Downregulation of CDX2 is associated with MMR-deficiency in colon cancer

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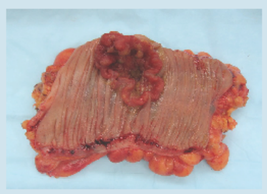
Introduction

Homeobox genes are often deregulated in cancer. They can have both oncogenic and tumor-suppressing potential. The *Caudal*-related homeobox transcription factor 2 (CDX2) is an intestine-specific transcription factor. It is implicated in differentiation, proliferation, cell-adhesion, and migration. CDX2 has been proposed as a tumor suppressor in colorectal cancer but its role is still controversial.

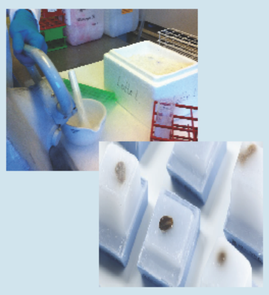
Aim

To investigate CDX2 mRNA and protein expression in relation to clinico-pathological characteristics and risk of recurrence in colon cancer.

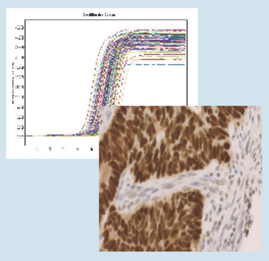
Methods



Tumor tissue and normal adjacent tissue were obtained from patients diagnosed with colon cancer.



Biopsies were fixed in liquid nitrogen for RNA extraction, and formalin for paraffin embedding (FFPE) for immuno-histochemical staining.



mRNA expression for *CDX2* was measured with RT-qPCR (B2M was used as reference gene). FFPE sections were stained for MLH1, MSH2, MSH6, PMS2 and CDX2.

Statistics: Groups were compared with t-test and Fisher's exact test. Survival analyses were carried out using Cox competing risk regression models.

Results

We found no significant difference in *CDX2* mRNA expression between tumor and normal tissue. *CDX2* mRNA expression was significantly lower in right-sided, poorly differentiated and MMR-deficient tumors.

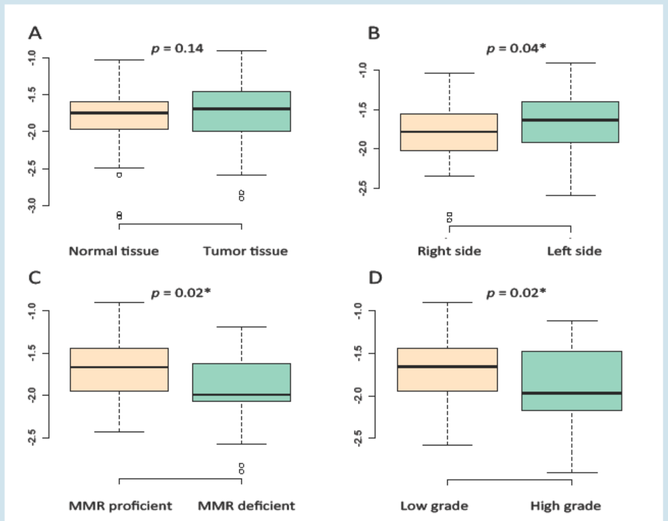


Fig 1: Showing *CDX2* mRNA expression in relation to different clinico-pathological characteristics. A: normal and tumor tissue. B: Right- and left sided tumors. C: MMR proficient and deficient tumors. D: Differentation grade. *: Significant at the 0.05 level.

Similarly was low CDX2 protein expression associated with right-sided tumors, poorly differentiated tumors and MMR-deficient tumors.

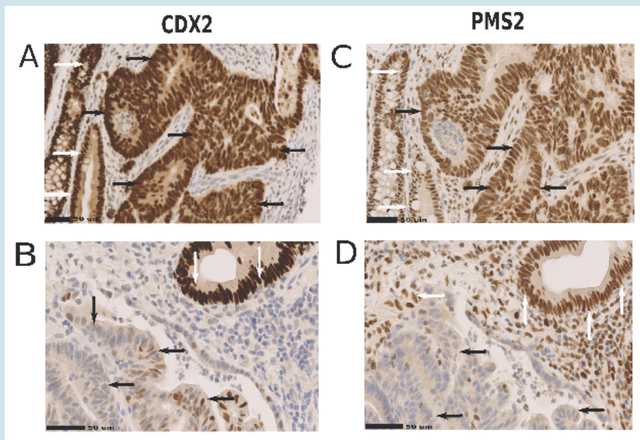


Fig 2: Immunohistochemistry for CDX2 and PMS2 protein expression. A: Normal CDX2 expression in tumor cells (black arrows) and normal cells (white arrows). B: Low CDX2 expression in tumor cells (black arrows) compared with normal cells (white arrows). C: Normal PMS2 expression in tumor cells (black arrows) and normal cells (white arrows). D: Low PMS2 expression in tumor cells (black arrows) compared with normal cells (white arrows).

Table 1. Fisher´s exact test for CDX2 protein expression

	CDX2 normal	CDX2 low	*p*-value
MMR status			<0.001*
MMR-proficient	168	5	
MMR-deficient	26	11	
Differentiation grade			<0.001*
Low grade	154	4	
High grade	40	12	
Tumor location			<0.01*
Left side	102	2	
Right side	92	14	

*: Significant at the 0.05 level.

Results -continued

Low CDX2 mRNA or protein expression was not associated with risk of recurrence in either unadjusted (p=0.18; p=0.71, respectively) or adjusted (data not shown) Cox competing risk regression models.

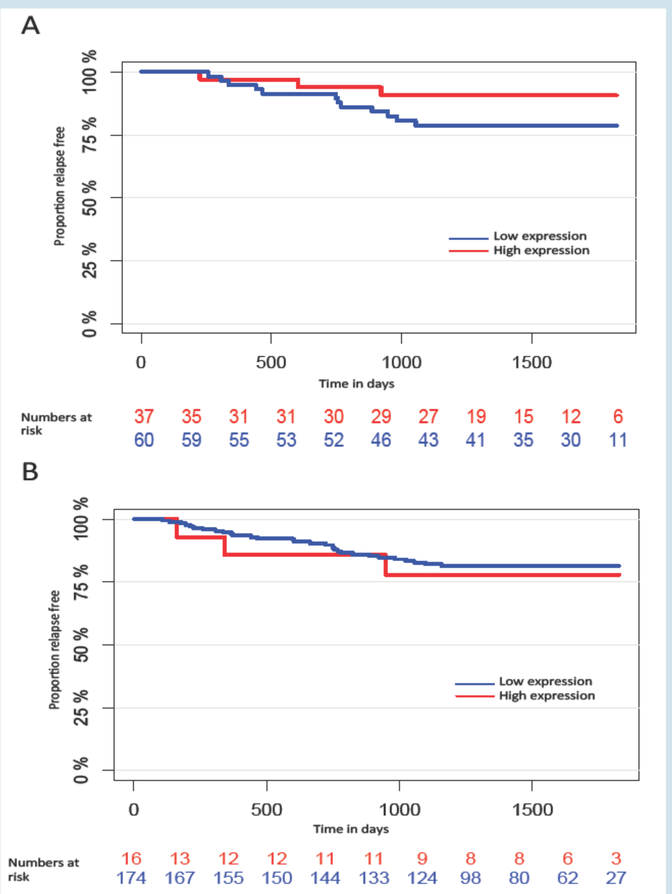


Fig 3: Kaplan-Meier curves for recurrence free survival with regard to CDX2 expression. A: High and low *CDX2* mRNA expression with cut-point from Youden-index. B: High/Normal and low CDX2 protein expression from immunohistochemistry.

Conclusion

We found that low CDX2 expression was associated with :

- MMR-deficiency
- Right-sided tumors
- Poorly differentiated tumors

This should be kept in mind when using CDX2 as a diagnostic biomarker in identification of tumor cells of unknown/gastrointestinal origin. We found no association between risk of recurrence and CDX2 expression.

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