001) / KLK6 (S01.236)
		26-DFDDFNLED-34	CD99 antigen-like protein 2		**DFDDFNLED**.AVKE	ADAMTS4 (M12.221) / CASP1 (C14.001)
		613-DGEAGAQGPpGPA-625	Collagen α-1(I) chain	ADAMTS4 (M12.221) / KLK6 (S01.236)	PAGK.**DGEAGAQGPpGPA**	
		657-KpGEQGVpGDLG-668	Collagen α-1(I) chain	ADAMTS4 (M12.221)	GEAG.**KpGEQGVpGDLG**	
		1007-GPpGESGREGApG-1019	Collagen α-1(I) chain		**GPpGESGREGApG**.AEGS	ADAMTS4 (M12.221)
		1701-GLpGEmGSpGEPG-1713	Collagen α-6(VI) chain	CASP1 (C14.001)	MISA.**GLpGEmGSpGEPG**	
		918-RpGEVGPpGPpGP-930	Collagen α-1(I) chain	ADAMTS4 (M12.221)	GPAG.**RpGEVGPpGPpGP**.AGEK	ADAMTS4 (M12.221)
		651-pPGEAGKpGEQGVP-664	Collagen α-1(I) chain		**pPGEAGKpGEQGVP**.GDLG	
		543-SpGSPGPDGKTGPpGPAG-560	Collagen α-1(I) chain	ADAMTS4 (M12.221) / CASP1 (C14.001)	GLTG.**SpGSPGPDGKTGPpGPAG.**QDGR	ADAMTS4 (M12.221)
		54-SGDSDDDEPPPLPRL-68	Membrane-associated progesterone receptor component 1		**SGDSDDDEPPPLPRL**.KRRD	ADAMTS4 (M12.221)
		288-EpGSpGENGApGQMGPR-304	Collagen α-1(I) chain	ADAMTS4 (M12.221)	GPKG.**EpGSpGENGApGQMGPR**.GLPG	CASP1 (C14.001)
		1084-ApGPQGPRGDkGETGERG-1101	Collagen α-1(III) chain		**ApGPQGPRGDkGETGERG**.AAGI	ADAMTS4 (M12.221)
		550-DGKTGpPGPAGQDGRPGPpGppG-572	Collagen α-1(I) chain	ADAMTS4 (M12.221)	SPGP.**DGKTGpPGPAGQDGRPGPpGppG.**ARGQ	ADAMTS4 (M12.221)
		189-kGQpGApGVkGEpGApGENGTpGQTGARG-217	Collagen α-2(I) chain		**kGQpGApGVkGEpGApGENGTpGQTGARG**.LPGE	ADAMTS4 (M12.221)
		780-DKGESGpSGpAGpTGARGApGDRGEpGppG-809	Collagen α-1(I) chain	ADAMTS4 (M12.221)	GAPG.**DKGESGpSGpAGpTGARGApGDRGEpGppG**	
		188-LkGQpGApGVKGEpGApGENGTPGQTGARG-217	Collagen α-2(I) chain	ADAMTS4 (M12.221)	GLDG.**LkGQpGApGVKGEpGApGENGTPGQTGARG.**LPGE	ADAMTS4 (M12.221)
		188-LkGQpGApGVkGEpGApGENGTpGQTGARG-217	Collagen α-2(I) chain	ADAMTS4 (M12.221)	GLDG.**LkGQpGApGVkGEpGApGENGTpGQTGARG.**LPGE	ADAMTS4 (M12.221)
		194-ESEELNGAYKAIPVAQDLNAPSDWDSRGKDSYETSQL-230	Osteopontin		**ESEELNGAYKAIPVAQDLNAPSDWDSRGKDSYETSQL**.DDQS	ADAMTS4 (M12.221)

* The MEROPS peptidase database available at https://www.ebi.ac.uk/merops/index.shtml was screened for experimentally confirmed protease to cleavage site associations for the differentially expressed peptides leading to the list of observed assignments in the upper part of the table . The lower part of the table consist of *in silico* predicted protease assignments made by the online software tool Proteasix which is based on the specificity weight matrices provided by the MEROPS peptidase database . The MEROPS specificity matrix is a measure for the frequency of specific amino acids at each position in the experimentally confirmed cleavage site of a given protease. Proteasix transforms the specificity matrices to probability matrices by dividing the number of occurrences for each of the 20 possible amino acids with the total number of experimental observations. From the 25 billion combinations only those were kept with a propability score greater than the 99th percentile. Moreover, in order to eliminate false positive predictions, a high confidence threshold was calculated based on six thousand random sequences generated by the Expassy RandSeq tool and only those protease to cleavage site associations were considered below this threshold.

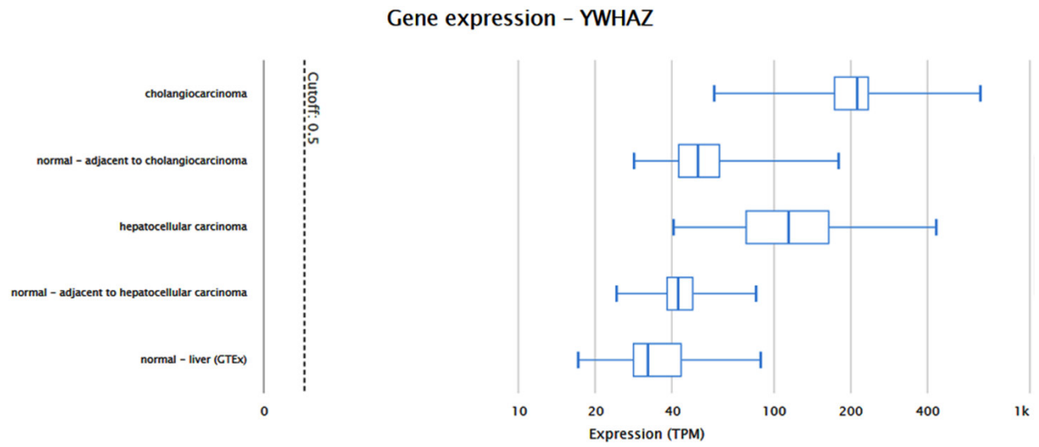
† Proteases were restricted to those of human origin. Proteases are specified with their gene names together with their MEROPS classification ID's in parentheses.

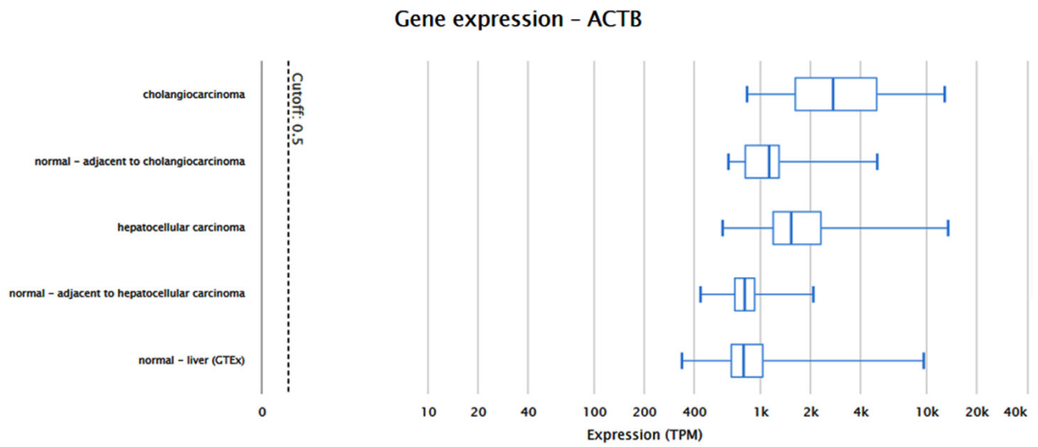
Reference list: [1] Bertenshaw GP, Turk BE, Hubbard SJ, Matters GL, Bylander JE, Crisman JM, et al. Marked differences between metalloproteases meprin A and B in substrate and peptide bond specificity. J Biol Chem. 2001;276:13248-55. **[2]** López-Pelegrín M, Cerdà-Costa N, Cintas-Pedrola A, Herranz-Trillo F, Bernadó P, Peinado JR, et al. Multiple stable conformations account for reversible concentration-dependent oligomerization and autoinhibition of a metamorphic metallopeptidase. Angew Chem Int Ed Engl. 2014;53:10624-30. **[3]** Shinkai-Ouchi F, Koyama S, Ono Y, Hata S, Ojima K, Shindo M, et al. Predictions of Cleavability of Calpain Proteolysis by Quantitative Structure-Activity Relationship Analysis Using Newly Determined Cleavage Sites and Catalytic Efficiencies of an Oligopeptide Array. Mol Cell Proteomics. 2016;15:1262-80. **[4]** Brindley PJ, Kalinna BH, Wong JY, Bogitsh BJ, King LT, Smyth DJ, et al. Proteolysis of human hemoglobin by schistosome cathepsin D. Mol Biochem Parasitol. 2001;112:103-12. **[5]** Vidmar R, Vizovišek M, Turk D, Turk B, Fonović M. Protease cleavage site fingerprinting by label-free in-gel degradomics reveals pH-dependent specificity switch of legumain. EMBO J. 2017;36:2455-65. **[6]** Schilling O, Overall CM. Proteome-derived, database-searchable peptide libraries for identifying protease cleavage sites. Nat Biotechnol. 2008;26:685-94. **[7]** Becker-Pauly C, Barré O, Schilling O, Auf dem Keller U, Ohler A, Broder C, et al. Proteomic analyses reveal an acidic prime side specificity for the astacin metalloprotease family reflected by physiological substrates. Mol Cell Proteomics. 2011;10:M111.009233.

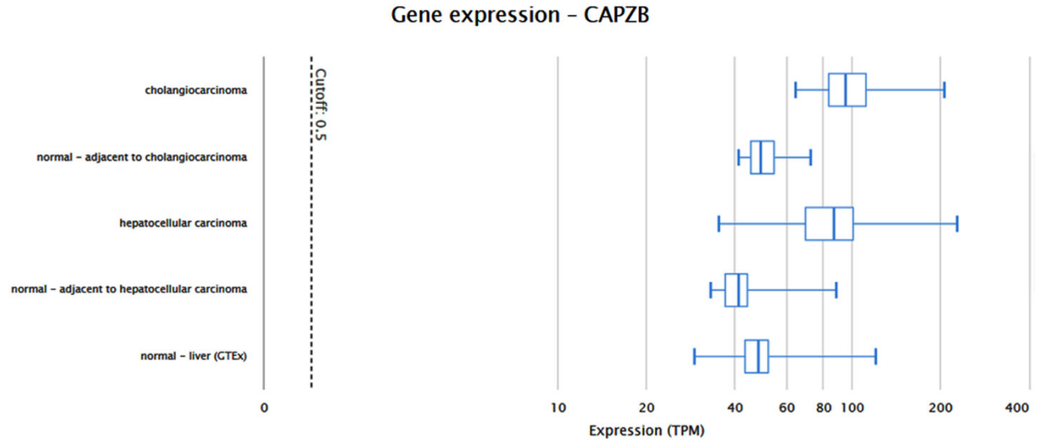
Table S3. Transcriptomics data table summarizing the results from differential gene expression analysis for all parental proteins and predicted proteases associated with the bile and urine CCA peptide markers. All tissue transcriptomics data sets were retrieved from the NCBI Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) and analyzed with GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/). The analysis was based on the following gene arrays: GSE76297 for CCA tumour and paired non-malignant tissue, GSE26566 for CCA tumour, matched non-malignant surrounding liver and normal bile duct tissue, GSE32879 for intrahepatic CCA tumour, matched non-malignant surrounding liver and benign liver lesions tissue derived from focal nodular hyperplasia patients, and GSE45001 for laser capture microdissected fibrous tissue from intrahepatic CCA tumour and non-malignant tissue. Differential tissue expression is reported as fold-change in CCA tissue versus control, supplemented by the adjusted p-value for false discovery rate and the identification number per gene array. Fold change ratios >1.00, representing increased expression in CCA tumour tissue, are highlighted in red font, whereas those <1.00, representing decreased expression in CCA tumour tissue, are highlighted in blue font. False discovery rate-adjusted p-values <0.05 are marked in black, those >0.05 in grey font.

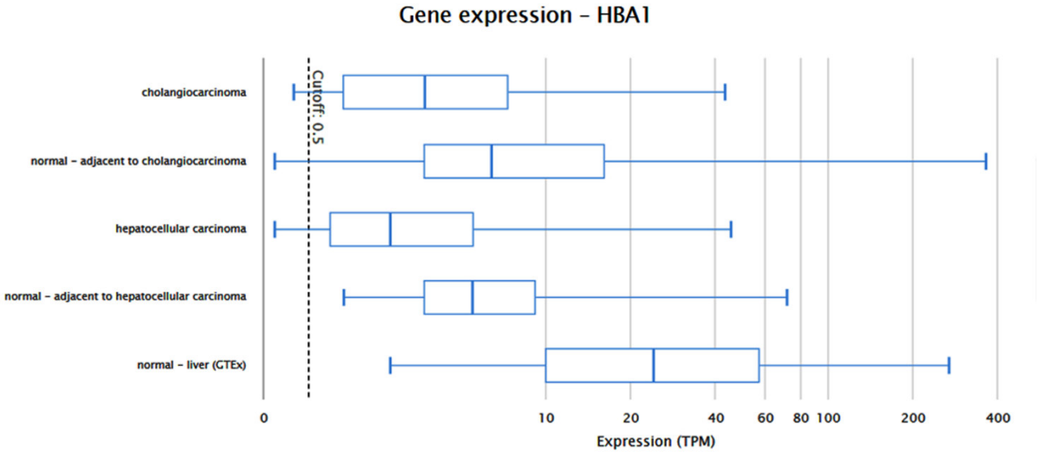
Protein specification			**Differential tissue transcriptomics analysis reported as fold change / adj. p-value / ID**						**Representation at the proteomic level**	
Protein name	**UniProt ID**	**Gene**	**GSE76297**	**GSE26566**		**GSE32879**		**GSE45001**	**Role**	**Differential peptide expression in CCA vs. PSC/BBD**
			CCA tumor tissue (n=91) - vs - Paired non-tumor tissue (n=92)	**CCA tumor tissue (n=104) - vs - Matched non-cancerous surrounding liver tissue (n=59)**	**CCA tumor tissue (n=104) - vs - Unmatched normal intrahepatic bile duct (n=6)**	**Intrahepatic CCA (n=16) - vs - Paired non-cancerous liver tissue (n=7)**	**Intrahepatic CCA (n=16) - vs - Unmatched benign liver lesions (FNH, n=5)**	**CCA tumoral stroma (n=10) - vs - Matched non-tumoral stroma (n=10)**		
14-3-3 protein ζ/δ	P63104	YWHAZ	2.37 / **2.65E-63** / TC08001485.hg.1	2.71 / **2.08E-27** / ILMN_1801928 3.23 / **4.03E-07** / ILMN_1669286	2.23 / **1.47E-03** / ILMN_1801928 3.53 / 5.67E-02 / ILMN_1669286	3.13 / **8.56E-09** / 8152096	2.53 / **5.64E-06** / 8152096	1.96 / **4.49E-02** / A_32_P198923 2.00 / 1.03E-01 / A_32_P226149	Source of bile peptide marker(s)	Up
Actin, cytoplasmic 1	P60709	ACTB	1.59 / **1.88E-43** / TC07001120.hg.1	1.11 / **1.12E-04** / ILMN_1343294 1.83 / **9.13E-22** / ILMN_2038777 2.38 / **1.39E-17** / ILMN_1777296	1.04 / 7.93E-01 / ILMN_1343294 2.10 / **7.23E-05** / ILMN_2038777 1.83 / 6.01E-02 / ILMN_1777296	1.65 / **3.47E-03** / 8137979	1.49 / 5.90E-02 / 8137979	1.29 / 5.71E-01 / A_32_P137939 1.04 / 9.56E-01 / A_23_P135769		Up
F-actin-capping protein subunit β	P47756	CAPZB	1.35 / **2.28E-25** / TC01002300.hg.1	1.17 / **1.12E-03** / ILMN_1798980	1.22 / 2.95E-01 / ILMN_1798980	1.34 / 1.17E-01 / 7913169	1.23 / 4.90E-01 / 7913169	1.32 / 4.96E-01 / A_33_P3235568 1.23 / 6.67E-01 / A_23_P126752		Up
Hemoglobin subunit α	P69905	HBA1	0.51 / **6.34E-21** / TC16000008.hg.1	0.34 / **4.71E-07** / ILMN_1667796	0.88 / 9.32E-01 / ILMN_1667796	0.3 / **2.20E-04** / 7991766	0.87 / 7.77E-01 / 7991766	N/A		Down / Up
Hemoglobin subunit β	P68871	HBB	0.62 / **8.16E-17** / TC11001330.hg.1	0.35 / **2.78E-06** / ILMN_1769753	0.57 / 6.33E-01 / ILMN_1769753	0.23 / **4.86E-07** / 7946033	0.71 / 3.06E-01 / 7946033	0.04 / **1.94E-03** / A_23_P203558		Down / Up
Inter-α-trypsin inhibitor heavy chain H2	P19823	ITIH2	0.04 / **4.55E-48** / TC10000066.hg.1	0.11 / **2.39E-13** / ILMN_1808494	0.26 / 2.80E-01 / ILMN_1808494	0.11 / **2.82E-03** / 7926061	0.1 / **1.87E-02** / 7926061	0.05 / **2.96E-04** / A_23_P202053		Down
Inter-α-trypsin inhibitor heavy chain H4	Q14624	ITIH4	0.07 / **1.52E-57** / TC03003413.hg.1	0.09 / **1.98E-25** / ILMN_1718525	0.18 / **2.65E-02** / ILMN_1718525	0.04 / **1.10E-09** / 8088020	0.04 / **1.41E-07** / 8088020	0.02 / **2.41E-07** / A_23_P109881		Up
Keratin, type I cytoskeletal 19	P08727	KRT19	9.67 / **4.92E-57** / TC17002906.hg.1	25.28 / **1.02E-29** / ILMN_1753924	8.46 / **6.82E-03** / ILMN_1753924	6.71 / **3.73E-03** / 8015349	7.5 / **1.84E-02** / 8015349	2.58 / 2.57E-01 / A_23_P66798		Down
Keratin, type II cytoskeletal 8	P05787	KRT8	1.81 / **3.55E-23** / TC12001539.hg.1 1.61 / **2.46E-16** / TC08000415.hg.1	1.97 / **3.22E-09** / ILMN_1753584	3.27 / **2.17E-03** / ILMN_1753584	2.08 / **4.20E-03** / 7963567	1.71 / 8.57E-02 / 7963567	2.55 / 3.54E-01 / A_24_P67395 **1.00** / 9.98E-01 / A_33_P3372368 **1.00** / 9.98E-01 / A_23_P14072		Down / Up
Serum albumin	P02768	ALB	0.08 / **7.17E-30** / TC04000403.hg.1	0.27 / **8.38E-06** / ILMN_1682763	0.24 / 2.88E-01 / ILMN_1682763	0.12 / **8.32E-03** / 8095628	0.12 / **4.52E-02** / 8095628	0.01 / **1.02E-07** / A_23_P257834		Up
Uromodulin	P07911	UMOD	0.91 / **2.84E-07** / TC16000924.hg.1	1.12 / 6.26E-01 / ILMN_1740585	1.04 / 9.76E-01 / ILMN_1740585	0.92 / 3.78E-01 / 7999936	0.98 / 8.94E-01 / 7999936	0.84 / 8.11E-01 / A_23_P158775	Source of urine peptide marker(s)	Down
Kininogen-1	P01042	KNG1	0.03 / **1.54E-51** / TC03001024.hg.1	0.04 / **3.04E-17** / ILMN_1753729	0.06 / **4.82E-02** / ILMN_1753729	0.02 / **1.13E-05** / 8084679	0.02 / **3.52E-04** / 8084679	0.003 / **9.23E-07** / A_23_P212258		Up
CD99 antigen-like protein 2	Q8TCZ2	CD99L2	0.65 / **1.15E-36** / TC0X001486.hg.1	0.59 / **7.35E-10** / ILMN_1700681	0.55 / 5.95E-02 / ILMN_1700681	0.68 / **2.90E-02** / 8175647	0.82 / 4.56E-01 / 8175647	0.75 / 7.19E-01 / A_23_P253052		Down
Collagen α-1(I) chain	P02452	COL1A1	4.66 / **2.91E-45** / TC17001682.hg.1	14.62 / **2.65E-30** / ILMN_1701308	5.17 / **1.01E-02** / ILMN_1701308	8.5 / **1.36E-08** / 8016646	3.61 / **8.47E-06** / 8016646	22.47 / **7.37E-04** / A_33_P3304668		Down / Up
Collagen α-6(VI) chain	A6NMZ7	COL6A6	0.76 / **6.97E-32** / TC03000705.hg.1	N/A	N/A	0.56 / **4.15E-05** / 8082597	0.71 / **3.04E-03** / 8082597	N/A		Up
Na^+/K^+-ATPase γ subunit	P54710	FXYD2	0.77 / **8.85E-25** / TC11003508.hg.1	1.42 / 1.80E-01 / ILMN_1781045 1.89 / 1.06E-01 / ILMN_1715301	0.60 / 7.22E-01 / ILMN_1781045 0.27 / 3.32E-01 / ILMN_1715301	2.26 / 9.14E-02 / 7951966	0.80 / 4.15E-01 / 7951977	0.47 / 4.22E-01 / A_23_P161769 0.72 / 7.31E-01 / A_33_P3228445		Down
Membrane-associated progesteronereceptor component 1	O00264	PGRMC1	0.42 / **9.08E-60** / TC0X000580.hg.1	0.47 / **1.99E-16** / ILMN_1684771	0.72 / 4.01E-01 / ILMN_1684771	0.28 / **1.97E-04** / 8169617	0.32 / **5.84E-03** / 8169617	0.49 / 1.72E-01 / A_33_P3332130		Down
Collagen α-1(III) chain	P02461	COL3A1	3.91 / **1.26E-34** / TC02001105.hg.1	4.79 / **7.60E-20** / ILMN_1773079	2.95 / 5.48E-02 / ILMN_1773079	4.47 / **5.27E-06** / 8046922	2.69 / **5.31E-03** / 8046922	3.86 / 3.31E-01 / A_24_P935491		Up
Collagen α-2(I) chain	P08123	COL1A2	5.96 / **9.87E-49** / TC07000559.hg.1	8.06 / **3.13E-22** / ILMN_1785272	1.78 / 5.08E-01 / ILMN_1785272	7.75 / **1.02E-08** / 8134263	3.07 / **5.47E-05** / 8134263	6.59 / **2.94E-02** / A_24_P277934		Up
Collagen α-1(II) chain	P02458	COL2A1	1.02 / 4.29E-01 / TC12001440.hg.1	1.40 / 6.82E-01 / ILMN_1686538 0.65 / **7.43E-03** / ILMN_1742840	1.15 / 8.76E-01 / ILMN_1742840	1.06 / 6.32E-01 / 7962703	1.09 / 6.24E-01 / 7962703	N/A		Down
α-1-antitrypsin	P01009	SERPINA1	0.36 / **6.71E-36** / TC14001466.hg.1	0.73 / **4.24E-03** / ILMN_1745961 2.60 / **6.70E-06** / ILMN_1764980 0.68 / 1.55E-01 / ILMN_1686098	0.67 / 4.72E-01 / ILMN_1745961 2.43 / 2.98E-01 / ILMN_1764980 0.73 / 8.33E-01 / ILMN_1686098	0.51 / **1.73E-02** / 7981068	0.48 / 5.18E-02 / 7981068	0.17 / **1.36E-03** / A_23_P218111 0.19 / **2.27E-02** / A_33_P3289659		Down
Collagen α-1(XVII) chain	Q9UMD9	COL17A1	N/A	14.32 / **1.83E-06** / ILMN_1799105 13.64 / **4.04E-11** / ILMN_1651282	9.99 / 3.52E-01 / ILMN_1799105 3.43 / 4.65E-01 / ILMN_1651282	1.24 / 6.17E-01 / 7936144	1.4 / 6.17E-01 / 7936144	N/A		Up
Collagen α-2(V) chain	P05997	COL5A2	2.46 / **2.39E-33** / TC02002612.hg.1	5.13 / **4.75E-21** / ILMN_1729117	2.43 / 1.53E-01 / ILMN_1729117	3.54 / **9.36E-05** / 8057620	2.59 / **1.43E-02** / 8057620	5.21 / 1.63E-01 / A_23_P33196		Up
Interleukin-1 receptor accessoryprotein-like 1	Q9NZN1	IL1RAPL1	0.94 / **8.15E-04** / TC0X000133.hg.1	0.66 / **2.82E-04** / ILMN_1756598	0.78 / 6.18E-01 / ILMN_1756598	1.09 / 6.56E-01 / 8166593	1.03 / 9.39E-01 / 8166593	N/A		Up
CD99 antigen	P14209	CD99	0.93 / **1.20E-02** / TC0X000014.hg.1 0.93 / **2.16E-02** / TC0Y000014.hg.1	0.93 / 4.06E-01 / ILMN_1785188	0.59 / 1.00E-01 / ILMN_1785188	0.83 / 2.39E-01 / 8176360	0.84 / 4.79E-01 / 8176360	0.77 / 6.57E-01 / A_24_P70993		Down
Osteopontin	P10451	SPP1	8.66 / **1.63E-33** / TC04000478.hg.1	8.63 / **9.98E-20** / ILMN_1651354	2.27 / 3.56E-01 / ILMN_1651354	53.74 / **9.66E-12** / 8096301	25.92 / **1.35E-09** / 8096301	10.06 / **1.34E-03** / A_23_P7313		Up
Kallikrein-4	Q9Y5K2	KLK4	0.88 / **5.98E-07** / TC19001761.hg.1	2.31 / 4.47E-01 / ILMN_1792363	N/A	0.89 / 2.65E-01 / 8038655	0.97 / 8.59E-01 / 8038655	N/A	Predicted protease	Up
Chymase	P23946	CMA1	0.83 / **1.74E-23** / TC14000979.hg.1	0.97 / 9.46E-01 / ILMN_1770772	2.25 / 5.14E-01 / ILMN_1770772	0.87 / 7.71E-02 / 7978343	0.78 / **2.84E-02** / 7978343	0.54 / 4.97E-01 / A_33_P3259708		Up
A disintegrin and metalloproteinase with thrombospondin motifs 4	O75173	ADAMTS4	1.06 / 3.39E-01 / TC01003421.hg.1	0.85 / 4.72E-01 / ILMN_1751489	0.13 / **4.26E-04** / ILMN_1751489	1.32 / 4.33E-01 / 7921821	1.58 / 2.80E-01 / 7921821	0.56 / 7.89E-01 / A_23_P360754		Up
Caspase-1 (Interleukin-1 converting enzyme)	P29466	CASP1	1.21 / **4.09E-04** / TC11003505.hg.1	0.93 / 5.72E-01 / ILMN_1742270 1.27 / 6.42E-01 / ILMN_1727762	0.68 / 4.69E-01 / ILMN_1742270 2.87 / 4.73E-01 / ILMN_1727762	1.19 / 5.21E-01 / 7951397	0.91 / 8.65E-01 / 7951397	1.13 / 8.91E-01 / A_23_P202978		Down
Kallikrein-6	Q92876	KLK6	1.96 / **4.71E-09** / TC19001764.hg.1	2.07 / **5.69E-05** / ILMN_1777541 26.72 / **1.10E-04** / ILMN_1780255	1.43 / 7.15E-01 / ILMN_1777541	1.19 / 7.21E-01 / 8038683	1.29 / 7.59E-01 / 8038683	N/A		Down

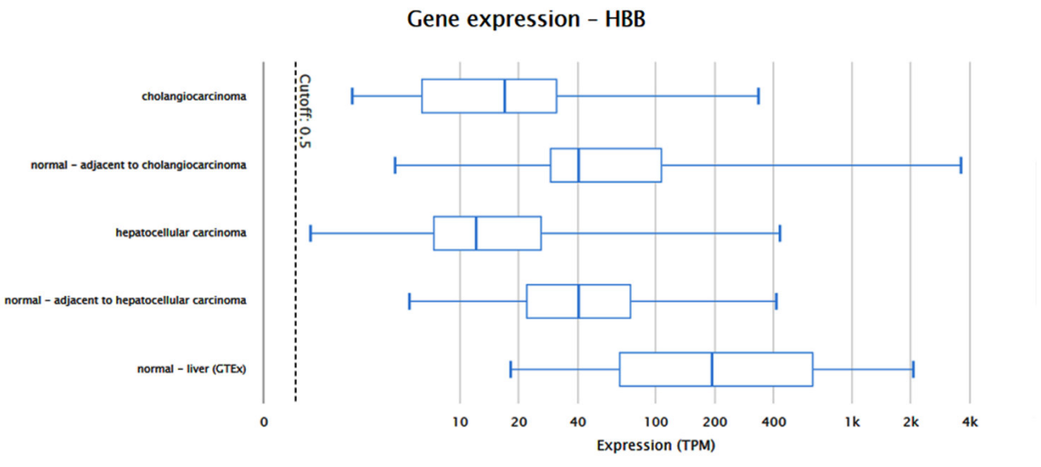
Figures S1-S24. Box-and-whisker plot representations of RNA-seq mRNA levels given as “transcripts per million” (TPM) for all parental proteins and predicted proteases associated with the bile and urine CCA peptide markers in 18 CCA, 18 CCA-adjacent, 100 HCC, 53 HCC-adjacent and 35 normal liver tissue replicates. Transcriptomics data sets were retrieved from the “Pan-Cancer Analysis of Whole Genomes” project RNA-Seq mRNA repository available at https://www.ebi.ac.uk/. No RNA-seq data was available for UMOD, COL6A6, COL2A1, IL1RAPL1, KLK4, CMA1 and KLK6.

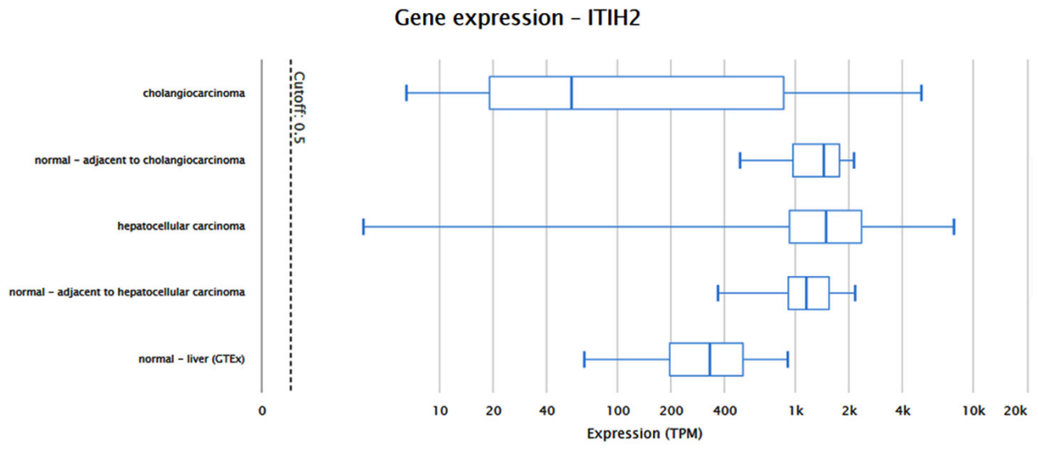




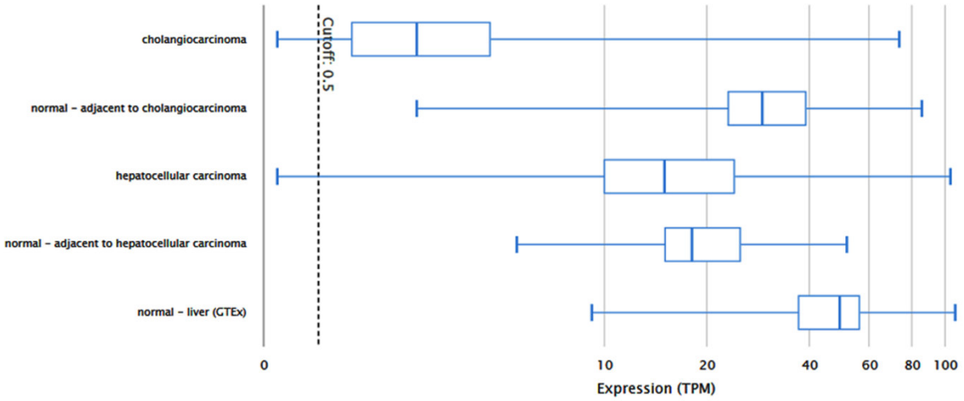




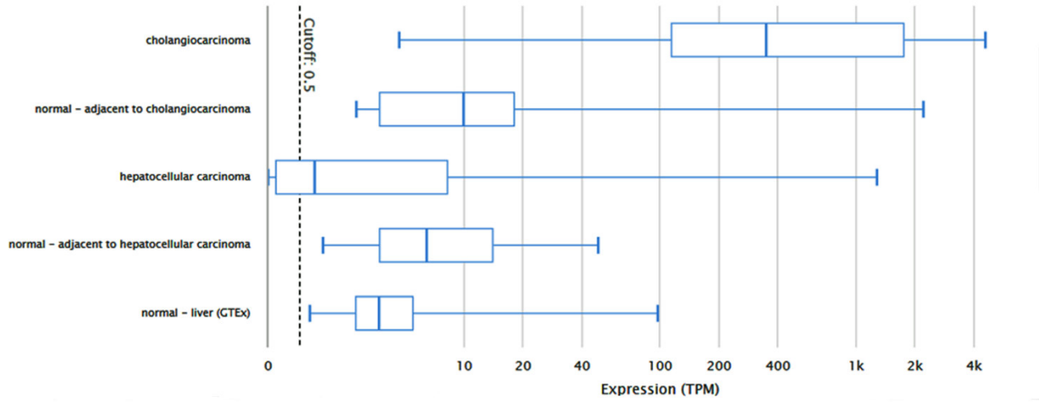




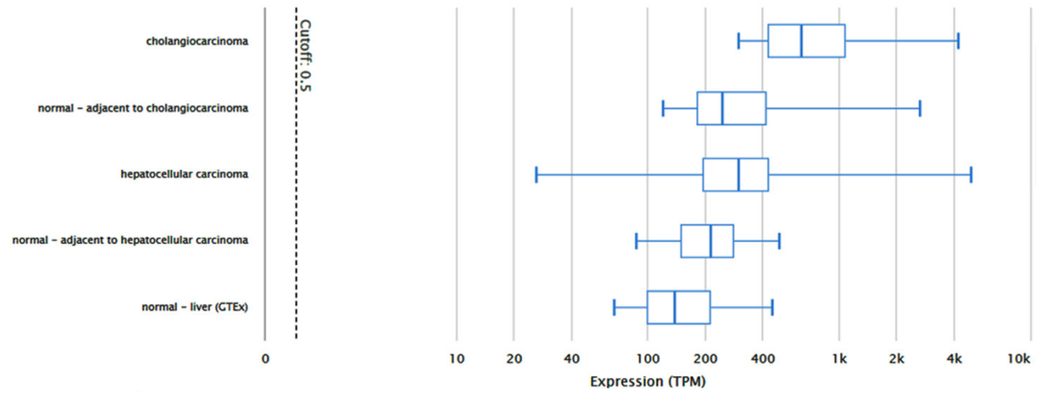
Gene expression – ITIH4



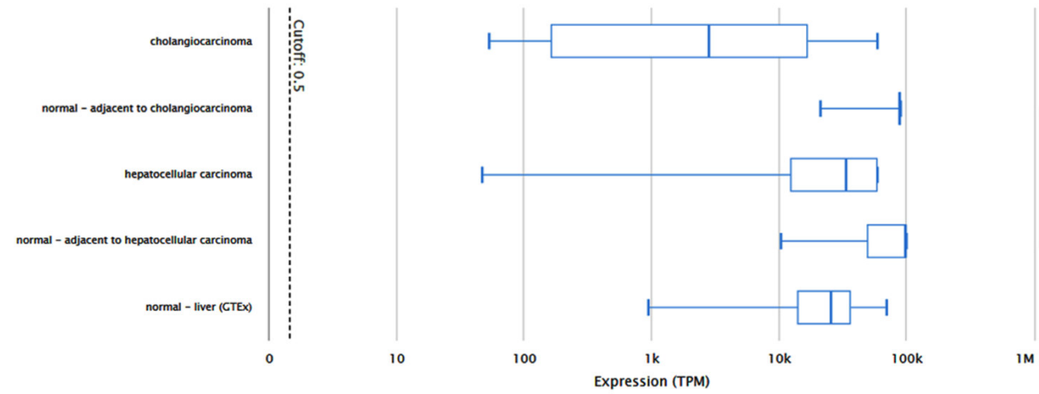
Gene expression – KRT19



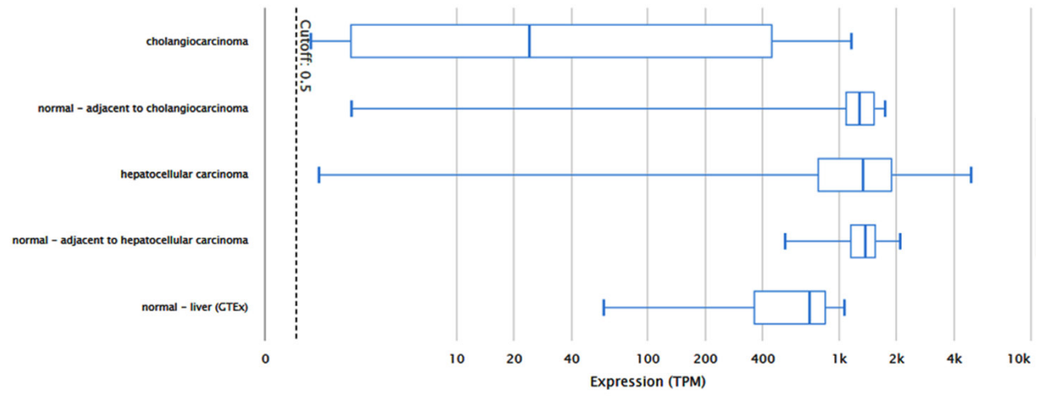
Gene expression – KRT8



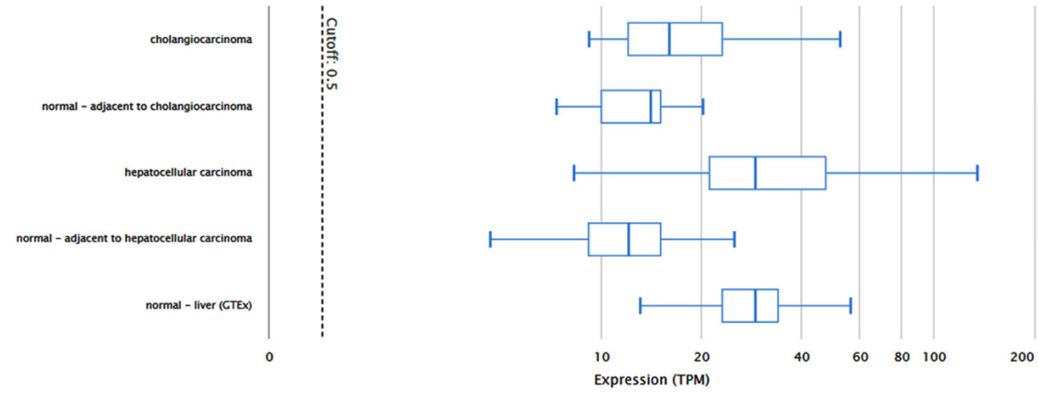
Gene expression – ALB



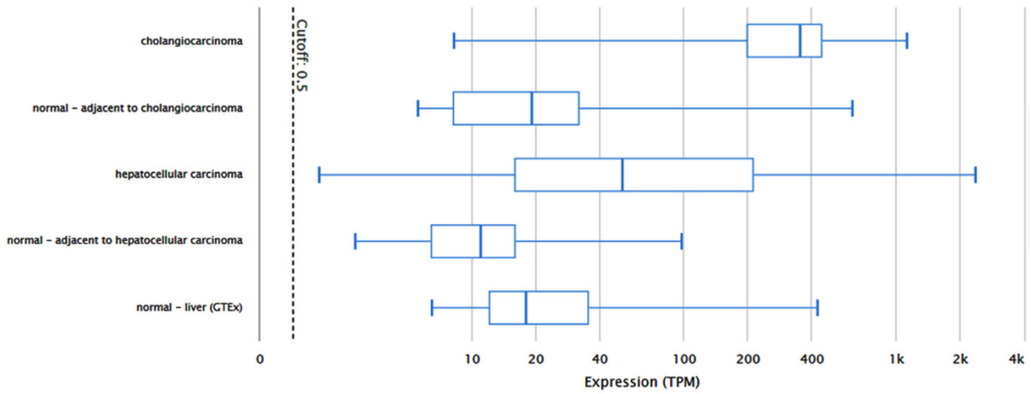
Gene expression – KNG1



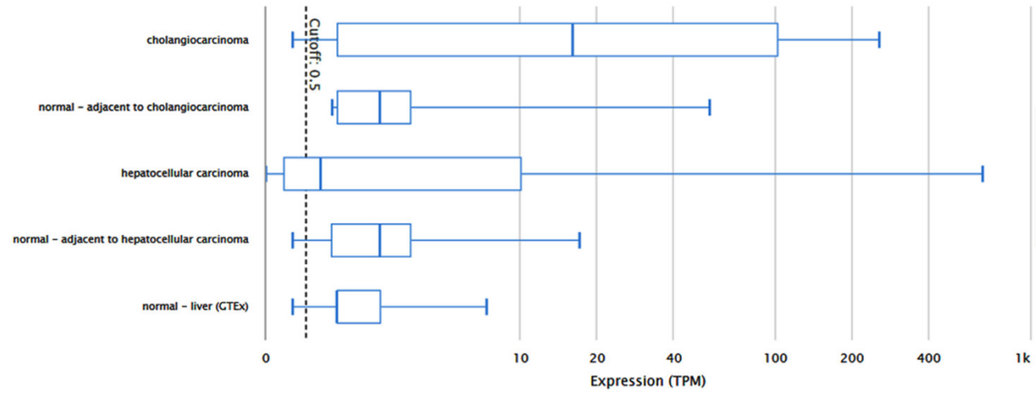
Gene expression – CD99L2



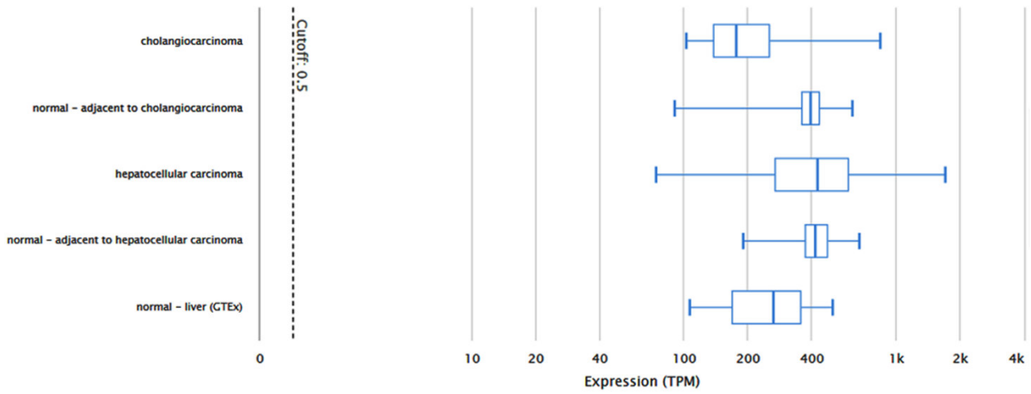
Gene expression – COL1A1



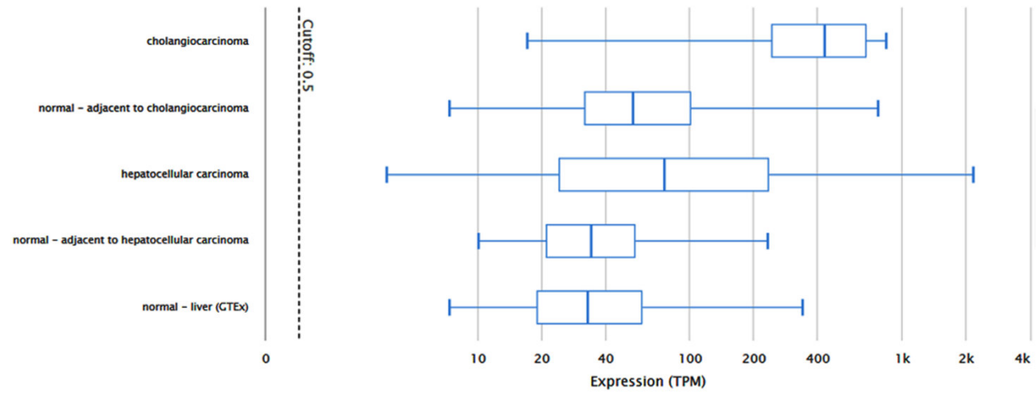
Gene expression – FXYD2



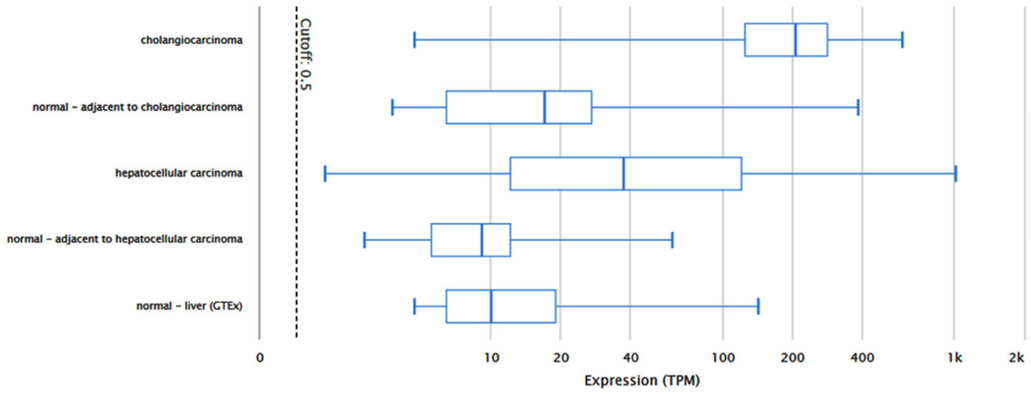
Gene expression – PGRMC1



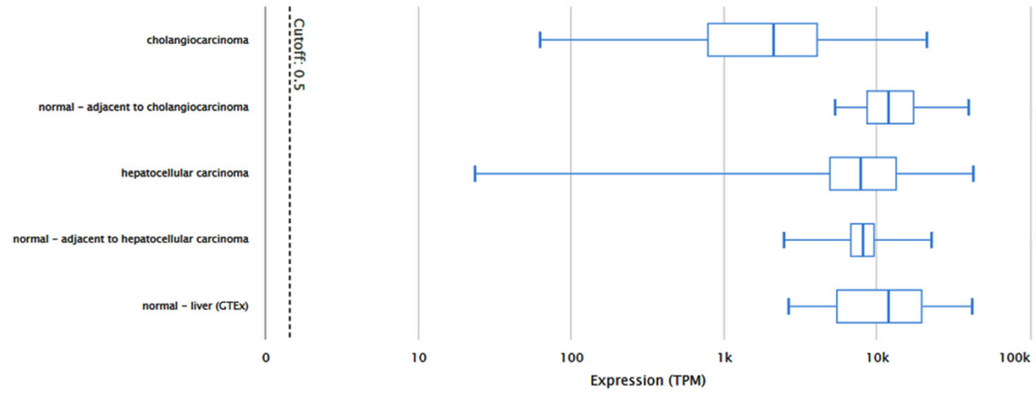
Gene expression – COL3A1

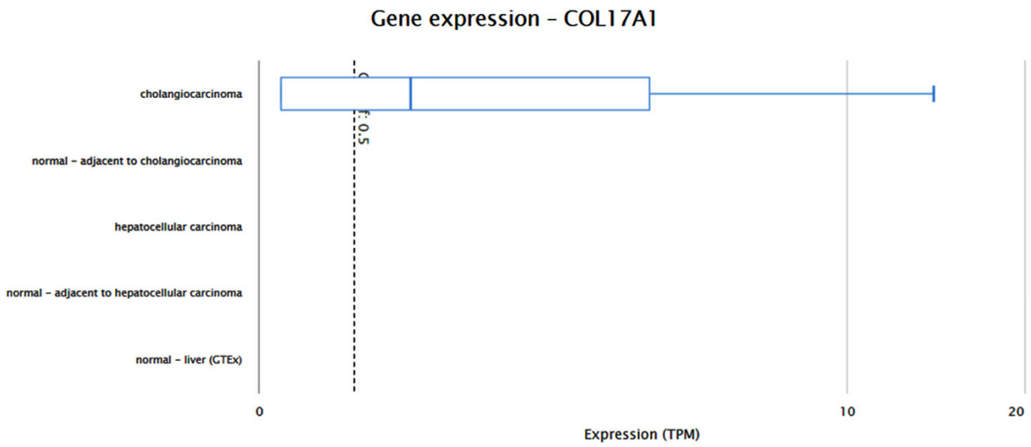


Gene expression – COL1A2



Gene expression – SERPINA1




Gene expression – COL17A1
cholangiocarcinoma
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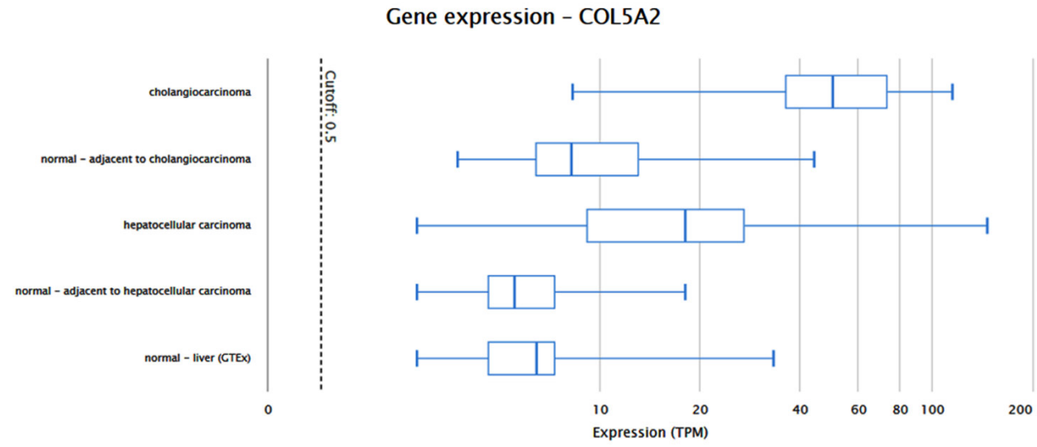
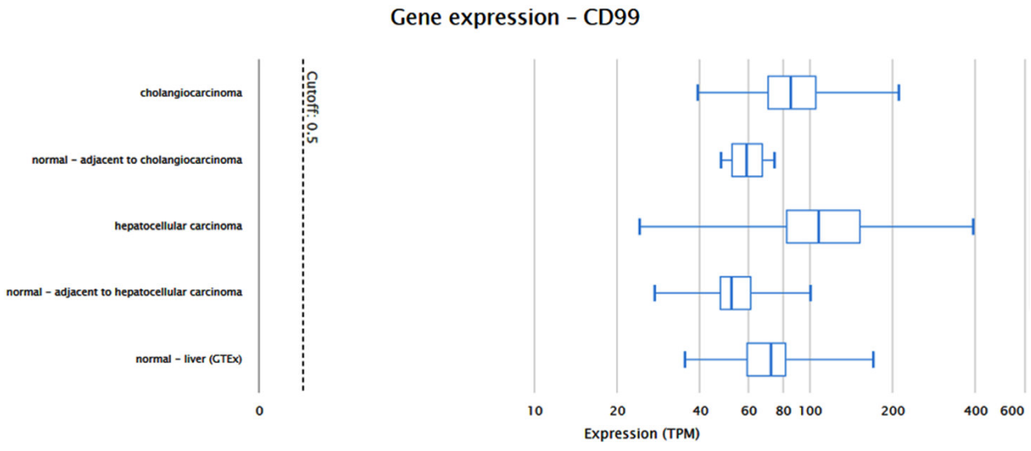
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
0
10
20
Expression (TPM)


Gene expression – COL5A2
cholangiocarcinoma
normal – adjacent to cholangiocarcinoma
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
0
10
20
40
60
80
100
200
Expression (TPM)


Gene expression – CD99
cholangiocarcinoma
normal – adjacent to cholangiocarcinoma
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
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20
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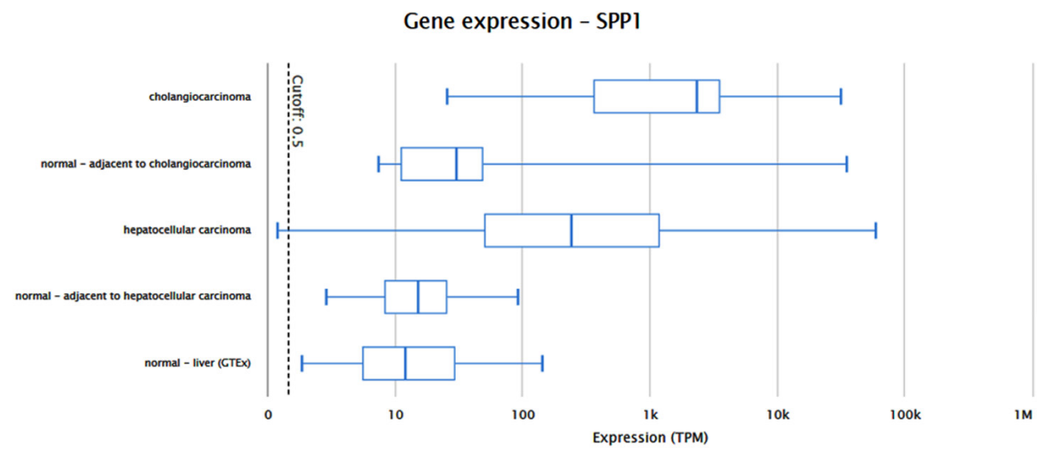
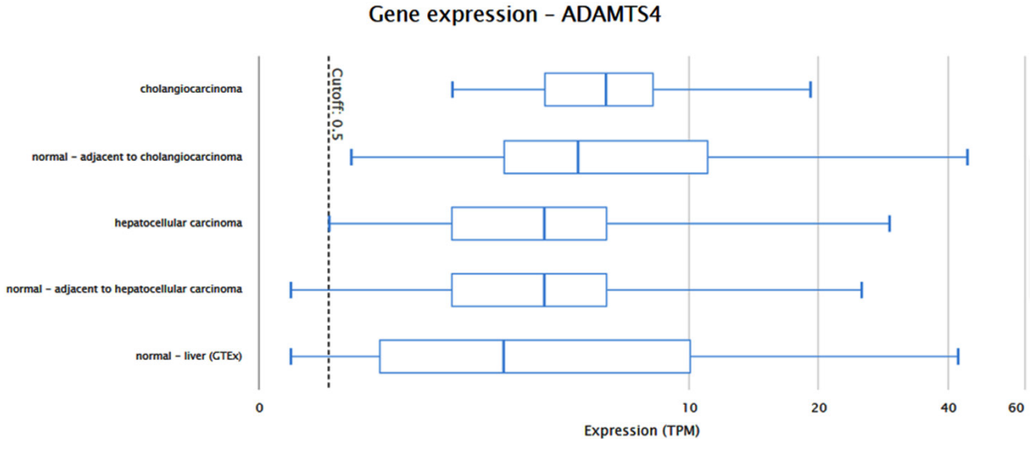
60
80
100
200
400
600
Expression (TPM)


Gene expression – SPP1
cholangiocarcinoma
normal – adjacent to cholangiocarcinoma
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
0
10
100
1k
10k
100k
1M
Expression (TPM)


Gene expression – ADAMTS4
cholangiocarcinoma
normal – adjacent to cholangiocarcinoma
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
0
10
20
40
60
Expression (TPM)

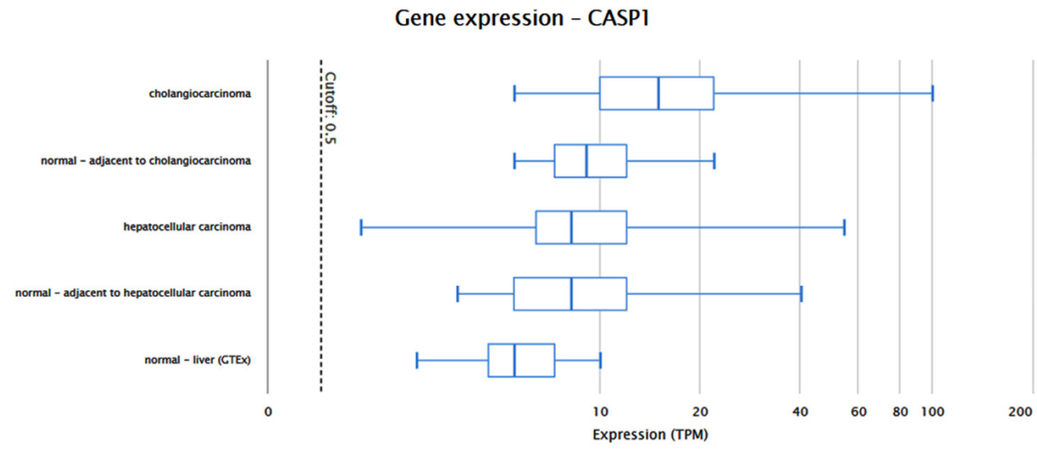

Gene expression – CASP1
cholangiocarcinoma
normal – adjacent to cholangiocarcinoma
hepatocellular carcinoma
normal – adjacent to hepatocellular carcinoma
normal – liver (GTEx)
Cutoff: 0.5
0
10
20
40
60
80
100
200
Expression (TPM)

Table S4. Physiological and cancer-specific pathological implications of the parental proteins from which the bile peptide markers for CCA diagnosis by bile proteome analysis are derived.

Protein	Characteristic physiological functions*	Link to cancer pathology	Relation to CCA pathology	Peptide marker	Peptide marker specific information
14-3-3 ζ/δ (YWHAZ)	Cell survival [1], autophagy [2], cell stress protection [2, 3].	EMT induction [4], tumor cell proliferation [5], chemoresistence [6].	Mediator of EMT, metastasis and invasion [4], prognostic marker for intrahepatic CCA [7], target for chemosensitivity enhancement [8].	28-SVTEQGAELSNEER-41	Release by trypsin 1 cleavage [9], Identification in urine during allograft kidney injury [10], epitope for HLA-A MHC I receptors in rats [11], inhibition of T cell migration [12].
Actin, cytoplasmic 1 (ACTB)	Cellular structure and cell motility [13], gene expression, cell division and proliferation [14].	Actin cytoskeleton reorganization during EMT [15], NO formation and platelet signaling [16].	Secreted by the CCA cell line huCCA-1 [17].	92-NELRVAPEEHPV-103 179-DLAGRDLTDYLm-190	Elevation of 92-NELRVAPEEHPV-103 in lung lavage fluid during bronchiolitis obliterans syndrome [18].
F-actin-capping protein subunit β (CAPZB)	Actin filament depolymerization and capping promoting cell motility [19].	Overexpression in tissue specimens of epithelioid sarcoma and association with cell growth and motility [20].	Upregulated in the membrane and cytosole of the human CCA cell line huCCA-1 [21].	76-SNKYDPPLEDGAMPS-90	Elevated in lung lavage fluid during bronchiolitis obliterans syndrome [18].
Hemoglobin subunit α and β (HBA1 and HBB)	Oxygen transport, heme binding, control of acid-base equilibrium	Peroxidase activity during inflammation and oxidative stress, and induction of cytotoxicity to macrophages by hemoglobin aggregate formation [22], hemoglobin release by cancer induced hemolysis [23].	Not systematically investigated, anemia is associated with CCA	**HBA1**: 27-AEALERmFL-35 33-MFLSFPTTK-41 63-VADALTNAVAHVDDMPNALSALSDLHAH-90 **HBB**: 2-VHLTPEEKSAVTA-14 43-FESFGDLSTPDAVmGNPK-60 67-KVLGAFSDGLA-77	Identification of 33-MFLSFPTTK-41 and 63-VADALTNAVAHVDDMPNALSALSDL HAH-90 as components of circulating exosomes in lung cancer [24], identification of 33-MFLSFPTTK-41 and 43-FESFGDLSTPDAVmGNPK-60 as injury marker in urine after kidney allograft transplantation [10], elevation of 2-VHLTPEEKSAVTA-14, 27-AEALERmFL-35 and 43-FESFGDLSTPDAVmGNPK-60 in lung lavage fluid during bronchiolitis obliterans syndrome [18].
Inter-α-trypsin inhibitor heavy chain H2 (ITIH2)	Plasma protease inhibitor activity [25], hyaluron carrier and binding mediator [26], contribution to extracellular matrix stability [27].	Tumor invasion and metastasis suppressor with loss of expression in invasive tumors [25, 28].	Reduced serum levels in CCA compared to benign biliary tract diseased patients [29].	628-LVIENEAGDER-638	-----
Inter-α-trypsin inhibitor heavy chain H4 (ITIH4)	Anti-inflammatory type II acute phase protein [30], formation of hyaluronan complexes [31], potentially involved in liver development and regeneration [32].	Prevention of tumor metastasis [33].	Upregulated in bile of malignant (CCA and pancreatic cancer) towards benign (mostly PSC) strictures [34].	381-ILLTDGDPTVGETNPR-396	Elevated in salvia of oral cancer patients [35].
Keratin, type I cytoskeletal 19 (KRT19)	Cytoskeletal component in epithelial cells [36], actin cytoskeletal organization [37].	Histology marker for adenocarcinomas and squamous cell carcinomas [38, 39].	Differentiation marker for CCA ($KRT19^+$) and HCC ($KRT19^-$) [40], KRT19 fragment CYFRA21-1 is a prognostic marker for intrahepatic CCA [41], reduced expression of KRT19 on CCA cell lines during EMT [42].	139-DKILGATIENS-149	-----

Protein	Characteristic physiological functions*	Link to cancer pathology	Relation to CCA pathology	Peptide marker	Peptide marker specific information
Keratin, type II cytoskeletal 8 (KRT8)	Cytoskeletal component in epithelial cells [43, 44], hepatobiliary epithelial marker with strongest expression in mature polarized cells.	Marker for epithelial tumors [45], reduced expression during EMT [46].	Secreted by the CCA cell line huCCA-1 [17], reduced expression in a sarcomatoid CCA cell line [47].	149-RQLETLGQEK-158 466-IETRDGKLVSESSDVLPK-483	Identification of 149-RQLETLGQEK-158 in the human fetal liver proteome [48].
Serum albumin (ALB)	Maintenance of oncotic pressure, transport of metabolites, antioxidant.	Immune modulation due to binding of pathogen and danger associated molecules and inflammatory mediators [49], evidence for intracellular blocking of inflammatory signaling pathways after endocytic internalization [50].	Reduced levels in intrahepatic CCA tumor tissue samples [51], levels > 3 g/dL are an independent predictor of overall survival in hilar CCA [52].	173-FYAPELLFFAK-183	Component of circulating exosomes in lung cancer[24], identification in urine during allograft kidney injury[10].

* According to the Uniprot knowledge database unless no other reference is given

Abbreviations: CCA, cholangiocarcinoma; EMT, epithelial–mesenchymal transition; HCC, hepatocellular carcinoma.

Table S5. Physiological and cancer-specific pathological implications of the parental proteins from which the urine peptide markers for CCA diagnosis by urine proteome analysis are derived.

Protein	Characteristic physiological functions*	Link to cancer pathology	Relation to CCA pathology	Peptide marker	Peptide marker specific information
Uromodulin (UMOD)	Salt and water retention, urinary host defense and protection against stone formation in the kidney [53], renal clearance of circulating cytokines [54], regulation of granulopoiesis via proximal epithelial activation of the IL-23/IL-17 axis [55].	Protection from kidney injury by inhibition of inflammation [56], immunomodulation of blood cells [57], expression under control of the cancer-associated transcriptional factor HNF1B [58, 59].	-----	589-SGSVIDQSR-597	Identification in human urine [60], differential urinary expression between muscle-invasive bladder cancer versus normal [61].
Kininogen-1 (KNG1)	Thiol protease inhibition [62], inhibition of endothelial cell proliferation and migration, angiogenesis and apoptosis [63], precursor of proinflammatory vasodilator kinins [64].	Serum biomarker for advanced colorectal adenoma and colorectal cancer [65].	Increased biliary expression in malignant versus benign strictures [34].	62-ATKTVGSDTF-71	Differential urinary expression during inflammatory bowel disease [66], cystic kidney disease [67] and heart failure [68].
CD99 antigen-like protein 2 (CD99L2)	Cell surface protein mediating intercellular adhesion and leukocyte extravasation through the endothelial basement membrane [69], enhanced surface expression by interaction with CD99 [70], Integrin β1-mediated downregulation inhibiting leukocyte transmigration [71].	Marker of a mesenchymal phenotype during EMT [72].	-----	26-DFDDFNLED-34	Identification in human urine [73], decreased urinary levels in cystic kidney disease [67].

Protein	Characteristic physiological functions*	Link to cancer pathology	Relation to CCA pathology	Peptide marker	Peptide marker specific information
Collagen α-1(I) (COL1A1)	Structural component of the extracellular matrix generated mainly from fibroblasts, binding of platelet-derived growth factor (PDGF) which is a potent mitogen for mesenchymal cells [74].	Overexpression in various cancer types promoting metastasis [75] and apoptosis inhibition in tumor cells [76].	Indicative for the presence of cancer-associated fibroblasts in the CCA tumor stroma [77]	222-PpGPpGKNGDDGEAGKP-238 288-EpGSpGENGApGQMGPR-304 543-SpGSPGPDGKTGPpGPAG-560 550-DGKTGpPGPAGQDGRPGPpGppG-572 613-DGEAGAQGPpGPA-625 657-KpGEQGVpGDLG-668 780-DKGESGpSGpAGpTGARGApGDRGEpGppG-809 918-RpGEVGPpGPpGP-930 1007-GPpGESGREGApG-1019 1021-EGSpGRDGSpGAKGDRGETGPA-1042	Differential urinary expression in chronic kidney [67, 78, 79], cardiovascular [68] and chronic inflammatory [66] diseases.
Collagen α-1(II) (COL2A1)	Main structural component of cartilaginous tissues [80], PDGF binding [74], proteoglycan binding [81].	Increased expression indicates tumor recurrence in high-grade serous ovarian cancer [82].	Among the genes that are associated with lymph node metastasis and perineural invasion of CCA [83].	1212-PGNPGPPGPPGPpGpGIDmSAFAG-1225	-----
Collagen α-1(III) (COL3A1)	Main structural component of reticular fibers in soft tissues such as liver along with type I collagen [84], binding to platelets [85].	Increased expression in bladder cancer with association to poor prognosis and focal adhesion [86].	Indicative for the presence of cancer-associated fibroblasts in the CCA tumor stroma [77].	1084-ApGPQGPRGDkGETGERG-1101	Differential urinary expression during rheumatoid arthritis [66].
Collagen α-2(I) (COL1A2)	Extracellular matrix structural component, PDGF binding [74].	Increased expression and prognostic marker in gastric cancer [87].	Altered lysine hydroxylation in a Pten$^{-/-}$ mouse model representing a mixed phenotype of HCC and CCA with impact on matrix remodeling and stiffening [88].	136-GPpGKAGEDGHpGKPGRpGERG-157 188-LkGQpGApGVKGEpGApGENGTPGQTGARG-217 188-LkGQpGApGVkGEpGApGENGTpGQTGARG-217 189-kGQpGApGVkGEpGApGENGTpGQTGARG-217	Increased urinary levels of 136-GPpGKAGEDGHpGKPGRpGERG-157, 188-LkGQpGApGVKGEpGApGENGTPGQTGARG-217 and 189-kGQpGApGVkGEpGApGENGTpGQTGARG-217 in lupus nephritis [79], differential expression of 136-GPpGKAGEDGHpGKPGRpGERG-157 in muscle-invasive bladder cancer [61], differential expression of 188-LkGQpGApGVkGEpGApGENGTpGQTGARG-217 in chronic kidney disease versus healthy controls [89].
Collagen α-2(V) (COL5A2)	Key determinant in the assembly of tissue matrices with binding affinity to DNA, heparan sulfate, thrombospondin, heparin, and insulin.	Increased expression in muscle-invasive bladder cancer associated with poor prognosis and tumor invasion [90].	-----	833-PGSRGENGPTGAVGFAGPQGPDGQPGVKGEP-863	Differential urinary expression during rheumatoid arthritis [66].
Collagen α-6(VI) (COL6A6)	Component of the basal lamina of epithelial cells potentially involved in the regulation of epithelial cell-fibronectin interactions [91].	Correlation of high tissue expression levels with early tumor stages in breast cancer [92].	Upregulation in a Pten$^{-/-}$ mouse model representing a mixed phenotype of HCC and CCA [88].	1701-GLpGEmGSpGEPG-1713	-----
Collagen α-1(XVII) (COL17A1)	Structural component of hemidesmosomes mediating adhesion of keratinocytes to the underlying epidermal basement membrane [93].	Overexpression in epithelial cancers due to aberrant epigenetic control promoting tumor invasion [94].	Elevated mRNA expression in cholangiocarcinoma tissue [95].	599-PGpQGpKGQKGSVGDpGMEGPmGQRGREG-627 628-PMGpRGEAGppGSGEKGERGAAGEPGp-654	-----

Protein	Characteristic physiological functions*	Link to cancer pathology	Relation to CCA pathology	Peptide marker	Peptide marker specific information
Na^+/K^+-ATPase γ subunit (FXYD2)	Modulation of sodium ATPase activity [96].	Increased expression in ovarian clear cell carcinoma under control of the transcriptional factor HNF1B [97].	Differential expression in CCA cells [98].	3-GLSMDGGGSPKGDVDP-18	Reduced urinary expression in chronic kidney disease [89] and overt heart failure [99].
Membrane-associated progesterone receptor component 1 (PGRMC1)	Compoment of a progesterone-binding membrane complex [100], progesterone binding [101], many other cellular functions like heme and cytochrome P450 binding, autophagy and apoptosis induction [100].	Regulation of cancer proliferation by EGF receptor and cytochrome P450 interaction [102], differential cell surface expression in various tumors like breast and bladder cancer [103, 104], negative regulation of hepatocarcinogenesis [105].	----	54-SGDSDDDEPPPLPRL-68	Reduced urinary expression in chronic kidney disease [89], cardiovascular disease [106], inflammatory bowel disease [66] and muscle-invasive bladder cancer [107].
α-1-antitrypsin (SERPINA1)	Acute phase protein with anti-inflammatory and immunoregulatory functions [108], serine protease inhibition including neutrophil elastase, plasmin, thrombin, kallikreins, matripase, caspase-3 [109], induction of IL-1 receptor antagonist expression [110].	Association of α-1-antitrypsin deficiency with increased risk of liver cirrhosis and hepatocellular carcinoma [111], lung disease [112] and ANCA-associated vasculitis [113].	Increased serum levels as marker for early CCA diagnosis [114], increased oxidation due to oxidative stress in CCA [115].	25-EDPQGDAAQKTDTSHHDQDHP-45	Reduced urinary expression during preclinical cardiac dysfunction before heart failure [68], increase in urinary expression by inhibition of the sodium/glucose cotransporter 2 with empagliflozin in patients with diabetic kidney disease [116].
Interleukin-1 receptor accessory protein-like 1 (IL1RAPL1)	Member of the TOLL/IL-1 receptor familiy [117], IL-38 binding [118], negative regulation of calcium-dependent exocytosis [119], evidence for selective activation of JNK [120], identification in exosomes of mesenchymal stem cells [121].	Upregulation upon γδ T cell activation [122], inhibition of cytokine release by macrophages upon antagonizing IL-38 binding [118].	Predicted as target for miR-10a-5p upregulation in human CCA cell lines [123].	74-LMWYKSSGPGDFEEPIAFDGSRmSKEED-101	----
CD99 antigen (CD99)	Cell surface protein involved in cell migration, adhesion, diapedesis, death and differentiation of leukocytes [69, 124], inhibition of cell-ECM adhesion by integrin 1-β suppression [125].	Cancer type specific marker for neuroectodermal and non-small cell lung carcinomas [126, 127], increased expression in inflammatory diseases [128].	Decreased expression in gastric and gallbladder carcinomas due to promoter methylation, loss of heterozygosity and transcription factor down-regulation associated with unfavorable prognosis [129, 130].	97-DGVSGGEGKGGSDGGGSHRKEGEEADAPGVIPGIVG-132	Differential expression in urine between muscle-invasive bladder cancer versus normal [61].
Osteopontin (SPP1)	Bone mineralisation [131], matricellular ECM component [132], CD44-dependent chemotaxis [133], mediation of type 1 immunity [134].	Overexpression in various cancer types with protumorigenic and premetastatic activity [135], contribution to scarring and liver fibrosis via TGF-β [136], immune checkpoint by CD44 binding promoting tumor invasion [137, 138].	Elevated serum levels in patients with CCA compared to healthy controls and patients with PSC [139], association of elevated serum levels with shorter overall survival and high probability of tumor relapse after curative resection in patients with intrahepatic CCA [140].	194-ESEELNGAYKAIPVAQDLNAPSDWDSRGKDSYETSQL-230	-----

* According to the Uniprot knowledge database unless no other reference is given

Abbreviations: CCA; cholangiocarcinoma; EMT; epithelial–mesenchymal transition; HCC, hepatocellular carcinoma.

Supplementary references – Literature review

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