



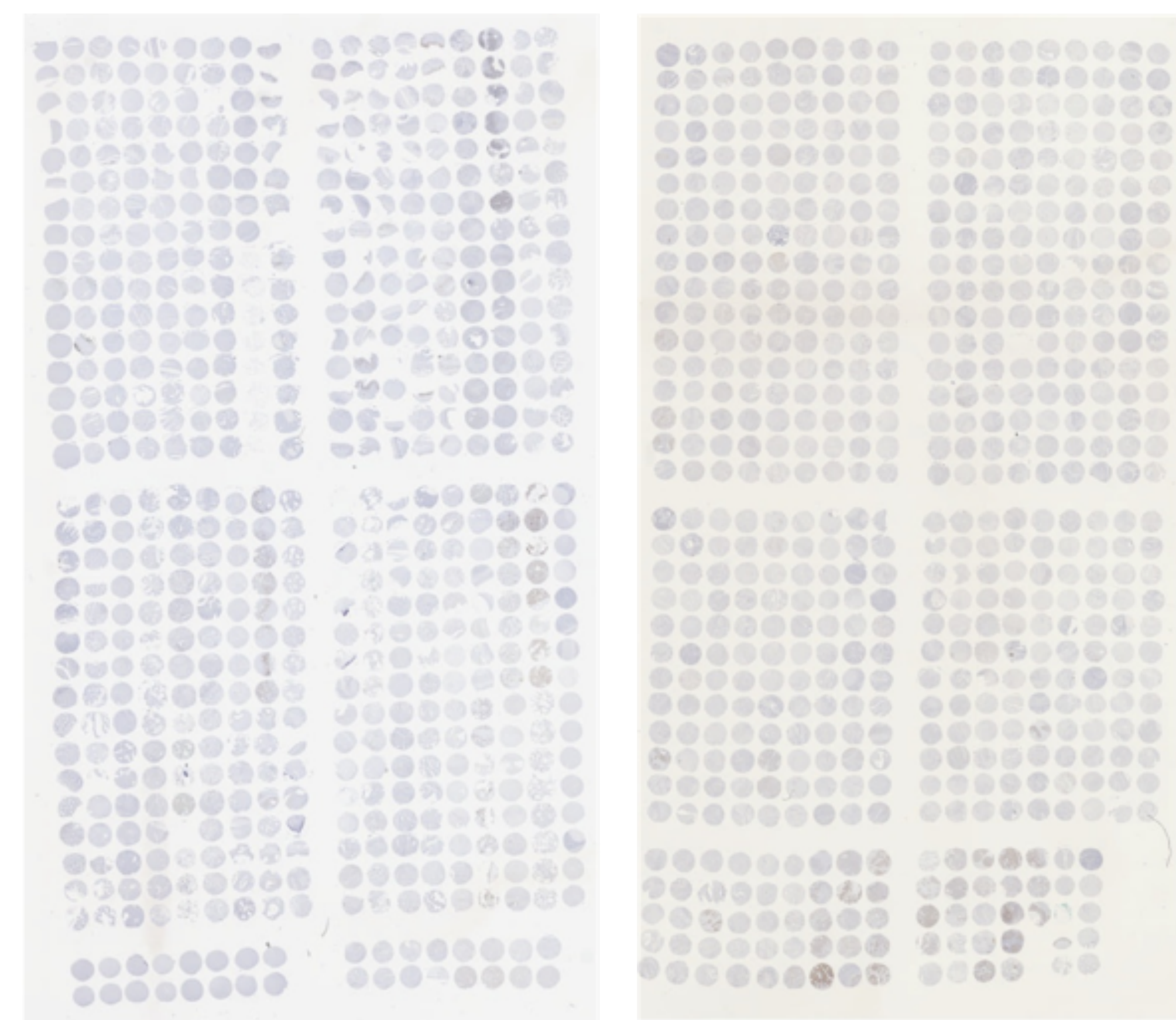
Introduction and Objectives

GATA Binding Protein 3 (GATA3) is a transcription factor with key importance for the differentiation of the breast and urothelium. Accordingly, in surgical pathology, GATA3 is commonly used as a diagnostic marker for these tissues. However, GATA3 may also become expressed in neoplasms originating from other tissues.

To evaluate GATA3 expression tumor tissues, we analyzed a tissue microarray containing 16,611 samples from 133 different tumor types by means of immunohistochemistry.

Materials & Methods

Tissue Microarrays (TMAs). The normal tissue TMA was composed of 8 samples from 8 different donors for each of 76 different normal tissue types (608 samples on one slide). The cancer TMAs contained a total of 16,611 primary tumors from 133 tumor types and subtypes.



Normal tissue TMA Multitumor TMA (total: 43 slides)

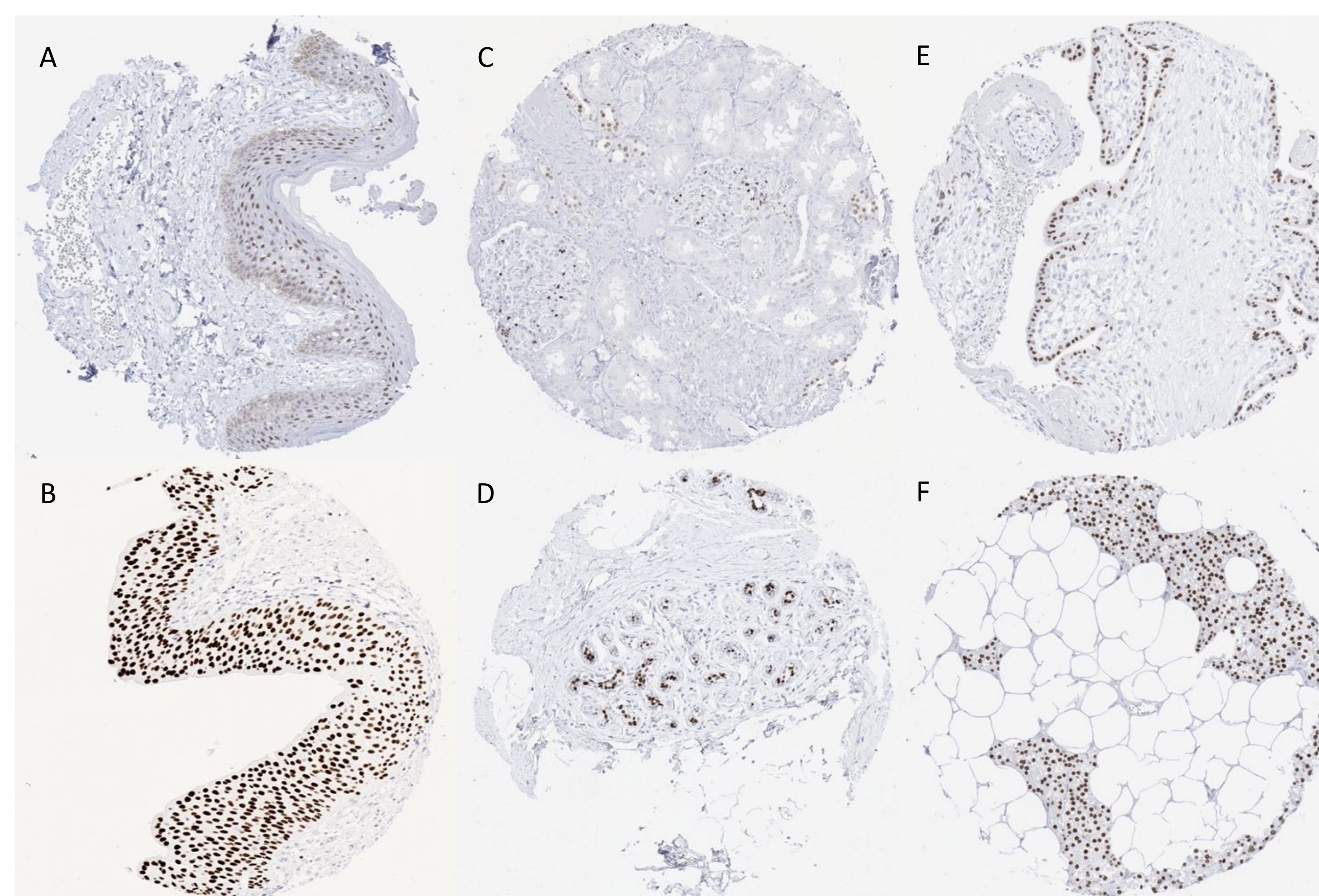
Immunostaining protocol and controls



- Antibody: MS validated antibodies, clone MSVA-450M, Mouse IgG, Dilution: 1:50
- Antigen retrieval: 5 min at 121°C (autoclave) in pH 7.8 buffer
- Controls:
 - Kidney: Moderate to strong nuclear staining reaction should be seen in a fraction of collecting duct cells and podocytes in glomeruli. Staining should be absent in proximal and distal tubuli as well as in blood vessels.
 - Tonsil: Most T helper cells should show weak to moderate nuclear staining, whereas staining should be absent in B-cells.

GATA3 in normal tissues

Nuclear GATA3 immunostaining was seen in urothelium (+++), squamous epithelium of the skin (+++; superficial cell layers >basal cell layers), hair follicles (+++), sebaceous glands (++), parathyroid gland (+++), trophoblastic cells (+ - +++; more intense in first than in the third trimester), chorion cells (+++), and amnion cells (+) of the placenta, collecting ducts (+++; not all) and glomerular podocytes (++) of the kidney, seminal vesicle epithelium (+++), tall columnar cells and basal cells (++) of the epididymis, a fraction of the luminal cells of breast glands (+++), basal cells in the prostate (+; not always visible), glandular cells (especially mucinous) of salivary glands (+ - ++), and a fraction of lymphocytes, most prominently in the thymus (++) . A faint cytoplasmic GATA3 staining was seen in gastric glands and goblet cells of respiratory epithelium, most likely representing non-specific background staining.



GATA3 immunostaining of normal tissues. The panels show a strong nuclear GATA3 positivity of predominantly suprabasal cells in the epidermis of the skin (A), urothelial cells of all layers (B), podocytes and collecting duct cells of the kidney (C) luminal cells of the breast (D), trophoblastic cells of the placenta (E) and epithelial cells of the parathyroid gland (F).

Conclusions

- GATA3 expression can occur in various tumor entities including breast, urothelial, salivary gland, squamous cell and other tumors.
- Particularly high frequency and levels of GATA3 occur in breast and urothelial carcinoma.
- A reduced level of GATA3 reflects cancer progression and poor patient prognosis in these tumor entities.

GATA3 in tumor tissues

Seventy (53%) of 133 tumor categories showed detectable GATA3 expression with 24 (18%) tumor categories including at least one case with strong positivity. The highest rate of positive staining and the highest levels of expression was found in various subtypes of breast and urinary bladder neoplasms as well as in basal cell carcinoma of the skin. At lower frequency and often at lower intensity, GATA3 immunostaining could be seen in various categories of salivary gland tumors, neuroendocrine tumors as well as in squamous cell carcinomas or tumors containing squamous cell elements such as endometrioid carcinomas.

Tumor entity	GATA3 immunostaining					
	on TMA (n)	interpr. (%)	neg. (%)	weak (%)	mod. (%)	strong (%)
Tumors of the skin	35	31	100.0	0.0	0.0	0.0
Pilomatricoma	35	31	100.0	0.0	0.0	0.0
Basal cell carcinoma	88	68	2.9	11.8	47.1	38.2
Benign nevus	29	22	100.0	0.0	0.0	0.0
Squamous cell carcinoma of the skin	90	77	84.4	14.3	0.0	1.3
Malignant melanoma	46	38	97.4	2.6	0.0	0.0
Merkel cell carcinoma	46	40	100.0	0.0	0.0	0.0
Tumors of the head and neck	109	103	98.1	1.9	0.0	0.0
Squamous cell carcinoma of the larynx	60	59	100.0	0.0	0.0	0.0
Squamous cell carcinoma of the pharynx	130	127	93.7	3.9	1.6	0.8
Oral squamous cell carcinoma (floor of the mouth)	50	46	100.0	0.0	0.0	0.0
Pleomorphic adenoma of the parotid gland	96	100	0.0	0.0	0.0	0.0
Warthin tumor of the parotid gland	104	100	0.0	0.0	0.0	0.0
Adenocarcinoma, NOS (Papillary Cystadenocarcinoma)	14	12	66.7	8.3	25.0	0.0
Salivary duct carcinoma	15	11	72.7	18.2	9.1	0.0
Acinic cell carcinoma of the salivary gland	181	142	96.5	2.8	0.7	0.0
Adenocarcinoma NOS of the salivary gland	108	77	84.4	9.1	1.3	5.2
Adenoid cystic carcinoma of the salivary gland	180	104	95.2	3.8	1.0	0.0
Basal cell adenocarcinoma of the salivary gland	25	21	95.2	0.0	4.8	0.0
Basal cell adenoma of the salivary gland	101	88	100.0	0.0	0.0	0.0
Epithelial-myoepithelial carcinoma of the salivary gland	53	50	76.0	12.0	12.0	0.0
Mucoepithelioid carcinoma of the salivary gland	343	257	93.0	4.3	1.2	1.6
Myoepithelial carcinoma of the salivary gland	21	19	84.2	5.3	10.5	0.0
Myoepithelioma of the salivary gland	11	8	87.5	0.0	12.5	0.0
Oncocytic carcinoma of the salivary gland	12	12	91.7	8.3	0.0	0.0
Polymorphous adenocarcinoma, low grade, of the salivary gland	41	31	100.0	0.0	0.0	0.0
Pleomorphic adenoma of the salivary gland	53	38	94.4	5.6	0.0	0.0
Tumors of the lung, pleura and thymus	138	138	99.3	0.0	0.0	0.7
Adenocarcinoma of the lung	80	50	98.0	2.0	0.0	0.0
Squamous cell carcinoma of the lung	16	11	100.0	0.0	0.0	0.0
Small cell carcinoma of the lung	39	30	93.3	6.7	0.0	0.0
Mesothelioma, epithelioid	76	54	83.3	11.1	5.6	0.0
Mesothelioma, other types	26	10	100.0	0.0	0.0	0.0
Thymoma	29	26	100.0	0.0	0.0	0.0
Tumors of the female genital tract	130	118	94.9	5.1	0.0	0.0
Squamous cell carcinoma of the vagina	128	119	91.6	5.9	1.7	0.8
Squamous cell carcinoma of the cervix	236	222	95.5	0.5	0.0	0.0
Endometrioid endometrial carcinoma	82	66	100.0	0.0	0.0	0.0
Endometrial serous carcinoma	48	38	100.0	0.0	0.0	0.0
Carcinosarcoma of the uterus	13	13	100.0	0.0	0.0	0.0
Endometrioid carcinoma, high grade, G3	8	7	100.0	0.0	0.0	0.0
Endometrioid clear cell carcinoma	110	82	95.1	2.4	0.0	2.4
Endometrioid carcinoma of the ovary	559	443	99.8	0.2	0.0	0.0
Serous carcinoma of the ovary	96	62	100.0	0.0	0.0	0.0
Mucinous carcinoma of the ovary	50	37	100.0	0.0	0.0	0.0
Clear cell carcinoma of the ovary	47	36	91.7	8.3	0.0	0.0
Carcinosarcoma of the ovary	9	9	55.6	0.0	44.4	0.0
Brenner tumor	1545	1137	7.7	3.6	4.9	83.8
Invasive breast carcinoma of no special type	293	232	1.7	3.4	9.1	85.8
Lobular carcinoma of the breast	26	26	57.7	7.7	15.4	19.2
Medullary carcinoma of the breast	27	22	0.0	9.1	18.2	72.7
Tubular carcinoma of the breast	58	42	4.8	4.8	4.8	85.7
Mucinous carcinoma of the breast	50	42	11.9	7.1	14.3	65.7
Phyllodes tumor of the breast	174	137	99.3	0.7	0.0	0.0
Tumors of the digestive system	50	46	100.0	0.0	0.0	0.0
Adenomatous polyp, low-grade dysplasia	50	46	100.0	0.0	0.0	0.0
Adenomatous polyp, high-grade dysplasia	1882	1587	100.0	0.0	0.0	0.0
Adenocarcinoma of the colon	176	145	99.3	0.7	0.0	0.0
Cholangiocarcinoma	113	105	100.0	0.0	0.0	0.0
Gastric adenocarcinoma, diffuse type	174	137	99.3	0.7	0.0	0.0
Gastric adenocarcinoma, intestinal type	82	56	100.0	0.0	0.0	0.0
Gastric adenocarcinoma, mixed type	83	51	100.0	0.0	0.0	0.0
Adenocarcinoma of the esophagus	76	33	97.0	3.0	0.0	0.0
Squamous cell carcinoma of the esophagus	89	80	92.5	3.8	3.8	0.0
Cholangiocarcinoma	105	100.0	0.0	0.0	0.0	0.0
Hepatocellular carcinoma	50	50	100.0	0.0	0.0	0.0
Ductal adenocarcinoma of the pancreas	612	430	97.2	1.9	0.9	0.0
Pancreatic/Ampullary adenocarcinoma	89	71	100.0	0.0	0.0	0.0
Acinar cell carcinoma of the pancreas	16	14	100.0	0.0	0.0	0.0
Gastrointestinal stromal tumor (GIST)	50	49	100.0	0.0	0.0	0.0

Breast carcinoma of no special type	Primary Tumor	Grade	Regional Lymph Nodes	GATA3 immunostaining result					P
				n	neg. (%)	weak (%)	mod. (%)	strong (%)	
	pT1	G1	pN0	566	4.9	3.2	3.5	88.3	0.032
	pT2	G2	pN1	394	7.4	3.8	5.1	83.8	
	pT3-4	G3	pN2	83	13.3	7.2	6.0	73.5	
			pN3	171	1.2	0.0	0.6	98.2	<0.0001
			positive	556	3.2	2.7	2.9	91.2	
			negative	350	15.7	6.9	8.9	68.6	
			ER status	497	5.6	4.0	5.0	85.3	0.9688
			positive	214	7.0	3.3	4.7	85.0	
			negative	66	6.1	4.5	6.1	83.3	
			HER2 status	56	7.1	5.4	8.9	78.6	0.0085
			positive	806	7.8	3.3	4.0	84.9	
			negative	106	3.8	9.4	7.5	79.2	
			PR status	181	34.3	17.7	14.9	33.1	<0.0001
			positive	688	0.3	0.6	1.6	97.5	
			negative	362	17.4	9.1	9.7	63.8	<0.0001
			Triple negative	544	1.1	0.7	1.3	96.9	<0.0001
			yes	720	1.3	1.9	2.4	94.4	<0.0001
			no	121	44.6	18.2	16.5	20.7	<0.0001

Low or absent GATA3 immunostaining was linked to adverse tumor features in breast cancers of no special type and in urothelial neoplasms.

Primary Tumor	Grade	Regional Lymph Nodes	GATA3 immunostaining result					P
			n	neg. (%)	weak (%)	mod. (%)	strong (%)	
pTa G2 low	G1	pN0	147	0.0	0.0	0.7	99.3	0.0109
pTa G2 high	G2	pN1	117	0.0	0.0	1.7	98.3	
pTa G3	G3	pN2	161	3.7	0.6	3.1	92.5	0.7605
		positive	132	25.8	13.6	19.7	40.9	
		negative	222	30.6	11.7	16.7	41.0	
		PR status	107	30.8	13.1	12.1	43.9	
		positive	275	30.2	14.2	18.9	36.7	0.1303
		negative	170	25.7	17.0	15.8	48.0	
		p63 status	25	28.0	0.0	28.0	44.0	0.0644
		positive	149	25.5	12.8	16.8	45.0	
		negative	149	25.5	12.8	16.8	45.0	