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Trophoblast cell surface antigen 2 (TROP2) expression in human tumors: A tissue microarray study on 18,563 tumors.

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Introduction and Objectives

Trophoblast cell surface antigen 2 (TROP2) is the target of sacituzumab govitecan (SG), an antibody-drug conjugate that was recently approved for previously treated triple negative breast cancer and urothelial carcinomas. In order to learn more about the role of TROP2 for tumor biology and identify other tumor types that might benefit from anti-TROP2 therapies, a comprehensive analysis of TROP2 protein expression across virtually all types of human normal and neoplastic tissues was performed.

Materials & Methods

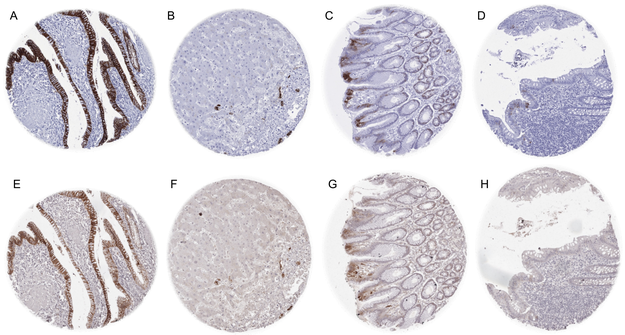
Tissue microarrays containing 18,563 samples from 150 different tumor types and subtypes as well as 608 samples of 76 different normal tissue types was analyzed by immunohistochemistry.

TROP2

Immunostaining protocol and controls

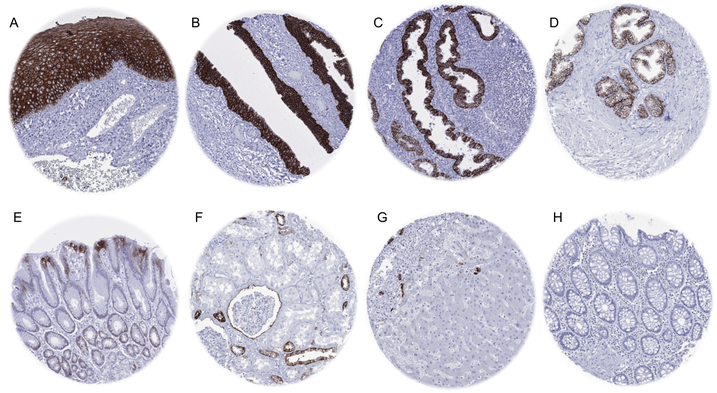
- Antibody: MS validated antibodies, clone MSVA-733R, Recombinant Rabbit IgG, Dilution: 1:150
- Antigen retrieval: 5 min at 121°C (autoclave) in pH 7.8 buffer
- Controls:
  - Positive: Strong membranous Trop-2 immunostaining should be seen in bile ducts of the liver.
  - Negative: Liver hepatocytes should not show any Trop-2 immunostaining.

Antibody validation by comparison of antibodies. The panels show a complete concordance of staining results obtained by two independent TROP2 antibodies. Using MSVA-733R, the stainings show a strong predominantly membranous staining of gallbladder epithelium (A) and of intrahepatic bile ducts (B) while staining is less intense and focused on surface epithelial cells and glands (weaker) of the stomach (C) and limited to few interspersed epithelial cells in the colon (D). Using clone AF650, nearly identical stainings are seen in gallbladder (E), liver (F), stomach (G), and the colon (H). The images A-D and E-H were taken from consecutive tissue sections. Due to the polyclonal nature of AF650, background staining is slightly higher than seen for MSVA-733R.



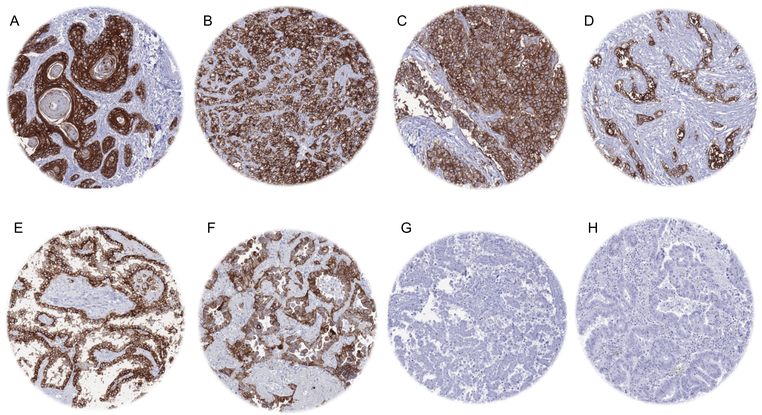
TROP2 immunostaining examples

TROP2 in normal tisues



TROP2 immunostaining was always membranous and found in many epithelial cell types. The panel shows strong TROP2 positivity of surface epithelial cells of the tonsil (A), urothelium of the urinary bladder (B), and the endometrium (C) as well as in acinar and basal cells of the prostate (D). TROP2 staining is somewhat weaker and largely limited to the most apical elements of the surface epithelium in the stomach antrum (E), distal tubuli and the visceral layer of the Bowman capsule of the kidney (F), and intrahepatic bile ducts of the liver (G). TROP2 immunostaining is lacking in colon epithelial cells (H).

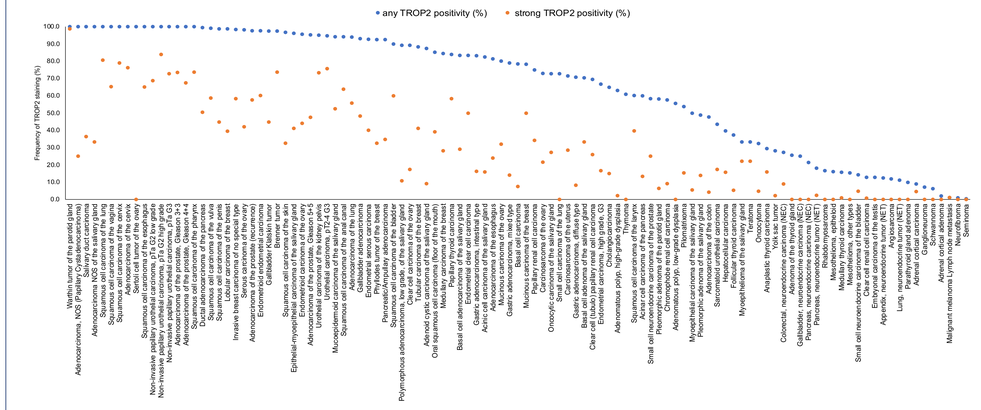
TROP2 in tumor tissues



Strong, membranous and cytoplasmatic TROP2 immunostaining in a squamous cell carcinoma of the oral cavity (A), a recurrent adenocarcinoma (Gleason 5+5=10) of the prostate (B), a breast cancer of no special type (C), a gastric adenocarcinoma (D), a papillary carcinoma of the thyroid (E), and an adenocarcinoma of the lung (F). TROP2 staining is absent in an epitheloid pleural mesothelioma (G) and a colorectal adenocarcinoma (H).

Ranking and prognostic value of TROP2 in tumor tissues

Ranking order of TROP2 immuno-staining in cancers. Both the frequency of positive cases (blue dots) and the frequency of strongly positive cases (orange dots) are shown.



High TROP2 expression was linked to adverse tumor features in colorectal cancer, gastric adenocarcinoma and papillary thyroid cancer. Low TROP2 expression was linked to advanced stage in urothelial carcinoma, high stage and grade and "triple negative receptor status" in breast cancer, as well as with high stage and grade in papillary renal cell carcinomas. No associations were found in clear cell renal cell, ovarian, pancreatic, and endometrium carcinomas.

			n	TROP2 immunostaining result: neg. (%)	weak (%)	mod. (%)	strong (%)	P
Colon adenocarcinoma	Primary Tumor	pT1	79	54.4	35.4	8.9	1.3	0.0069
		pT2	406	53.2	34.5	7.4	4.9	
		pT3	1157	53.5	32.2	11.2	3.1	
		pT4	419	49.6	30.1	13.4	6.9	
	Regional Lymph Nodes	pN0	1088	57.9	30.6	8.1	3.4	<0.0001
		pN+	963	46.6	34.2	14.1	5.1	
	Venous Invasion	V0	1479	54.9	31.3	9.6	4.2	0.0012
		V1	543	45.9	35.5	14.2	4.4	
	Lymphatic Invasion	L0	661	58.9	31.2	7	3	<0.0001
		L1	1368	49.3	33	12.9	4.8	
	Tumor localization	left colon	1122	52	35	8.9	4.1	0.0273
		right colon	425	53.2	29.2	13.4	4.2	
	MMR status	defective	86	51.2	34.9	10.5	3.5	0.9848
		proficient	1071	51.1	35.5	9.4	4	
	RAS mutation status	mutated	325	48.3	38.5	9.8	3.4	0.2722
		wildtype	414	54.8	32.6	8.5	4.1	
	BRAF mutation status	mutated	14	42.9	14.3	28.6	14.3	0.1262
		wildtype	90	56.7	28.9	10	4.4	
Papillary thyroid carcinomas	Primary Tumor	pT1	151	11.9	17.9	9.3	60.9	0.0487
		pT2	76	26.3	14.5	11.8	47.4	
		pT3-4	96	12.5	11.5	7.3	68.8	
	Regional Lymph Nodes	pN0	89	20.2	13.5	7.9	58.4	0.0013
		pN+	122	4.1	10.7	7.4	77.9	
Breast carcinoma of no special type	Primary Tumor	pT1	899	0.9	6.8	30.1	62.2	0.0024
		pT2	796	2	8.3	33.5	56.2	
		pT3-4	182	4.9	8.8	35.2	51.1	
	Grade	G1	215	0.5	2.8	22.3	74.4	<0.0001
		G2	1050	1.8	5.6	33.2	59.3	
		G3	659	2.3	12.3	33.2	52.2	
	Regional Lymph Nodes	pN0	872	1.9	7.1	32.3	58.6	0.286
		pN1	406	1.5	8.6	31.3	58.6	
		pN2	148	1.4	6.1	35.8	56.8	
		pN3	100	4	6	44	46	
	HER2 status	negative	995	1.9	9.9	30.3	57.9	0.6044
		positive	125	0.8	12	32.8	54.4	
	ER status	negative	233	1.7	19.7	24.9	53.6	<0.0001
		positive	822	1.9	8	31.4	58.6	
	PR status	negative	457	2.2	13.1	29.5	55.1	0.0305
		positive	654	1.7	7.8	31.5	59	
	Triple negative	no	858	2	9	31.2	57.8	0.001
		yes	158	1.3	20.3	24.1	54.4	

			n	TROP2 immunostaining result: neg. (%)	weak (%)	mod. (%)	strong (%)	P
Urinary bladder carcinoma	Primary Tumor	pTa G2 low	125	0	1.6	29.6	68.8	<0.0001
		pTa G2 high	106	0	1.9	14.2	84	
		pTa G3	133	0.8	6	26.3	66.9	
		pT2	122	3.3	0.8	13.9	82	
		pT3	203	3	3.4	17.2	76.4	
		pT4	97	8.2	2.1	16.5	73.2	
	Regional Lymph Nodes	pN0	242	3.7	2.1	16.1	78.1	0.9068
		pN+	170	3.2	3.2	16	77.6	
Gastric carcinoma	Laurén type	diffuse	66	30.3	24.2	43.9	1.5	0.0208
		intestinal	81	22.2	38.3	29.6	9.9	
		mixed	57	21.1	22.8	42.1	14	
	Primary Tumor	pT1-2	48	35.4	27.1	29.2	8.3	0.1352
		pT3	114	22.8	21.9	42.1	13.2	
		pT4	111	17.1	27.9	46.8	8.1	
	Regional Lymph Nodes	pN0	69	31.9	30.4	30.4	7.2	0.0246
		pN1	58	27.6	19	39.7	13.8	
		pN2	55	16.4	18.2	47.3	18.2	
		pN3	90	16.7	30	47.8	5.6	
	Mismatch repair status	MMR defective	32	46.9	18.8	18.8	15.6	0.0002
		MMR proficient	233	14.6	24.9	48.9	11.6	
Papillary renal cell carcinomas	ISUP stage	1	41	17.1	22	19.5	41.5	0.0005
		2	134	14.9	17.2	25.4	42.5	
		3	81	39.5	14.8	28.4	17.3	
		4	7	57.1	14.3	14.3	14.3	
	Fuhrmann grade	1	4	0	50	0	50	<0.0001
		2	183	14.2	17.5	25.1	43.2	
		3	83	41	18.1	24.1	16.9	
		4	11	45.5	9.1	36.4	9.1	
	Thoenes grade	1	58	13.8	17.2	22.4	46.6	0.1706
		2	157	26.1	17.8	24.2	31.8	
		3	18	33.3	16.7	33.3	16.7	
	UICC stage	1	102	23.5	17.6	22.5	36.3	0.0097
		2	15	13.3	13.3	46.7	26.7	
		3	5	80	0	0	20	
		4	11	36.4	0	54.5	9.1	
	Primary Tumor	1	208	21.2	17.8	24.5	36.5	0.0009
		2	48	10.4	18.8	33.3	37.5	
		3-4	33	54.5	9.1	21.2	15.2	
	Regional Lymph Nodes	0	25	36	4	28	32	0.4776
		≥1	15	33.3	6.7	46.7	13.3	
	Distant Metastasis	0	27	25.9	11.1	25.9	37	0.2267
		≥1	12	41.7	8.3	41.7	8.3	

Conflicts of interest: The TROP2 antibody clone MSVA-733R was provided by MS Validated Antibodies GmbH (owned by a family member of GS)

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