LMTK3 gene expression and the molecular landscape of colorectal cancer (CRC)

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Introduction

- Lemur tail kinase 3 (LMTK3) is a serine/threonine protein kinase with roles in multiple cellular pathways, including Wnt signaling, KIT modulation, and the estrogen receptor pathway.
- LMTK3 polymorphisms have previously been associated with clinical outcomes in CRC patients.
- In CRC, LMTK3 and estrogen-mediated signaling have been shown to play a crucial role in tumorigenesis *in vitro*.
- Our study aimed to characterize the molecular features associated with LMTK3 gene expression in CRC.

Methods

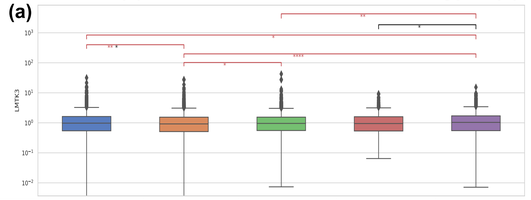
- 20,219 CRC samples were analyzed by Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or WES) and RNA (WTS).
- LMTK3 expression was stratified by quartiles where top quartile transcripts per million (TPM) were considered high (Q4) and bottom quartile low (Q1).
- Consensus molecular subtypes (CMS) were assessed using RNAseq.
- Cell infiltration (CI) in the tumor microenvironment (TME) was estimated by RNA deconvolution analysis using QuantiSEQ.
- Gene expression profiles were analyzed for signatures of immunotherapy response (Interferon-gamma and T-cell inflamed signature scores).
- X^2 and Fisher-Exact tests were used, and statistical significance was determined as a P-value adjusted for multiple comparisons (q < 0.05).

Patient Demographic

LMTK3 Expression	Q1	Q4	P-value	Q-value
Count (N)	5055	5055		
Median Age (range)	62 [15 - >89]	63 [17 - >89]	0.009	0.01
Male	55.6%	54.5%	No statistical difference in gender	
Female	44.4%	45.5%		

Results

Figure 1. *LMTK3* Expression According to Primary Tumor Side (a), and Consensus Molecular Subtypes (b).

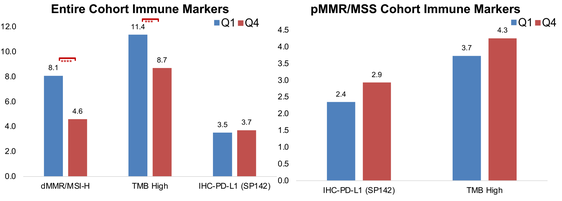


Site	Left	Rectal	Right	Transverse	Unclear
Median TPM	0.98	0.92	0.96	0.95	1.03

Site	CMS1	CMS2	CMS3	CMS4
Median TPM	0.88	0.98	0.70	1.09

LMTK3 expression was highest in left-sided (0.98 median TPM) followed by right-sided (0.96) and lowest in rectal tumors (0.92, all intergroup q < 0.05). In the pMMR/MSS cohort, LMTK3 expression was highest in CMS4 (1.09 median TPM) followed by CMS2 (0.98), CMS1 (0.88), and lowest in CMS3 (0.70, all intergroup q < 0.05).

Figure 2. Association of LMTK3 Expression with Immune-related markers.



Low *LMTK3* TPM was associated with dMMR/MSI-H (8.1 vs 4.6%, q < 0.001) and TMB-high (≥ 10 Mut/Mb, 11.4 vs 8.7%, q < 0.0001). In the pMMR/MSS cohort, these associations were no longer significant.

Figure 3. Association of *LMTK3* Expression with Molecular Alterations (only significant results, q<0.05).

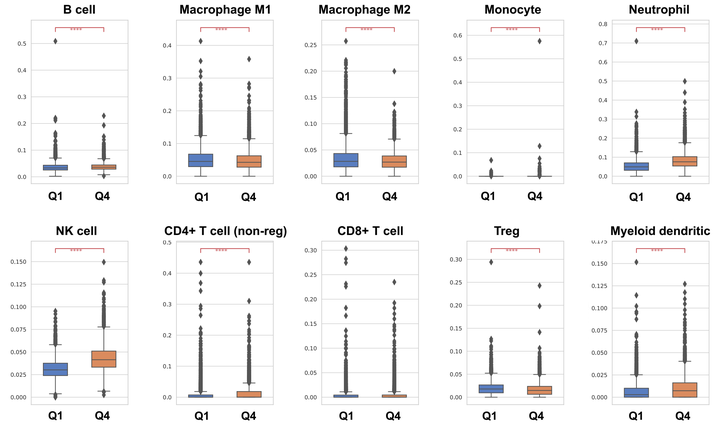
High LMTK3 expression showed differential rates of mutations and copy number alterations (CNA) in several genes, including higher mutation rates in APC, TP53, and CDX2 CNA, and lower mutation rates of KMT2A/D, ASXL1, ATM, SMAD4, RNF43 and AMER1. In the pMMR/MSS cohort, the associations with APC, TP53, SMAD4 and ATM mutations and CDX2 CNA still held true.

CONCLUSIONS

Our data show a strong association between LMTK3 gene expression and distinct molecular features and TME immune cell infiltration in CRC.

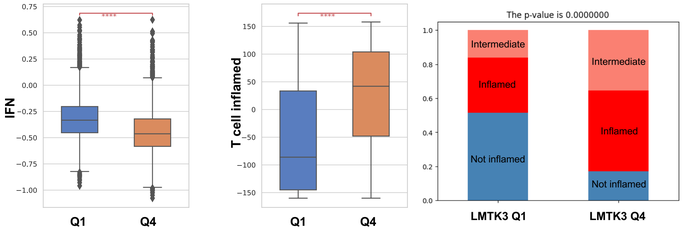
These findings suggest that LMTK3 may be an important molecular factor that plays a role in determining the composition of the TME, thus targeting LMTK3 could represent a novel strategy in selected CRC subgroups.

Figure 5. TME Immune Cell Infiltration According to *LMTK3* Expression.



High LMTK3 expression was associated with higher TME immune cell infiltration in B cells, monocytes, neutrophils, NK cells, CD4+ T cells, and dendritic cells, but lower macrophage and Treg infiltration (fold change: 0.83-2.4, all q < 0.0001). In the pMMR/MSS cohort, these findings still held true.

Figure 6. Association between *LMTK3* Expression and IFNγ & TIS scores.



High *LMTK3* expression was associated overall with a lower IFNγ score, but higher TIS score (all *q* < 0.0001). In the pMMR/MSS cohort, these findings still held true. Distribution of T cell inflamed tumors was significantly higher in Q4 when compared to Q1.

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