Multi-omic analysis reveals distinct molecular profiles of uterine and non-uterine leiomyosarcoma

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Background

- Leiomyosarcoma (LMS) is a rare group of mesenchymal malignancies found in the uterus, retroperitoneum, skin, or other soft-tissue sites[1]
- Histologically, all LMS tumors have similar appearance with elongated cells with abundant cytoplasm and a high presence of smooth muscle actin and desmin, yet their behavior and clinical characteristics vary dramatically[2]
- Treatment for LMS is extrapolated from trials including both uterine (uLMS) and non-uLMS subtypes
- Whether they respond similarly and have similar outcomes from treatment is not clear[3]
- We used the Caris POA to examine molecular composition of LMS by site of origin to better inform future drug development and trial design
- Caris precision oncology alliance (POA) best-in-class collaborative research network focusing on precision oncology to identify predictive and prognostic markers that help in improving the outcomes and clinical care of patients with cancer

METHODS

- We reviewed 1115 specimens with LMS histology tested by Caris Life Sciences for:
  - targeted exome (NextSeq, 592 gene panel)
  - whole exome
  - whole transcriptome sequencing (NovaSeq)
- Specimens were stratified into uLMS, rpLMS (retroperitoneal), and otherLMS (non-uterine/retroperitoneal) subgroups based on tumor origin sites
- Genomic data was analyzed for mutations, copy number aberrations, and fusions
- RNA expression profiling included evaluation of individual genes and gene set enrichment analysis (GSEA)
- P-value adjustment performed by the Benjamini-Hochberg procedure.

Results

Characteristic	All cases	Uterine LMS	Retroperitoneal LMS	Other LMS	P-value (Test)
Total, N specimens (% of total) - N patients (% of total)	1115 (100%) 1044 (100%)	701 (62.9%) 645 (61.8%)	166 (14.9%) 159 (15.2%)	248 (22.2%) 240 (23.0%)	--------
Median Age, years (SD) - Age Range, years	59 (11.7) 9-90+	*57 (10.7) 23-90+	63 (12.9) 21-90+	64 (12.5) 9-88	*P<0.0001 (Mann-Whitney U)
Female, N specimens - (% Female)	961 (86.2%)	*701 (100%)	*129 (77.7%)	*131 (52.8%)	*P<0.0001 (Chi-square)
Metastatic+Local recurrence, N specimens - (% Metastatic+Local recurrence)	561 (50.3%)	356 (50.8%)	81 (48.8%)	124 (50.0%)	P=0.82 (Chi-square)

Note: *uLMS age significantly lower than rpLMS and otherLMS.
Gender distribution significantly different between all pairwise group comparisons.

Table 1

Cohort Demographics:

- The study cohort was comprised of 62.9% uLMS (n=701), 14.9% rpLMS (n=166) and 22.2% otherLMS (n=248) specimens

Mutli-omic Results:

- LMS specimens most frequently harbored TP53 (64%, n=612), ATRX (30%, n=219), RB1 (22%, n=156), and MED12 (16%, n=94) mutations, with these genes accounting for 74.4% (n=1044) of all observed pathogenic/likely pathogenic mutations
- RB1 mutations were significantly less common in uLMS (15%) compared to rpLMS (30%, p<0.05) and otherLMS (33%, p<0.01)
- MED12 mutations were almost exclusive to uLMS (22% vs 1% rpLMS, 3% otherLMS, p<0.05)
- MAP2K4 copy number amplification were more common in rpLMS (22%, p<0.001) and otherLMS (14%, p<0.182) compared to uLMS (7%), with frequent co-amplification of nearby genes (FLCN, GID4, SPECC1, GAS7, PER1, and AURKB) located at chr17p11-13
- Actionable gene fusions involving ALK (2.1%, n=11), FGFR1 (0.2%, n=1), and NTRK1/2 (0.2%, n=1 each) were rare overall, with similar prevalence across subtypes
- Genomic alteration rates were not significantly different between rpLMS and otherLMS subtypes
- RNA expression profiling identified significant upregulation of PI3K/AKT/mTOR, DDR, WNT/Beta-Catenin pathway genes in non-uLMS
- GSEA indicated several immune-related gene sets were enriched in rpLMS and otherLMS compared to uLMS.

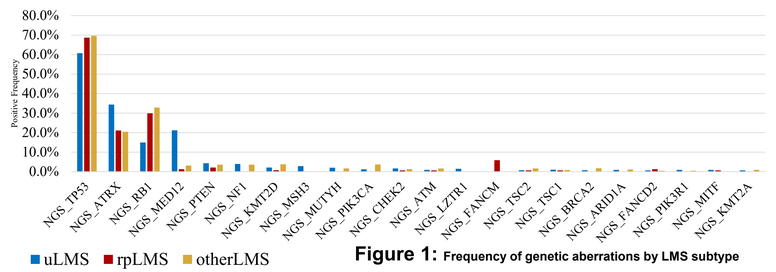

Figure 1: Frequency of genetic aberrations by LMS subtype

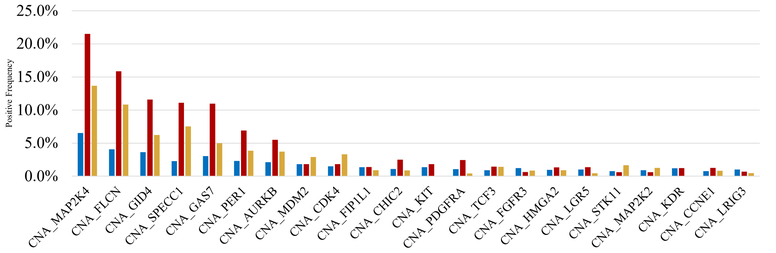

Figure 2: Frequency of copy number alterations by LMS subtype and gene

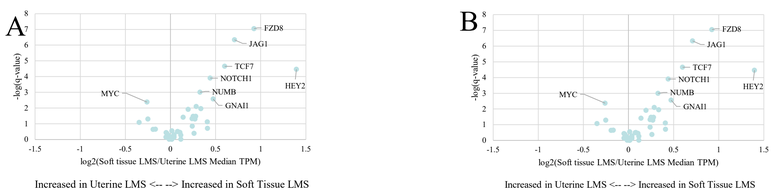

Figure 3: Relative upregulation of DDR (A) and WNT/Beta-Catenin (B) pathways in STLMS

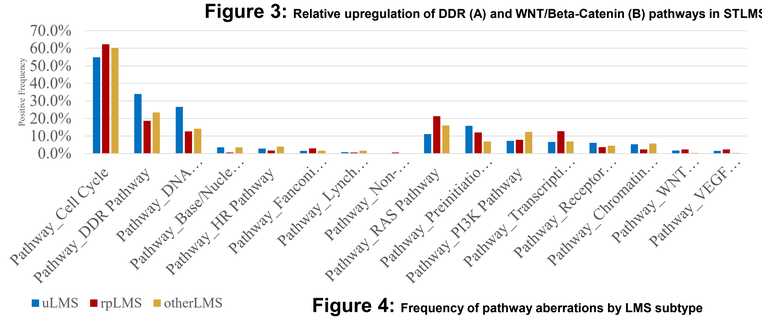

Figure 4: Frequency of pathway aberrations by LMS subtype

Discussion

- Uterine and ST-LMS both have remarkably few genetic aberrations with 4 genes accounting for 74.4% of all pathogenic mutations
- ST-LMS are largely driven by amplification of genes at chr17p11-13 as well as RB1 mutations
- Copy number alterations are largely absent in ULMS
- Actionable gene fusions are exceedingly rare, but overall consistent with pan-cancer observations
- Pathway alterations are driven by a single gene in that pathway (eg. ATRX in DDR pathway)
- ST LMS have significantly more active genomes than ULMS based on RNA expression profiling with significant upregulation of multiple cancer-associated pathways
- No genomic aberrations with associated with survival or response to chemotherapy, but this was limited by available clinical data

CONCLUSIONS

- Comprehensive molecular profiling suggests that LMS originating from the uterus represents a molecularly distinct disease compared to other primary sites of origin
- We identified key genomic patterns which have potential for targeted therapy
- These data provide insight for the framework of future clinical trials designed to separate uLMS from non-uLMS histologies, although further subdivision does not appear to be warranted

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