Comprehensive characterization of molecular features distinguishing uterine leiomyoma from leiomyosarcomas

809P

X. Liu[1], X. Peng[2], T. Sun[1], X. Wei[2], X. Guo[2], H. Li[2], H. Yang[1]

[1]Department of Obstetrics and Gynecology, PUMCH - Peking Union Medical College Hospital/Beijing Xiehe Hospital - Dongdan Campus, Beijing, China,

[2]Precision Scientific (Beijing) Ltd., Beijing 100085, China

Background

Uterine leiomyosarcomas (LMS) is a highly aggressive but rare uterine tumor. However, it is almost impossible to distinguish LMS from the most common benign uterine leiomyomas (LM) through pre-operative diagnosis, leading to poor prognosis of LMS patients. Thus, it is clinically important to identify molecular differences between LMS from LM, which would not only advance our understanding on tumorigenesis of LMS but also lay a foundation for developing effective early detection strategy.

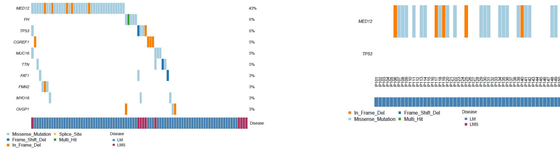
Methods

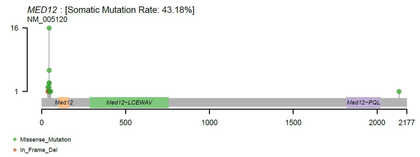
We performed whole-exome sequencing from 78 LM and 10 LMS treatment-naïve tumor samples along with their matched normal samples as well as RNA-sequencing on 4 LM and 10 LMS samples. We employed a comprehensive bioinformatics analysis based on WES and RNAseq data to identify differential molecular features between the two diseases. The first author has declared no conflicts of interest.

Results

❑ Mutational landscape difference between LM and LMS

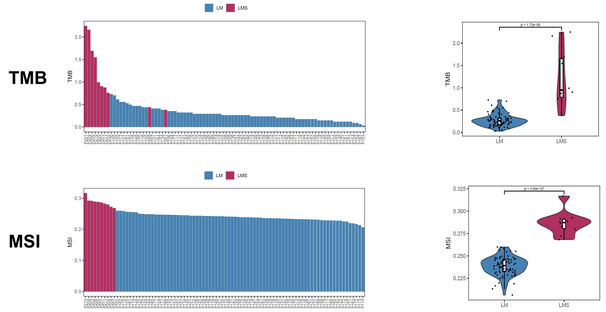
TP53 loss-of-function mutations were exclusively observed in LMS (5 out of 10 LMS samples, 0 out of 78 LM samples; Fisher's exact test, $p = 5.8\times10^{-5}$), whereas *MED12*, a cervical cancer driver gene, was significantly mutated in LM group (1 out of 10 LMS samples, 37 out of 78 LM samples; Fisher's exact test, $p = 3.9\times10^{-3}$).





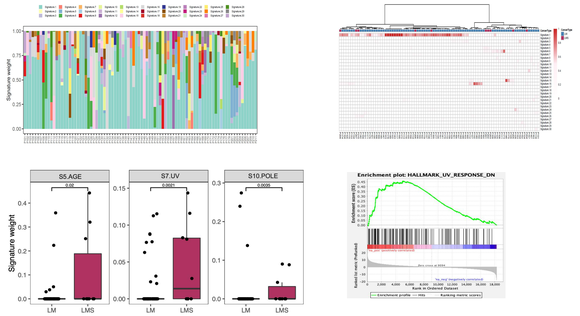
❑ Significantly higher tumor mutation burden and microsatellite instability in LMS

LMS tumors harbored a higher tumor mutation burden ($p = 1.72\times10^{-6}$, two-tailed Wilcoxon rank-sum test) and higher microsatallite instability ($p = 3.04\times10^{-7}$, two-tailed Wilcoxon rank-sum test).



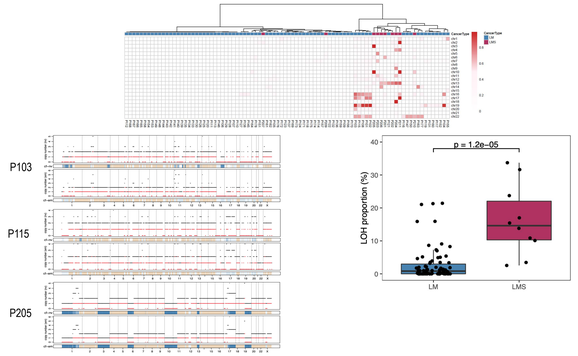
❑ Age, UV and POLE as the key factors responsible for higher mutation level in LMS

Compared with LM, mutational Signature 5, 7, 10 show relatively higher contributions in LMS (Signature 5, Age, $p = 2.0\times10^{-2}$; Signature 7, Ultraviolet, $p = 2.1\times10^{-3}$; Signature 10, POLE, $p=3.5\times10^{-3}$; two-tailed Wilcoxon rank sum test).Consistent with the Signature 7 signal, UV_response_DN pathway was significantly upregulated in LMS.



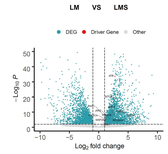
❑ Genome-wide loss of heterogeneity contributing to tumorigenesis in LMS

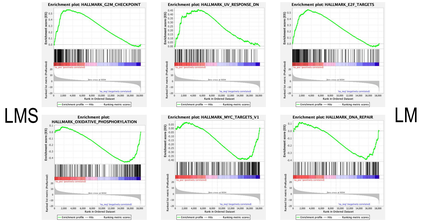
LMS tumors also showed much significantly higher fractions of loss of heterogeneity (LOH, $p=1.2\times10^{-5}$, two-tailed Wilcoxon rank sum test), suggesting the genome-wide instability.



❑ DNA repair pathway dysregulated in LMS

We also noted the well-known cancer hallmark genes are consistently upregulated in LMS, including *EGFR*, *BRAF*, *PIK3CA*, *PIK3CB*, *JAK1/2* and *mTOR*.





Conclusions

Using unbiased genome-wide molecular profiling data, we systematically identified the mutation and gene expression features that distinguish LMS from LM. LMS appears to be more driven by *TP53* mutations, accompanied with genome-wide instability and cancer-hallmark pathway dysregulation. These results will help develop biomarker-driven early detection methods for LMS.