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Original contribution

Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers ☆

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Summary Prostate-specific membrane antigen (PSMA), a type II transmembrane metallo-peptidase highly overexpressed in prostate cancer cells, has been studied as a targeting molecule in prostate cancer. Recently, PSMA has also been found to be expressed in the neovasculature of multiple nonprostatic solid tumors. Because of its unique expression pattern limited to tumor-associated endothelial cells, PSMA may also be an interesting molecule for vascular targeting. In this study, PSMA expression was determined by immunohistochemistry in 119 cases of primary gastric adenocarcinoma, 130 cases of primary colorectal adenocarcinoma, and 24 metastasis of colorectal adenocarcinoma. Expression data were correlated with clinicopathologic information. PSMA expression was detected in tumor-associated neovasculature of 79 (66%) of 119 gastric and 110 (85%) of 130 colorectal carcinomas. Furthermore, the neovasculatures of 16 (84%) of 19 liver and 4 (80%) of 5 nodal metastases from colorectal carcinomas were prostate-specific membrane antigen positive. There was a trend for high-grade tumors to higher PSMA expression (Spearman $r = 0.18$, $P = .046$) in colorectal cancers. No association between PSMA expression and overall- or disease-free survival was observed in gastric or colorectal cancers. This study provides the first in-depth look at PSMA expression in gastric and colorectal cancer. Because of its highly tumor-restricted expression

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and its accessibility to targeted therapy, PSMA represents a promising therapeutic and diagnostic target in colorectal and gastric cancer.

1. Introduction

Selectively inhibiting neoangiogenesis in solid tumors has been shown to be an important therapeutic strategy [1]. This inhibitory effect on tumor neoangiogenesis can be accomplished either by indirectly interfering with angiogenic growth factors or by directly targeting tumor-associated blood vessels. In this respect, it is of practical importance that neovascular endothelial cells show an altered protein expression pattern when compared with normal endothelial cells [1-3]. Proteins selectively expressed in tumor-associated endothelial cells therefore represent promising targets enabling tumor-specific antiangiogenic cancer therapy.

Prostate-specific membrane antigen (PSMA, folate hydrolase 1, glutamate carboxypetidase II) is a zinc-dependent exopeptidase. It is predominantly expressed in the prostate [4]: heterogeneously and at low levels in the normal prostatic secretory epithelium, but to a much higher, more homogeneous level in prostatic adenocarcinoma where PSMA expression increases directly with a higher tumor grade, stage, and adverse clinical outcome [5,6]. PSMA has an extracellular domain accessible for antibodies and drugs making it an interesting therapeutic target [7]. Numerous approaches targeting PSMA have been developed in recent years for diagnostic and therapeutic purposes [8-11], and recent clinical trials using a radiolabeled monoclonal antibody against PSMA have supported the potential of targeting PSMA in the treatment of metastatic prostate cancer [12,13].

Several groups have shown that PSMA is also selectively expressed in the vasculature of solid tumors but not in normal tissues [14-16] making it an ideal molecule for vascular targeting. Two recent proof-of-principle trials in patients with multiple solid tumor types demonstrated successful targeting of metastatic tumor sites using a humanized anti-PSMA antibody (J591), suggesting that PSMA allows targeting the vasculature of solid tumor metastasis [17,18].

Thus far, PSMA expression in solid tumor neovasculature has been reported for only a limited number of tumor types and in a limited number of cases. Effort in this area has been limited as the available antibodies worked weakly or not at all on paraffin-fixed tissues. As a result, little is known about the expression level, frequency, and association with tumor type or possible relationship to survival. More recently, an anti-PSMA monoclonal antibody has become commercially available that performs well on fixed, paraffinized tissue. Because of the potentially important therapeutic and diagnostic implications of selective PSMA expression in the neovasculature of solid tumors, we sought to determine PSMA expression in a large collection of primary and metastatic gastric and colonic adenocarcinomas.

2. Patients and methods

2.1. Patients

Tissue specimens from the primary site were obtained from 119 patients who underwent surgery for gastric adenocarcinoma, and 130 patients who were surgically treated for colorectal adenocarcinoma in the Department of Surgery, Innsbruck Medical University were included in the study. In addition, 19 liver and 5 lymph node metastasis from patients with primary colorectal adenocarcinoma were

Table 1 Clinicopathologic features

	Gastric		Colorectal	
Number	119		130	
Sex				
Male	76	(63.9)	67	(51.5)
Female	43	(36.1)	63	(48.5)
Age at diagnosis				
Mean	66.0		69.8	
Range	27-94		46-90	
Overall survival (mo)				
Mean	81		58	
95% Confidence interval	67-95		48-66	
Deaths	65	(54.6)	71	(54.6)
Stage				
pT1	15	(12.6)	5	(3.8)
pT2	72	(60.5)	23	(17.7)
pT3	28	(23.5)	86	(66.2)
pT4	4	(3.4)	16	(12.3)
Nodal status				
pN0	48	(40.3)	60	(46.2)
pN1	30	(25.2)	33	(25.4)
pN2	32	(26.9)	35	(26.9)
pN3	9	(7.6)	0	(0)
Missing	0	(0)	2	(1.5)
Metastasis				
pM0	109	(91.6)	100	(76.9)
pM1	10	(8.4)	30	(23.1)
Grade				
1	4	(3.4)	10	(7.7)
2	37	(31.1)	99	(76.2)
3	77	(64.7)	19	(14.6)
4	1	(0.8)	2	(1.5)

Data in parenthesis are percentages.