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

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Background

- Leiomysarcoma (LMS) is a rare group of mesenchymal malignancies found in the uterus, retroperitoneum, skin, or other soft-tissue sites1.
- 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 dramatically2.
- 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 clear3.
- 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 (NovoSeq)
- Specimens were stratified into uLMS, rLMS (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

- LMS specimens most frequently harbored TP53 (64%, n=612), ATRX (30%, n=219), RB1 (22%, n=156), and MED12 (12%, n=110) 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 rLMS (30%, p<0.005) and otherLMS (33%, p<0.01).
- MED12 mutations were almost exclusive to uLMS (22% vs 1% rLMS, 3% otherLMS, p<0.05).
- MAP2K4 copy number amplification were more common in rLMS (7%), frequent co-amplification of nearby genes (FLCN, GID4, SPECC1, GAS7, PER1, and AURKB) located at chr17p11-13 (7%), with frequent co-amplification of nearby genes (FLCN, GID4, SPECC1, GAS7, PER1, and AURKB) located at chr17p11-13.
- Actionable gene fusions involving AKT (2%, n=111), 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 rLMS 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 rLMS and otherLMS compared to uLMS.

CONCLUSIONS

- Uterine and ST-LMS both have markedly 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 survival or response to chemotherapy, but this was limited by available clinical data.

REFERENCES


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.

REFERENCES