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

Pooja Mittal1,2, Francesco Battaglini1, Yasmine Baca2, Joanne Xiul, Alex Farrell3, Shivani Soni, Jae Ho Lo4, Lesly Torres-Gonzalez5, Sandra Algaze5, Priya Jayachandran1, Karam Ashour1, Wu Zhang1, Benjamin A. Weinberg1, Emil Lou5, Anthony F. Shields6, Richard M. Goldberg1, John L. Marshall7, Sanjay Goel8, Indrakant K. Singh9, Heinz-Josef Lenz10

1 Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; 2 USC Cancer Institute, University of Southern California, Los Angeles, CA, USA; 3 Scottish Center for the Cure of Gastrointestinal Cancers, Linda National Cancer Institute, Presbyterian Cancer Center, Georgetown University Medical Center, Washington, DC, USA; 4 Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota, USA; 5 Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detriot, MI, USA; 6 West Virginia University Cancer Institute, Morgantown, WV, USA; 7 Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; 8 Molecular Biology Research Lab, Deblinitchou College, University of Delhi, New Delhi, India

Abstract ID:3085

Introduction

- Myeloid 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 chemotherapy drugs and multi-kinase inhibitor regorafenib.
- Our study aimed to characterize the molecular features associated with CRC-MCL-1 gene expression in CRC.

Methods

- 28,576 CRC samples were analyzed by Caris Life Sciences (Phoenix, AZ) with WTS (Umina NovaSeq) and NextGen DNA sequencing (NextSeq, 532 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 QuantiSEQC.
- Interferon-γ and T-cell infiltration were identified based on RNA expression 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.

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

Results

- MCL-1 high was associated with higher mutation rates of CDX2, BRCA2, KRAS and SMAD2, while lower mutation rates of TP53, PIK3CA, PTEN, BRAF, APC, FBXW7, AMER1, SCDX9, and SMAD2 and copy number amplifications in several genes (q < 0.001).
- Figure 4. Association between MCL-1 expression and survival in all CRC and MSS patients.

Figure 2. Association with Immune-related Markers.

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 tumor immunity and TME and a potential biomarker in CRC.

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

Figure 6. Association between MCL-1 Expression and Interferon-gamma and TIM3 score.