Comprehensive Genomic and Transcriptomic Profiling of Acral Lentiginous Melanoma

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BACKGROUND

Acral lentiginous melanoma (ALM) is a rare melanoma subtype found on the palms, soles and nailbeds. ALM is poorly responsive to immune checkpoint blockade and outcomes are poor for patients with advanced or metastatic disease. As such, novel treatment approaches are needed.

METHODS

- A total of 699 primary CM and 18 primary ALM samples underwent DNA next generation sequencing (592 Gene Panel, NextSeq, or WES, NovaSeq), and whole transcriptome sequencing (NovaSeq, WTS).
- MAPK pathway activity score (MPAS, Wagle Precision Onc, 2018), xCell, HLA subtyping, neoantigen load (HBA: high binding affinity; IBA: intermediate binding; LBA: low binding), and IFNγ score (Ayers JCI, 2017) were calculated by mRNA expression.
- Global differentially regulated genes were assessed via limma R package (C: log fold change).
- Wilcoxon, Fisher's exact test were used to determine statistical significance (displayed as p value without and q value with multi comparison correction).

RESULTS

Table 1. Basic demographic features of ALM and CM.

	CM	ALM	p	q
Count(N)	699	18		
Average Age (range)	66.3 (3 - >89)	69.4 (55 - 87)	0.29	0.49
Male	59.5% (416/699)	50.0% (9/18)	0.42	0.49
Female	40.5% (283/699)	50.0% (9/18)		
TMB (mut/Mb)	9	1.5	<0.0001	<0.0001
PD-L1 (SP142) - High	11.8%	38.2%	<0.05	0.83

Figure 1. Top 10 co-alterations in ALM (A) and CM (B), and genomic alterations that were differentially regulated (p<0.05) between ALM and CM (C).

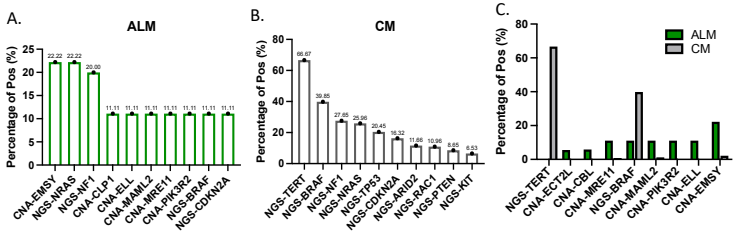


Figure 2. MAPK pathway activation scores were lower for ALM (blue) vs CM (orange) for all patients (A), BRAF mutated (B), and NRAS mutated tumors (C), but not NF1 mutated (D).

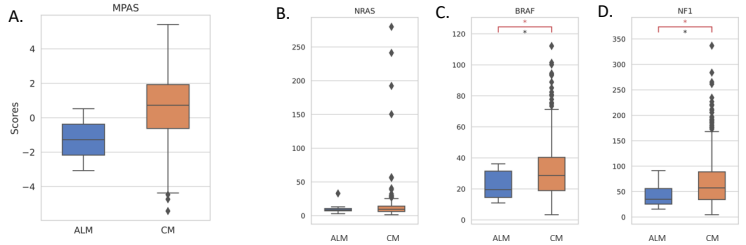
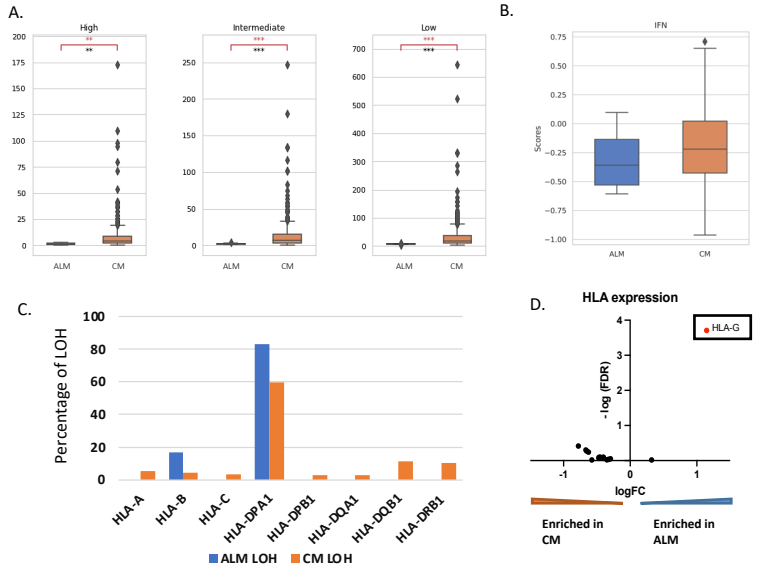


Figure 3. Immunogenicity of ALM (blue) vs CM (orange): (A) neoantigen load with different binding affinities to MHC in ALM vs CM; (B) IFNγ scores in ALM vs CM; (C) Loss of heterozygosity of HLA-family proteins in ALM vs CM; (D) differentially expressed HLA-family mRNA in ALM vs CM.



- Neoantigen load was lower in ALM vs CM, regardless of MHC binding affinity.
- HLA-G RNA expression was significantly upregulated in ALM with respect to CM (logFC = 1.14, FDR <0.001).
- There was a trend towards lower IFNγ in ALM compared to CM.

Table 2. Immune /stromal cell types in ALM vs CM (p<0.05).

Immune Cell Types	ALM	CM	p-value
T cell CD4+ Th1	0.059	0.091	0.003
Macrophage	0.037	0.067	0.012
Macrophage M2	0.047	0.066	0.019
B cell plasma	0.010	0.011	0.024
T cell CD4+ central memory	0.036	0.022	0.025
Cancer associated fibroblast	0.000	0.004	0.025
Endothelial cell	0.034	0.023	0.025
stroma score	0.017	0.014	0.028
T cell gamma delta	0.000	0.004	0.033
Plasmacytoid dendritic cell	0.016	0.034	0.045

- ALM showed less CD4+ T cell Th1, B cell plasma, and γδ T cells, but more CD4+ T cell central memory cell, stroma score, and endothelial cells, versus CM.

Table 3. Differentially regulated pathways between ALM vs. CM via Reactome.

Pathway name	Entities FDR
Formation of the cornified envelope	1.11E-16
Keratinization	7.73E-14
Developmental Biology	9.25E-06
Amyloid fiber formation	2.67E-04
Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	9.00E-04
FLT3 signaling by CBL mutants	9.36E-04
Signaling by EGFR in Cancer	0.001144896
Maturation of protein E	0.001217916
DNA Double Strand Break Response	0.001360504
EGFR downregulation	0.001730136

- Pathways related to keratinization and amyloid fiber formation were enriched in ALM, due to overexpression of KRT16 , KRT6B and KRT17 , among others.

CONCLUSIONS

- ALM has distinct immunologic features, including a) upregulation of HLA-G, and b) lower MAPK activation, compared to CM, highlighting the need for novel therapeutic approaches in the treatment of this rare melanoma subtype.

REFERENCES

- Oncologist 2016 Johnson et al
- Cancer 2016 Shoushtari et al

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