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Research Paper

SATB2 is a Promising Biomarker for Identifying a Colorectal Origin for Liver Metastatic Adenocarcinomas

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ABSTRACT

SATB2 (Special AT-rich sequence-binding protein 2) has recently been shown to be a specific biomarker of colorectal cancer (CRC). The aim of this study was to investigate the diagnostic potential of SATB2 as a means of detecting a CRC origin for liver metastases. SATB2 expression was examined in a resection cohort of 101 CRC and 273 non-CRC adenocarcinoma samples using immunohistochemistry (IHC). The diagnostic accuracy of CRC origins of liver metastases based on SATB2 and a three marker panel of SATB2, CK20 and CDX2 was evaluated using an independent cohort of 192 liver biopsies. IHC showed 97 of the 101 (96.0%) primary CRC samples were SATB2 positive, compared to only 6 of the 273 (2.1%) samples of other cancer types. The sensitivity, specificity and AUC values of SATB2 expression in resection samples were 97%, 97.1% and 0.977, respectively. Meanwhile, for the liver biopsy samples, the sensitivity, specificity and AUC values of a CRC liver metastases was 92.2%, 97.8% and 0.948 for SATB2, 95.1%, 91.0% and 0.959 for CK20, and 100%, 85.4% and 0.976 for CDX2, respectively. Further analysis demonstrated that all three-marker positivity was detected in 92/103 (89.3%) CRC and 2/89 (2.2%) non-CRC liver metastases sampled by biopsy. Our findings suggest that SATB2, as measured by IHC, could serve as a promising diagnostic biomarker of CRC metastases. Combining evaluation of SATB2 with CK20 and CDX2 to form a three marker panel further improved the detection of metastatic CRCs in liver biopsy tissues.

1. Introduction

Colorectal cancer (CRC) liver metastasis is one of the major causes of tumor-related death worldwide (Disibio and French, 2008). Recent advances in the detection and treatment of CRC have resulted in a significant increase in the 5-year overall survival rate and reduced the recurrence rate of CRC patients with liver metastasis (Chan et al., 2014; Pinson et al., 1996; Sharma et al., 2008). The benefit of complete hepatic resection is well recognized in CRC patients with liver metastasis, with 5-year overall survival rate up to 60% (Abdalla et al., 2004). Therefore, improving methods of identifying if the liver neoplasm originated from a CRC could increase the proportion of patients who are candidates for complete surgical treatment or preoperative chemotherapy, and, thus, aid in patient survival. Preoperative examinations, which include assessing signs and symptoms and imaging and laboratory studies, can be very informative, but are not perfect means of detection (Berger et al., 2000; Soyer et al., 1994; Tan et al., 2009; Zhou et al., 2006). Liver needle biopsies are generally recommended as follow-up studies to confirm assessments of hepatic nodules not satisfactorily addressed by imaging (Bruix et al., 2005). Troublingly, liver metastases with CRC origins often mimic the histological patterns of other cancers with other primary origins, as well as cholangiocarcinomas. For example, CRC liver metastases are usually tubular, but may also be mucinous, signet-ring, papillary, cystic or undifferentiated. Therefore, distinguishing between liver metastases of CRC origin and other forms of adenocarcinomas can be difficult, and diagnostic panels of immunohistochemical staining are needed. Importantly, histological analysis of liver needle biopsies is based solely on the analysis of tiny fragments of tissue, thus making it very difficult to make a histological distinction between metastatic CRC and other forms of adenocarcinoma, resulting in diagnostic delays.

Specific immunohistochemical markers play a very important role when making a histological distinction between metastatic CRC and other forms of adenocarcinoma in the liver. It is well known that CRCs typically express cytokeratin 20 (CK20) and caudal-type homeobox 2

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Table 1
Clinicopathological features of 7 types of human adenocarcinomas.

Colorectal adenocarcinoma	$n = 101$	Cholangiocellular adenocarcinoma	$n = 56$
Gender		Gender	
Male	61	Male	30
Female	50	Female	26
Average age of patient (year)	58 (35–85)	Average age of patient (year)	55 (23–85)
Average size of tumor (cm)	4.6 (1.5–10.5)	Average size of tumor (cm)	5.3 (0.7–11)
Tumor grade		Tumor grade	
1	10	1	0
2	66	2	46
3	25	3	10
TNM stage		TNM stage	
1	23	1	15
2	39	2	23
3	29	3	18
4	10	4	0
Gastric adenocarcinoma	$n = 97$	Lung adenocarcinoma	$n = 32$
Gender		Gender	
Male	65	Male	12
Female	32	Female	20
Average age of patient (year)	58 (24–89)	Average age of patient (year)	59 (44–77)
Average size of tumor (cm)	4.5 (0.3–13)	Average size of tumor (cm)	2.9 (1–7)
Tumor grade		Tumor grade	
1	0	1	5
2	56	2	24
3	41	3	3
TNM stage		TNM stage	
1	14	1	17
2	24	2	6
3	46	3	8
4	13	4	1
Pancreatic adenocarcinoma	$n = 30$	Breast adenocarcinoma	$n = 31$
Gender		Gender	
Male	17	Male	0
Female	13	Female	31
Average age of patient (year)	57 (35–79)	Average age of patient (year)	52 (23–80)
Average size of tumor (cm)	3.5 (0.5–6)	Average size of tumor (cm)	3.1 (0.8–11)
Tumor grade		Tumor grade	
1	4	1	15
2	18	2	11
3	8	3	5
TNM stage		TNM stage	
1	10	1	14
2	15	2	11
3	4	3	6
4	1	4	0
Duodenal adenocarcinoma	n = 27		
Gender			
Male	13		
Female	14		
Average age of patient (year)	55 (44–77)		
Average size of tumor (cm)	3.4 (0.3–12)		
Tumor grade			
1	2		
2	19		
3	6		
TNM stage			
1	12		
2	11		
3	4		
4	0		

(CDX2). However, although CK20 is a highly sensitive marker, it is also expressed in several other types of adenocarcinomas (Tot, 1999). Meanwhile, while CDX2 is helpful when diagnosing metastatic CRCs, it is non-specific and can be expressed in cholangiocarcinomas, gastric carcinomas, and ovarian mucinous tumors (Dennis et al., 2005; Werling et al., 2003). Overall, the availability of better and more specific immunohistochemical markers by which to identify metastatic CRCs would be advantageous when making diagnoses.

The special AT-rich sequence-binding protein 2 (SATB2) was initially introduced as a novel marker of osteoblastic differentiation (Sheehan-Rooney et al., 2010). Recent studies have shown that SATB2 could serve as a clinically useful diagnostic marker for CRCs (Dragomir et al., 2014; Kim et al., 2016; Lin et al., 2014; Magnusson et al., 2011; Ordonez, 2014) as 71–97% of primary and metastatic CRCs have been

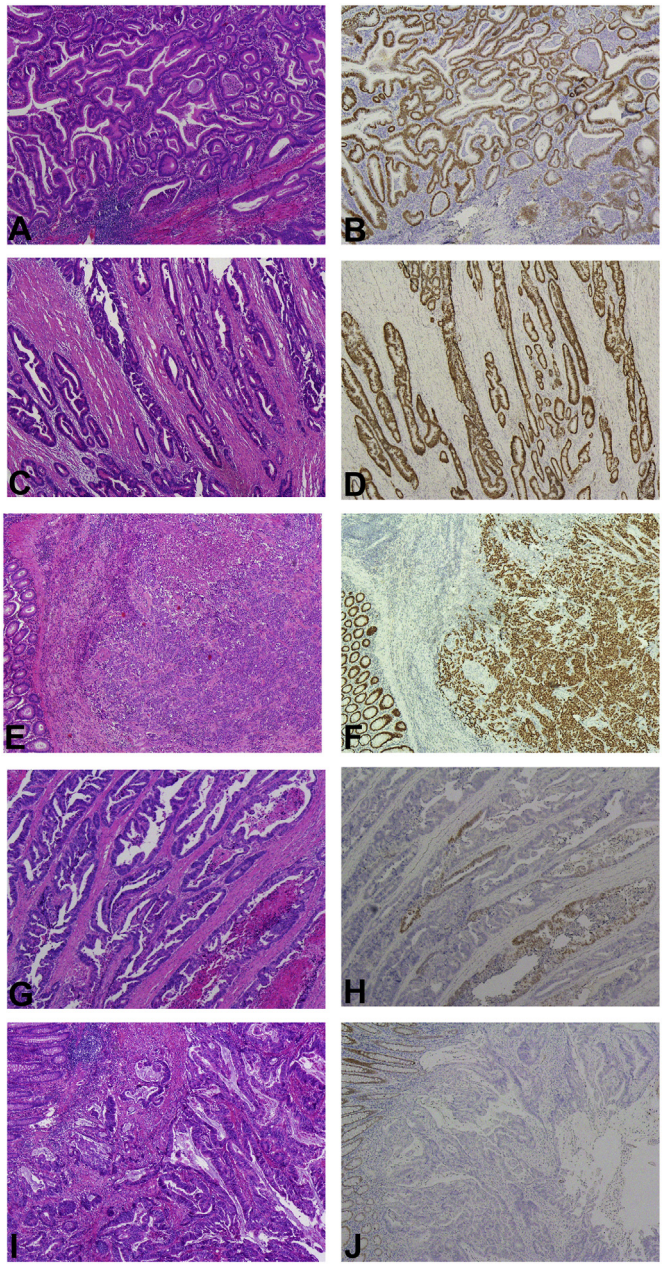

Fig. 1. The expression pattern of SATB2 in colorectal cancer. SATB2 protein expression is distinctive with high intensity nuclear staining occurring in CRCs, regardless of high (A, HE and B, IHC), moderate (C, HE and D, IHC) or poor (E, HE and F, IHC) differentiation. There are still some of cases showing focal positive SATB2 expression (G, HE and H, IHC). There are a few cases showing negative SATB2 expression (I, HE and J, IHC).