Characterization of MCL-1 in patients with colorectal cancer (CRC): Expression, molecular profiles, and outcomes

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Abstract ID:3085

Introduction

- Myeloid cell leukemia 1 (MCL-1) is a member of the BCL-2 protein family and is anti-apoptotic/pro-survival in function.
- Dysregulation of MCL-1 expression has been reported in several solid tumors, including lung and breast cancer.
- In CRC, MCL-1 has been associated with resistance to chemotherapeutic drugs and multi-kinase inhibitor regorafenib.
- Our study aimed to characterize the molecular features associated with MCL-1 gene expression in CRC.

Methods

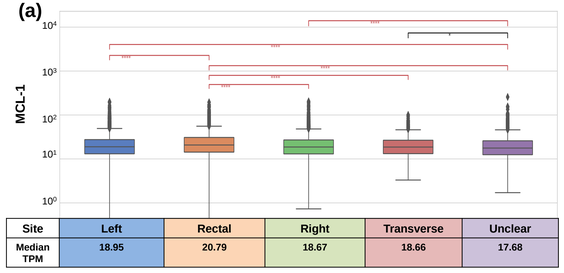
- 28,576 CRC samples were analyzed by Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES).
- MCL-1 expression was stratified by quartiles where top quartile transcripts per million (TPM) were considered high (Q4) and bottom quartile low (Q1).
- Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by RNA deconvolution analysis using QuantiSEQ.
- Interferon-gamma and T-cell inflamed signatures were also calculated from RNA data.
- X2 and Fisher-Exact tests were used, and statistical significance was determined as a P-value adjusted for multiple comparisons (q < 0.05).
- Real world survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patients.

Patient Demographic

MCL-1 Expression	Q1	Q4	P-value	Q-value
Count (N)	7144	7144		
Median Age (range)	64 [13 - >89]	64 [14 - >89]	No statistical difference in age or gender	
Male	53.2%	54.6%		
Female	46.8%	45.4%		

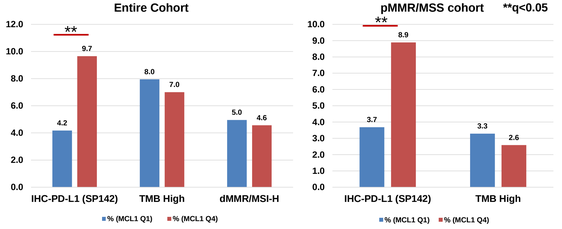
Results

Figure 1. *MCL-1* Expression According to Primary Tumor Side (a), and Consensus Molecular subtypes (b).



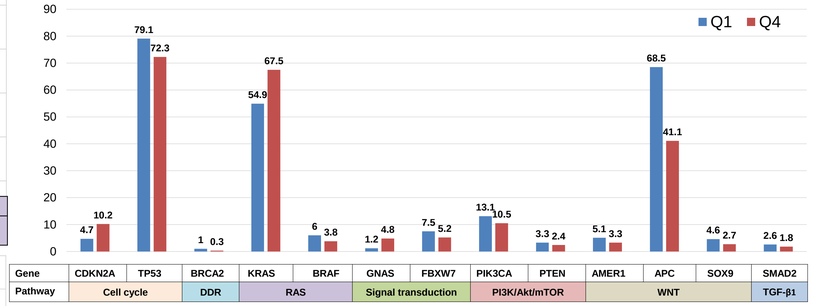
No significant difference was observed in right- versus left-sided tumors, however rectal tumors showed the highest *MCL-1* expression ($P < 0.05$). Among the CMS subtypes, CMS4 tumors showed highest *MCL-1* expression ($P < 0.05$).

Figure 2. Association with Immune-related Markers.



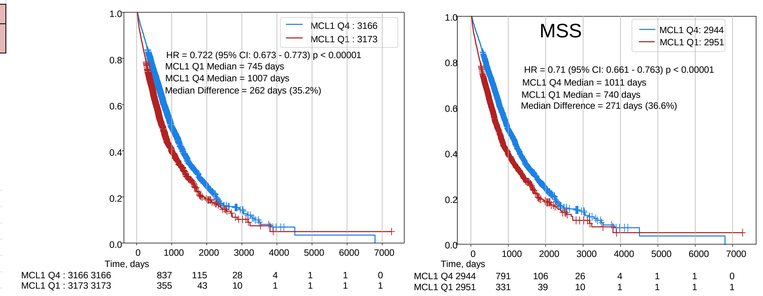
Overall, high *MCL-1* TPM was positively correlated with PD-L1 expression (9.7% vs 4.2%) ($q < 0.01$); while TMB-high shows a trend for negative correlation with MCL-1 expression (4.6% vs 5.0%). These association hold true in the pMMR/MSS cohort. No significant association was found with dMMR/MSI-H cohort.

Figure 3. Association of *MCL-1* Expression with Tumor Molecular Characteristics (only significant results).



MCL-1 high was associated with higher mutation rates of *CDKN2A, BRCA2, KRAS* and *GNAS*, while lower mutation rates of *TP53, PIK3CA, PTEN, BRAF, APC, FBXW7, AMER1, SOX9,* and *SMAD2* and copy number amplifications in several genes (q < 0.0001).

Figure 4. Association between *MCL-1* expression and survival in all CRC and MSS patients.



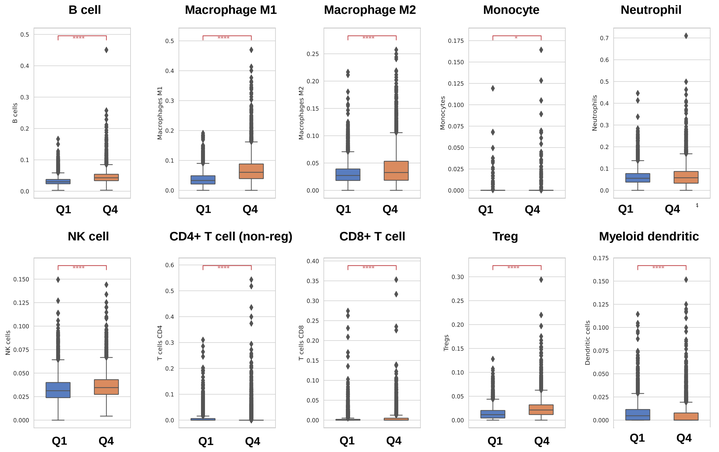
Patients with high *MCL-1* expressing CRC had longer survival ($P < 0.0001$).

CONCLUSIONS

Our data show a strong correlation between distinct immune biomarkers, TME cell infiltration and MCL-1 expression in CRC. Furthermore, increased tumor MCL-1 expression improved patient prognosis and treatment outcomes.

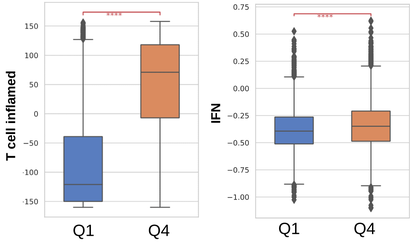
These findings suggest a key clinical role for MCL-1 as an important modulator of anti-tumor immunity and TME and a potential biomarker in CRC.

Figure 5. TME Cell Infiltration According to *MCL-1* Expression in pMMR/MSS Tumors.



M1 and M2 macrophages, Monocytes, B cells, NK cells and T-reg infiltration was positively associated (more abundant in the TME of tumors) with high MCL-1 expression, while dendritic cells and CD4+ T cell infiltration was negatively associated with MCL-1 expression, in the MSS and entire CRC cohort (all $q < 0.001$).

Figure 6. Association between *MCL-1* Expression and Interferon-gamma and TIS score.



MCL-1 expression was associated with a higher TIS and IFN score ($q < 0.001$) in MSS cohort.

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