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Loss of CDX2 and high COX2 (*PTGS2*) expression in stage-IV colorectal cancer

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Introduction

Lack of expression of the tumor suppressor protein CDX2 is associated with stage II/III colorectal cancer (CRC) poor outcomes. Its potential prognostic and predictive values in metastatic CRC (mCRC), and correlation with other potential biomarkers are of great interest. Overexpression of the *PTGS2* gene encoding cyclooxygenase 2 (COX2) has shown a significantly direct association with advanced CRC stages. Reduced CDX2 in CRC has been suggested to enhance NF-κB-mediated inflammatory response, upregulating COX2 expression. However, the relationship between both markers in mCRC pathogenesis remains undetermined. We aimed to assess CDX2 and COX2 expression in mCRC tumor samples from a clinically characterized cohort.

Cohort and Methods

Three hundred forty-six out of 720 patients with mCRC seen between Jan. 2010 and Dec. 2019 had primary tumor and/or metastasis tumor tissues appropriate for analysis. Tissue microarrays (TMA) were assembled and analyzed by IHC with anti-CDX2 and -COX2 antibodies. Negative CDX2 (CDX2-) samples were defined as complete lack of the CDX2 protein staining and/or scattered faint nuclear labelling in few cancer cells. COX2 intensity and extent staining was positive (COX2+) if the final score was ≥3 (0-7). Retrospective demographic, clinical and survival data were analyzed. Comparisons of overall survival (OS) between groups were performed by log rank.

Results

CDX2 loss was found in 27 (7.8%) samples and was significantly enriched among poorly differentiated tumors (26.1% vs 8.1%; p = 0.009) and those with the *BRAF* p.V600E variant (42.9% vs 5.4%; p = 0.0002). CDX2- was not associated with age, sex, tumor sidedness, *RAS* mutation or presence of microsatellite instability. COX2+ tumors were the majority (93.4%) and not associated with CDX2 IHC expression. Median OS for CDX2- and CDX2+ mCRC patients was 30 and 53 months, respectively (p < 0.0008), and not significant for the COX2 comparison (p < 0.140). The median PFS in first-line chemotherapy was significantly lower for those with CDX2- tumors (6 vs. 10 months; p < 0.026).

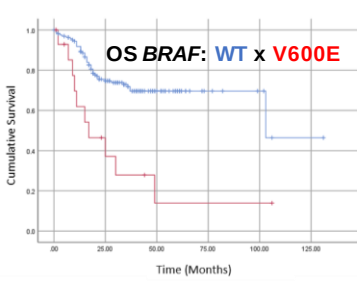
Demographic characteristics according to CDX2 and COX2 protein expression

Characteristics	All patients	Negative CDX2	Positive CDX2	*p* Value	All patients	Negative COX2	Positive COX2	p Value
CDX2 expression	346	27 (7.8%)	319 (92.2%)		332	22 (6.6%)	310 (93.4%)	
Age		Median 56	Median 60					
Sex				1.00				1.00
Male	185/346 (53.5%)	14 (51.9%)	171 (53.6%)		177/332 (53.3%)	12 (54.5%)	165 (53.2%)	
Female	161/346 (46.5%)	13 (48.1%)	148 (46.4%)		155/332 (46.7%)	10 (45.5%)	145 (46.8%)	
Histology				0.007				0.042
GH1 - Well differentiated	25/319 (7.2%)	3 (13.0%)	22 (7.4%)		24 (7.8%)	2 (9.5%)	22 (7.7%)	
GH2 – Moderately differentiated	264/319 (76.3%)	14 (60.9%)	250 (84.5%)		255 (83.1%)	14 (66.7%)	241 (84.3%)	
GH3 - Poor differentiated	30/319 (8.7%)	6 (26.1%)	24 (8.1%)		28 (9.1%)	5 (23.8%)	23 (8.0%)	
Tumor sidedness				$(\chi 2)$ 0.187				$(\chi 2)$ 0.477
Right	87/344 (25.1%)	10 (37.0%)	77 (24.3%)		82/330 (24.8%)	4 (18.2%)	78 (24.8%)	
Left	87 /344 (25.1%)	8 (29.6%)	79 (24.9%)		84/330 (25.5%)	8 (36.4%)	76 (25.5%)	
Rectum	170/344 (49.1%)	9 (33.3%)	161 (50.8%)		164/330 (49.7%)	10 (45.5%)	154 (49.7%)	
Tumor Biology								
BRAF w/t	165/180 (91.7%)	8 (57.1%)	157 (94.6%)	0.0002	161/176 (91.5%)	5 (100%)	156 (91.2%)	1.00
BRAF Mut	15/180 (8.3%)	6 (42.9%)	9 (5.4%)		15/176 (8.5%)	0 (0%)	15 (8.8%)	
KRAS w/t/NRAS w/t	178/346 (51.4%)	15 (55.6%)	163 (51.1%)	0.807	172/332 (51.8%)	8 (4.6%)	164 (95.3%)	0.201
KRASMut/NRAS Mut	168/346 (48.5%)	12 (44.4%)	156 (48.9%)		160/332 (48.2%)	14 (8.1%)	146 (84.9%)	
MSS	270/279 (96.8%)	14 (93.3%)	256 (97.0%)	0.396	259/268 (96.6%)	18 (94.7%)	241 (96.8%)	0.489
MSI-high (MSI-H)	9/279 (3.2%)	1 (6.7%)	8 (3.0%)		9/268 (3.4%)	1 (5.3%)	8 (3.2%)	

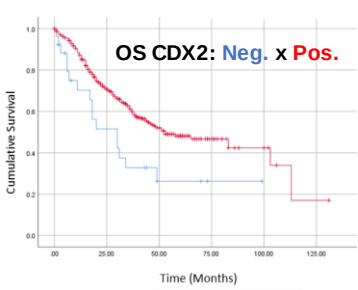
Site of metastases at diagnosis	
Lymph node	34/346 (9.8%)
Pulmonary	59/346 (17.1%)
Peritoneal	74/346 (21.4%)
Bone	2/346 (0.6%)
Hepatic	153/346 (44.2%)
Other	24/346 (6.9%)

First-line chemotherapy	First-line chemotherapy	Second-line chemotherapy
Cetuximab	28 (8.1%)	17 (4.9%)
Panitumumab	19 (5.5%)	06 (1.7%)
Bevacizumab	171 (49.4%)	134 (38.7%)
Irinotecan	109 (31.5%)	114 (32.9%)
Oxaliplatin	205 (59.2%)	61 (17.6%)
Capecitabine	17 (4.9%)	17 (4.9%)
5-fluorouracil (5-FU)	305 (88.2%)	177 (51.2%)
Others	2 (0.6%)	8 (2.3%)

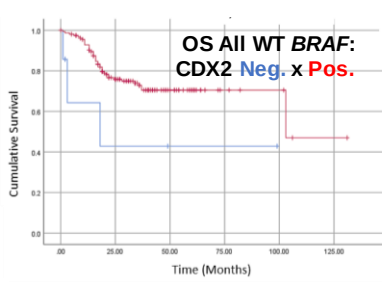
Overall Survival



Median OS - Log Rank (Mantel-Cox)
BRAF mut (N=15): 17 months
BRAF WT (N=165): 103 months
p= 0.000098



Median OS - Log Rank (Mantel-Cox)
CDX2 negative (N=27): 30 months
CDX2 positive (N=319): 53 months
p= 0.0008



Median OS - Log Rank (Mantel-Cox)
CDX2 negative (N=08): 18 months
CDX2 positive (N=157): 103 months
p= 0.043

Conclusions

Loss of CDX2 expression in mCRC was associated with a higher risk of death and progression after first-line treatment, poor differentiated tumors and the *BRAF* p.V600E variant. In the absence of the *BRAF* p.V600E variant, the lack of CDX2 protein significantly correlated with poor OS, although fewer WT *BRAF* cases had lost CDX2 expression (30%). COX2 was highly expressed in mCRC and did not correlate with the investigated parameters.

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