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Immunohistochemical analysis of CDX2 expression in normal choroid plexus epithelium and choroid plexus tumors

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Summary. Background: The Wnt and BMP signaling pathways are involved in the morphogenesis of both gastrointestinal and choroid plexus epithelium. In the intestine, Wnt signaling represses the expression of the tumor suppressor gene CDX2 via SOX9, a transcription factor, which is also expressed in the choroid plexus. Recently, an inverse correlation between CDX2 expression and tumor grade, tumor stage and lymph node metastasis in colorectal adenocarcinomas has been reported. Besides intestinal tissues, expression of CDX2 has also been reported in various other epithelial tissues and carcinomas. To date, no data exist on expression of CDX2 in normal and neoplastic choroid plexus epithelium. Aim: To investigate CDX2 expression in normal and neoplastic choroid plexus. Materials and Methods: Paraffin-embedded samples from 60 normal choroid plexus, including 23 fetal tissue samples and from 65 choroid plexus tumors (47 choroid plexus papillomas WHO grade I, 16 atypical choroid plexus papillomas and 2 choroid plexus carcinomas WHO grade III) were examined by immunohistochemistry. Samples from normal choroid plexus were collected from 45 autopsy cases and from 15 neurosurgical specimens. Results: Normal and neoplastic choroid plexus lacked CDX2 expression. Conclusion: In our series, immunohistochemistry shows no evidence for a role of CDX2 in development or differentiation of normal choroid plexus from the 9th gestational week until adulthood. Since choroid plexus tumors reliably lack CDX2 immunoreactivity, this marker may be helpful in distinguishing cerebral metastases from CDX2-positive adenocarcinomas and choroid plexus neoplasms.

Key words: Cauda-related homeobox transcription factor, CDX2, Choroid plexus papilloma, Choroid plexus carcinoma, Development

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Introduction

In many different species, the gut develops in a stereotypical manner by using a basic epithelial-mesenchymal interaction (Roberts, 2000; Kwek et al., 2008). Except for the most anterior (mouth) and posterior (anus) regions, which are derived from ectoderm, the gastrointestinal epithelium is of endodermal origin. The gut endoderm also essentially provides the anlage and signals to form the many gut derived organs (Roberts, 2000). Wnt and bone morphogenetic protein (BMP) signalling is supposed to play an important role in gut endoderm differentiation and maturation (Blache et al., 2004; De Santa Barbara et al., 2005; Barros et al., 2008; Kwek et al., 2008). On the other hand, inhibition of Wnt signalling is required for stomach-specific differentiation and the formation of the so-called gut-derived organs, such as thyroid, lungs, liver and pancreas (Roberts, 2000; Kwek et al., 2008).

The choroid plexuses are located throughout the ventricular system of the brain. After neural tube closure, choroid plexus sequentially develops in the IVth ventricle, followed by the lateral and IIIrd ventricles (Dziegielewska et al., 1984; Strazielle and Ghersi-Egea, 2000). In addition to its role in cerebrospinal fluid

production and the maintenance of the blood-brain barrier, it metabolizes enzymes and assists in repair through secretion of neuroprotective and neuro-regenerative substances (Strazielle and Ghersi-Egea, 2000; Emerich et al., 2004; Redzic and Segal, 2004; Emerich et al., 2005). The choroid plexus consists of two components of different embryological origin; i.e. the external epithelium and the vascularized connective core. The choroidal epithelium shows typical epithelial features with the presence of tight intercellular junctions, underlying basement membrane and the expression of keratins and epithelial membrane antigen (Miettinen et al., 1986; Doglioni et al., 1987; Redzic and Segal, 2004). While the choroidal epithelium originates from evaginated neuroepithelial lining of the neural tube, the stromal core is derived from the adjacent primitive mesenchyme (Dziegielewska et al., 1984, 2001; Strazielle and Ghersi-Egea, 2000; Redzic et al., 2005).

Although of endodermal and neuroectodermal origin, respectively, there are some parallels in development of the gastrointestinal and the choroidal epithelium, such as a relevant epithelial-mesenchymal interaction, as well as a role of Wnt- and bone morphogenic protein signalling in morphogenesis (Strazielle and Ghersi-Egea, 2000; De Santa Barbara et al., 2005; Sailer et al., 2005; Kwek et al., 2008; Barros et al., 2008).

The caudal-related homeobox transcription factor CDX2 (previously called CDX3 in humans, located on chromosome 13q12.3) has been found to be important in the development and differentiation of the intestine in mice. In mice, CDX2 expression has been reported in gastrointestinal tissue from 9.5 days postcoitum (earliest embryonic day evaluated) (Silberg et al., 2000) till 18 months (Beck et al., 1995), as well as in the neural tube (Valcanis et al., 1997). Yet, data is lacking on the expression of CDX2 in adult rodent brains and human gastrointestinal epithelium during the whole development. However, CDX2 is constantly expressed in normal human colorectal mucosa of adults and is less frequently observed in several other epithelial tissues (Moskaluk et al., 2003).

Furthermore, there is evidence for a functional link between Wnt signalling and expression/function of CDX2 in rodents. CDX2 genes are expressed in early stages of neural tube development (Beck et al., 1995; van Den et al., 2002). Wnt signalling influences the expression and function of CDX2 in gastrointestinal epithelium through SOX9, a transcription factor gene, which is also expressed in the choroid plexus epithelium (Pompolo and Harley, 2001; Blache et al., 2004).

It is also noteworthy that epithelium from the small and large intestine, which require Wnt signalling during development, expresses CDX2 in adulthood, whereas gut-derived tissues that require inhibition of Wnt signalling during development usually lack CDX2 expression in adulthood (Moskaluk et al., 2003).

Recently, Bakaris and coworkers reported an inverse correlation between CDX2 expression and tumor grade, tumor stage and lymph node metastasis in colorectal adenomas and adenocarcinomas (Bakaris et al., 2008). Similarly, progressively decreased CDX2 expression has been reported in human gastric intestinal metaplasia, dysplasia and cancer (Liu et al., 2007). It was hypothesized that downregulation of CDX2 may cause dedifferentiation of gastrointestinal epithelium and may play an important role in tumorigenesis of these neoplasms (Bakaris et al., 2008).

CDX2 has long been thought to be intestine-specific (Suh and Traber, 1996; Almeida et al., 2003). However, the expression of CDX2 has recently been reported in several other epithelial neoplasms derived from organs outside the gastrointestinal tract. These include ovary (Mazziotta et al., 2005), lung (Mazziotta et al., 2005; Onofre et al., 2007), urinary bladder (Werling et al., 2003; Suh et al., 2005), endometrium (Saegusa et al., 2007; Houghton et al., 2008; Wani et al., 2008), breast (Onofre et al., 2007), thyroid and prostate (Herawi et al., 2007). Although CDX2 expression was observed less frequently in these tumors than in gastrointestinal carcinomas, it was recognized that CDX2 expression is not restricted to intestinal epithelial cells.

So far, some studies have investigated CDX2 expression in a few brain samples and reported lack of CDX2 in neurons and astrocytes (Moskaluk et al., 2003; Strickland-Marmol et al., 2007). However, to the best of our knowledge, no data has been provided on CDX2 expression in normal or neoplastic choroid plexus or its derived neoplasms. For this reason we now investigated CDX2 expression in the human choroid plexus and its possible role in differentiation, dedifferentiation or tumorigenesis of choroid plexus epithelium.

Material and methods

We investigated paraffin-embedded samples from normal and neoplastic choroid plexus by immunohistochemistry. Clinicopathological data on investigated cases (normal choroid plexus and choroid plexus tumors) including age, gender and site of choroid plexus sample are summarized in Tables 1 and 2. Normal choroid plexus samples were collected from 60 cases including 23 fetal cases (9th to 40th gestational week) and 37 cases ranging in age from day 1 till 81 years (mean age of postnatal cases 39.6 years). These samples were taken from routine autopsy brains (n=6) and from neurosurgical specimens (n=12). In the latter examples, surgery was performed for a variety of reasons (e.g. intracerebral hemorrhage, colloid cyst of the third ventricle) and the tissue sample contained choroid plexus tissue by chance. Paraffin blocks from autopsy cases (including all fetal cases) contained choroid plexus tissue and brain parenchyma, including gray and white matter, either from frontal lobe and cerebellum or from hippocampus and brain stem in all other cases.

Two representative samples (1.0 mm in diameter) from routinely paraffin-embedded surgical specimens from each tumor were selected to prepare tissue

Table 1. CDX2 immunoreactivity in normal choroid plexus samples.

#	age	sex	site	CDX2	Further data on brain pathology
1	9. gw	n.d.	n.d.	-	normal brain
2	9. gw	n.d.	LV	-	dysplastic brain
3	11. gw	n.d.	LV	-	normal brain
4	12. gw	n.d.	LV	-	normal brain
5	12. gw	n.d.	LV	-	normal brain
6	13. gw	n.d.	LV	-	hypoxic/ischemic
7	14. gw	n.d.	4V	-	malformation
8	14. gw	n.d.	LV	-	hypoxic/ischemic
9	15. gw	n.d.	LV	-	infection
10	15. gw	f	LV	-	infection
11	16. gw	n.d.	LV	-	brain tumor
12	18. gw	n.d.	LV	-	brain tumor
13	19. gw	f	LV	-	dysplastic brain
14	22. gw	m	4V	-	hypoxic/ischemic
15	22. gw.	n.d.	4V	-	hypoxic/ischemic
16	23. gw	n.d.	LV	-	dysplastic brain
17	24. gw	n.d.	4V	-	brain tumor
18	29. gw.	n.d.	LV	-	Colloid cyst of the 3V
19	31. gw	f	n.d.	-	Colloid cyst of the 3V
20	34. gw	m	LV	-	brain tumor
21	36. gw	n.d.	4V	-	brain tumor
22	39. gw	f	LV	-	Colloid cyst of the 3V
23	40. gw	f	LV	-	brain tumor
24	1 day	f	4V	-	brain tumor
25	1 day	f	LV	-	cavernoma
26	0.6 y	f	LV	-	hypoxic/ischemic
27	1.3 y	f	n.d.	-	hypoxic/ischemic
28	3 y	m	LV	-	neurodegeneration
29	9 y	m	LV	-	brain tumor
30	14 y	f	4V	-	brain tumor
31	16 y	m	LV	-	hypoxic/ischemic
32	17 y	f	4V	-	normal brain
33	22 y	f	3V	-	normal brain
34	23 y	f	LV	-	tumor
35	25 y	f	LV	-	hypoxic/ischemic
36	26 y	m	LV	-	neurodegeneration
37	27 y	m	LV	-	malformation
38	29 y	m	3V	-	hypoxic/ischemic
39	31 y	f	3V	-	normal brain
40	37 y	m	LV	-	normal brain
41	38 y	m	LV	-	normal brain
42	38 y	f	LV	-	normal brain
43	38 y	f	LV	-	malformation
44	45 y	f	LV	-	normal brain
45	45 y	f	4V	-	normal brain
46	45 y	m	LV	-	normal brain
47	49 y	f	LV	-	normal brain
48	53 y	m	4V	-	normal brain
49	55 y	m	LV	-	normal brain
50	55 y	m	LV	-	normal brain
51	60 y	f	n.d.	-	normal brain
52	65 y	m	n.d.	-	normal brain
53	68 y	m	3V	-	normal brain
54	71 y	m	4V	-	normal brain
55	71 y	m	LV	-	normal brain
56	72 y	f	LV	-	normal brain
57	78 y	f	LV	-	hydrocephalus
58	78 y	m	LV	-	normal brain
59	80 y	m	LV	-	normal brain
60	81 y	m	LV	-	normal brain

gw, gestational week; n.d., not documented; y, years; m, male, f, female; LV, lateral ventricle; 3V, 3rd ventricle; 4V, 4th ventricle.

Table 2. CDX2 immunoreactivity in choroid plexus tumors (CPTs).

#	diagnosis	age	sex	site	CDX2	primary/recurrent tumor
1	CPC	0.1 y	f	n.d.	-	primary
2	CPP	0.2 y	f	n.d.	-	primary
3	atyp. CPP	0.2 y	m	n.d.	-	primary
4	CPP	0.4 y	f	n.d.	-	primary
5	CPP	0.5 y	f	LV	-	primary
6	atyp. CPP	0.7 y	f	LV	-	primary
7	CPP	0.9 y	m	n.d.	-	primary
8	CPP	2 y	m	LV	-	primary
9	CPP	6 y	m	3V	-	primary
10	CPP	6 y	m	3V	-	1 st recurrence of CPT #9
11	CPP	7 y	m	LV	-	primary
12	CPP	10 y	m	n.d.	-	primary
13	CPP	11 y	m	4V	-	primary
14	CPP	15 y	f	n.d.	-	primary
15	CPP	15 y	m	n.d.	-	primary
16	CPP	16 y	f	4V	-	primary
17	atyp. CPP	16 y	f	n.d.	-	primary
18	atyp. CPP	18 y	m	LV	-	primary
19	atyp. CPP	18 y	m	LV	-	1st recurrence of CPT #18
20	atyp. CPP	23 y	f	4V	-	primary
21	CPP	24 y	f	4V	-	1st recurrence of CPT #16
22	atyp. CPP	25 y	f	LV	-	primary
23	CPP	25 y	f	4V	-	primary
24	CPP	37 y	f	4V	-	primary
25	CPP	27 y	m	n.d.	-	primary
26	CPP	36 y	f	n.d.	-	primary
27	CPP	31 y	f	4V	-	2nd recurrence of CPT #16
28	CPP	31 y	m	4V	-	primary
29	CPP	33 y	m	4V	-	primary
30	CPP	34 y	f	4V	-	primary
31	CPP	35 y	m	4V	-	primary
32	CPP	36 y	f	n.d.	-	1st recurrence of CPT #26
33	CPP	36 y	f	4V	-	primary
34	CPC	36 y	m	n.d.	-	primary
35	CPP	37 y	m	4V	-	primary
36	CPP	38 y	m	n.d.	-	1st recurrence of CPT #29
37	CPP	38 y	f	4V	-	1st recurrence of CPT #23
38	CPP	38 y	m	n.d.	-	primary
39	CPP	41 y	m	n.d.	-	1 st recurrence of CPT #38
40	CPP	42 y	f	n.d.	-	primary
41	CPP	43 y	f	n.d.	-	1 st recurrence of CPT #40
42	CPP	44 y	m	4V	-	1 st recurrence of CPT #31
43	atyp. CPP	45 y	f	n.d.	-	2 nd recurrence of CPT #40
44	CPP	47 y	m	4V	-	2 nd recurrence of CPT #31
45	CPP	49 y	f	4V	-	primary
46	CPP	50 y	f	4V	-	primary
47	atyp. CPP	51 y	m	4V	-	2 nd recurrence of CPT #29
48	atyp. CPP	51 y	f	n.d.	-	primary
49	atyp. CPP	52 y	m	L3-L5	-	drop metastasis of CPT # 29
50	CPP	57 y	f	4V	-	primary
51	CPP	54 y	m	n.d.	-	primary
52	CPP	56 y	m	4V	-	primary
53	CPP	58 y	f	LV	-	primary
54	atyp. CPP	56 y	f	n.d.	-	primary
55	CPP	57 y	m	4V	-	primary
56	CPP	64 y	f	4V	-	primary
57	CPP	63 y	f	4V	-	primary
58	CPP	65 y	f	LV	-	primary
59	atyp. CPP	66 y	f	n.d.	-	primary
60	CPP	67 y	f	4V	-	1st recurrence of CPT # 53
61	atyp. CPP	68 y	f	4V	-	2nd recurrence of CPT # 53
62	atyp. CPP	70 y	m	4V	-	primary
63	CPP	70 y	m	4V	-	primary
64	CPP	70 y	m	4V	-	primary
65	atyp. CPP	74 y	m	4V	-	1st recurrence of CPT # 62

CPP, choroid plexus papilloma; atyp. CPP, atypical choroid plexus papilloma; CPC, choroid plexus carcinoma; n.d., not documented; y, years; m, male, f, female; LV, lateral ventricle; 3V, 3rd ventricle; 4V, 4th ventricle.

microarrays using a tissue microarrayer (Beecher Instruments, Sun Prairie, Wisconsin, USA). These included 65 samples of choroid plexus tumors from 48 cases (34 female, 31 male; age range 0.1-74 yrs., mean age 35.3 yrs.), among them 17 samples from 11 cases with recurrent tumors. Choroid plexus tumors included 47 choroid plexus papillomas (WHO grade I), 16 atypical choroid plexus papillomas and 2 choroid plexus carcinomas (WHO grad III). Among those cases, 3 tumors showed progression from choroid plexus papilloma (WHO grad I) to atypical choroid plexus papilloma at recurrence. For cases of choroid plexus carcinoma (n = 2), slides representing the whole area of the paraffin block were analyzed because of possible greater intratumoral heterogeneity.

Samples were immunolabelled for CDX2 expression using a monoclonal mouse IgG1 antibody directed against the full length human CDX2 protein (Zytomed Systems, Berlin, Germany; clone CDX2-88, dilution 1:25) using an automated immunohistochemistry slide staining system (BenchMark®, Ventana Medical Systems, Tucson, Az, USA). The automated standard protocol is based on an indirect biotin-avidin system that used an universal biotinylated immunoglobulin secondary antibody and diaminobenzidine substrate. The sections were counterstained with haematoxylin. Negative controls consisted of sections incubated in the absence of the primary antibody. Normal adult human colon served as positive control (Fig. 1A). Only nuclear immunoreactivity was considered as positive staining for CDX2. Diagnosis of choroid plexus tumors was confirmed in all cases by positive immunostaining with antibodies Kir7.1 (donated by S. Hirose, polyclonal rabbit, dilution 1:6000) and BAF47/INI1 (BD Transduction Labs, San Jose, CA, USA; clone 25, monoclonal mouse IgG2a, dilution 1:400).

This study was carried out according to the ethical guidelines of the University of Tuebingen, Germany.

Results

CDX2 expression in normal choroid plexus and normal brain

All samples lacked expression of CDX2 in choroid plexus epithelium. More specifically, neither fetal choroid plexus (Fig. 1B) nor samples from children or adults (Fig. 1C) showed CDX2 immunoreactivity. Furthermore, in samples from autopsy brains, CDX2 immunolabelling was not detected in other brain tissues that were embedded within the same paraffin-block (i.e. ependyma, gray and white matter from different brain regions, including neurons, astrocytes and oligodendrocytes, leptomeninges; data not shown). In neurosurgical specimens, CDX2 expression was not observed in neighbouring brain tissue, including ependyma or epithelium of a colloid cyst of the third ventricle.

In cases with different pathological alterations of the brain (e.g. brain tumor, ischemia, infection), appropriate morphological changes could be found in the brain parenchyma and/or leptomeninges, and in one case of schistosomiasis affecting the choroid plexus also within the choroid plexus. However, no specific histological or immunohistochemical changes could be found in the choroid plexus epithelium in these cases.

CDX2 expression in choroid plexus tumors

Nuclear CDX2 immunostaining was not found in any of the 65 choroid plexus tumors, including 47 choroid plexus papillomas (Fig. 1D), 16 atypical choroid plexus papillomas and two choroid plexus carcinomas. In samples that also contained neighbouring ependymal or brain tissue, CDX2 immunoreactivity was also absent in these structures.

Discussion

The choroid plexus develops from invaginations of the single-layered roof plate and is covered by a homogeneous cuboidal epithelium with typical epithelial features and function (Dziegielewska et al., 1984, 2001; Miettinen et al., 1986; Felix et al., 1987; Doglioni et al., 1987; Gaudio et al., 1998; Gyure and Morrison, 2000; Strazielle and Ghersi-Egea, 2000; Redzic et al., 2005). These cells are generally considered to be modified ependymal cells and are referred to as choroidal epithelial cells (Emerich et al., 2004).

In development of the choroid plexus, there are some parallels to the development of the gastrointestinal tract, especially the small and large intestine, which also require Wnt signaling to develop their default stage of differentiation (Blache et al., 2004; De Santa Barbara et al., 2005; Barros et al., 2008; Kwek et al., 2008). Furthermore, expression of SOX9, which is regulated through Wnt signaling and influences CDX2 expression/function, has been reported in both tissues (Pompolo and Harley, 2001; Blache et al, 2004). In the gastrointestinal mucosa, CDX2 is mostly active in the villi, a morphological structure also typical for the choroid plexus epithelium (Silberg et al., 2000; Strazielle and Ghersi-Egea, 2000; Emerich et al., 2004; Blache et al., 2004).

CDX2 expression is inversely correlated with tumor grade, tumor stage and metastasis in colorectal epithelial neoplasms (Bakaris et al., 2008) and has recently also been recognized in several epithelial tumors outside the intestine (Werling et al., 2003; Mazziotta et al., 2005; Suh et al., 2005; Saegusa et al., 2007; Onofre et al., 2007; Herawi et al., 2007; Houghton et al., 2008; Wani et al., 2008).

In our series we included samples from normal fetal choroid plexus (22nd gw to 39th gw), as well as post natal normal (1 day to 81 yrs.) and neoplastic (0.1 to 74 yrs.) choroid plexus. Among them, there was no single case showing CDX2 expression in choroid plexus cells.

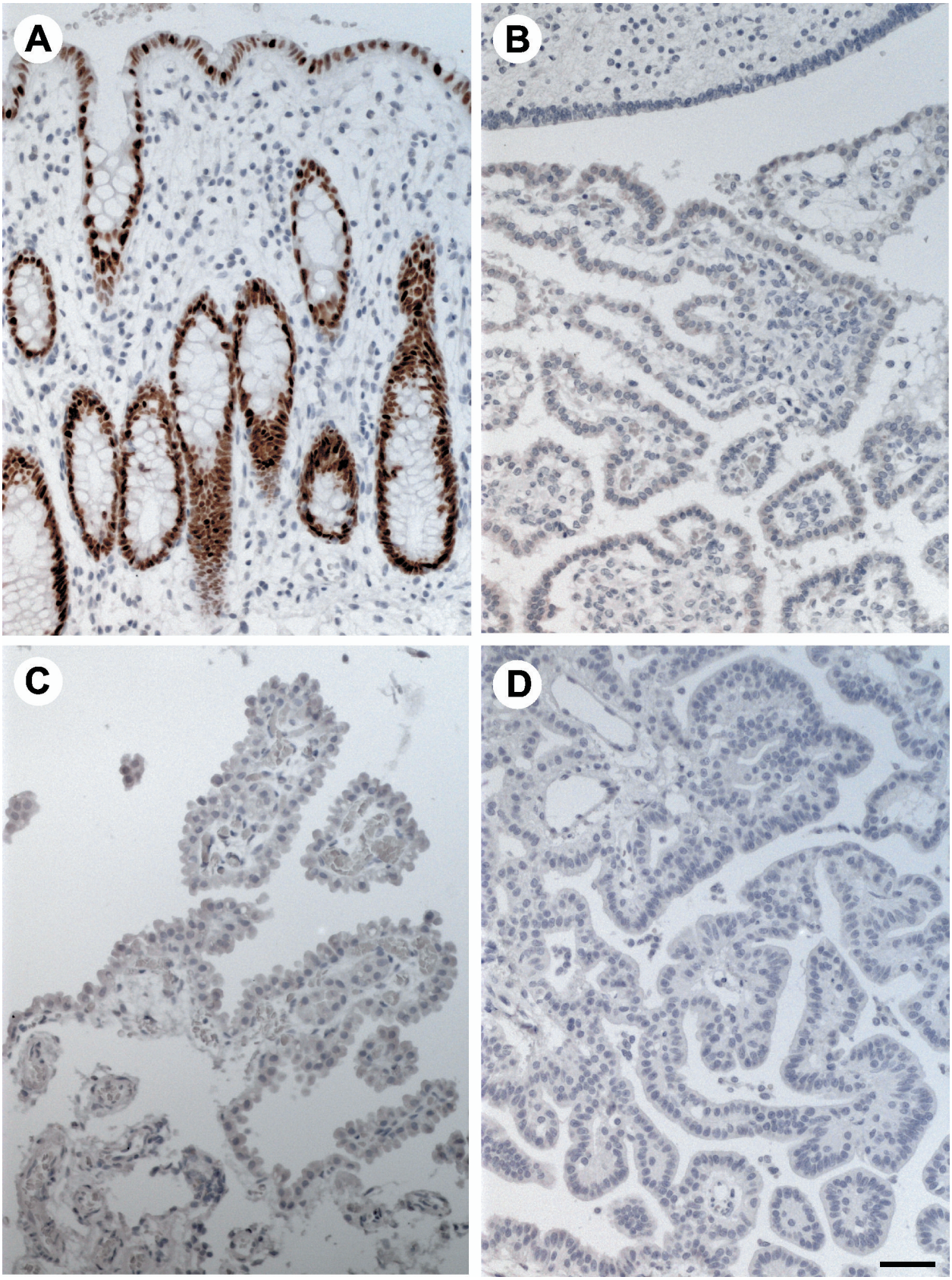

Fig. 1. Strong nuclear expression of CDX2 in normal colorectal mucosa **(A)**. Normal choroid plexus epithelium lacks CDX2, both in the prenatal (**B**, 22nd gestational week) and during the postnatal period (**C**, 29 year-old man operated for a colloid cyst of the 3rd ventricle). Likewise, choroid plexus tumors do not express CDX2 (**D**, choroid plexus papilloma WHO grade I). Scale bar: 50 µm.

Thus, immunohistochemistry shows no evidence that CDX2 might play a role in differentiation of the normal choroid plexus epithelium or in tumorigenesis of choroid plexus tumors. Since CDX2 acts as a tumor-supressor through inhibition of the Wnt/beta-catenin pathway (Bonhomme et al., 2003; Saegusa et al., 2007), one might expect that the Wnt/beta-catenin signalling pathway also does not play a major role in choroid plexus neoplasms.

It is noteworthy that neighbouring or additionally collected CNS tissue, such as ependyma, neurons, astrocytes and oligodendrocytes in gray and white matter were also reliably negative for CDX2. Thus, we have confirmed previous observations reporting the absence of CDX2 in neuronal and astrocytic cells (Moskaluk et al., 2003; Strickland-Marmol et al., 2007).

There are no clear data on the frequency of metastases to the plexus choroideus deriving from CDX2 positive primary carcinomas. Overall, metastatic tumors are the most common CNS neoplasms and carcinomas are the most frequent source of brain metastases. Among them, the colon is the primary site of brain metastases in 5-9.5% (Nussbaum et al., 1996; Ellison et al., 2008). Choroid plexus tumors account for about 0.3% of all intracranial neoplasms (Paulus and Brandner, 2007; CBTRUS, 2008). Although less common, metastatic carcinomas, including colorectal carcinomas, can also be located within the choroid plexus or at sites where native choroid plexus may be present (intraventricular, cerebellopontine angle) (Kohno et al., 1996; Cha et al., 2000; Gopal et al., 2008). The incidence of solitary metastases to the choroid plexus accounts for approximately 0.14% of all brain metastasis (Gopal et al., 2008). Taken together these data, the incidence of primary choroid plexus tumors is approximately only twice as high as the incidence of solitary metastasis. Thus, metastatic adenocarcinomas within the choroid plexus, cerebral ventricles and at the cerebellopontine angle may even outnumber choroid plexus tumors.

Distinction of choroid plexus tumors from metastatic carcinomas according to histolopathologival criteria may be challenging. Currently, there are only very few markers expressed in choroid plexus tumors that enable a significant distinction from metastatic carcinomas, e.g. Kir7.1 (Hasselblatt et al., 2006) and EAAT-1 (Beschorner et al., 2006), or normal choroid plexus (EAAT-1) (Beschorner et al., 2009). However, these antibodies are either not commercially available (Kir7.1) or lack immunoreactivity in approximately one fifth of choroid plexus tumors (EAAT-1). CDX2 has previously been noted to be useful to determine the primary site of metastatic adenocarcinomas to the brain (Strickland-Marmol et al., 2007).

Especially in adult cases, the possibility of metastasis should always be taken into account when making the diagnosis of a choroid plexus tumor. In equivocal cases, additional staining may be useful, in particular, CDX2 might be added to the diagnostic panel to 'exclude' a metastatic colorectal carcinoma.

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