Genomic, epigenomic and transcriptomic inter- and intra-tumor heterogeneity in desmoid tumors

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ABSTRACT

Desmoid tumors are histologically bland fibroblastic tumors that do not metastasize, but can frequently develop local recurrence even after complete resection. Desmoid tumors are considered neoplastic monoclonal proliferations and it remains unknown whether they undergo clonal evolution, as seen in malignant high-grade tumors. Previously published transcriptomic studies proposed two distinct prognostic signatures to predict recurrence of desmoid tumors. However, neither of these signatures were introduced into clinical practice and identifying markers predictive of recurrence after surgery remains a subject of active investigation. Here, we sought to develop a new prognostic signature for desmoid tumors and validate the previously published signatures. This analysis revealed substantial variability in the expression of distinct transcriptomic signatures within individual tumors, both in patients who did or did not progress. This observation led us to a comprehensive investigation of molecular intra- and inter-tumor heterogeneity of desmoid tumors. Multi-omic profiling showed remarkable heterogeneity of genomic, epigenomic and transcriptomic patterns within individual tumors, and between primary and recurrent tumors from the same patient. We also identified co-existing subclonal *CTNNB1* mutations in different regions of a recurrent tumor.

This study demonstrates an unexpected degree of intra- and inter-tumor molecular heterogeneity in desmoid tumors. Our analysis shows that prognostic classification based on gene expression signatures may vary substantially with the area of the tumor that is analyzed. Thus, molecular analysis of a single tumor biopsy may underestimate the magnitude of molecular alterations. Our multi-omic study also shows that recurrent desmoid tumors acquire multiple alterations that are not present in the patient-matched primary tumor. This study demonstrates that molecular intra- and inter-tumor heterogeneity is an important consideration in drug development and validation of prognostic and predictive biomarkers for desmoid tumors.