Molecular subtypes of osteosarcoma identified by reducing tumor heterogeneity through an interspecies comparative approach.

The heterogeneous and chaotic nature of osteosarcoma has confounded accurate molecular classification, prognosis, and prediction for this tumor. The occurrence of spontaneous osteosarcoma is largely confined to humans and dogs. While the clinical features are remarkably similar in both species, the organization of dogs into defined breeds provides a more homogeneous genetic background that may increase the likelihood to uncover molecular subtypes for this complex disease. We thus hypothesized that molecular profiles derived from canine osteosarcoma would aid in molecular subclassification of this disease when applied to humans. To test the hypothesis, we performed genome wide gene expression profiling in a cohort of dogs with osteosarcoma, primarily from high-risk breeds. To further reduce inter-sample heterogeneity, we assessed tumor-intrinsic properties through use of an extensive panel of osteosarcoma-derived cell lines. We observed strong differential gene expression that segregated samples into two groups with differential survival probabilities. Groupings were characterized by the inversely correlated expression of genes associated with 'G2/M transition and DNA damage checkpoint' and 'microenvironment-interaction' categories. This signature was preserved in data from whole tumor samples of three independent dog osteosarcoma cohorts, with stratification into the
two expected groups. Significantly, this restricted signature partially overlapped a previously defined, predictive signature for soft tissue sarcomas, and it unmasked orthologous molecular subtypes and their corresponding natural histories in five independent data sets from human patients with osteosarcoma. Our results indicate that the narrower genetic diversity of dogs can be utilized to group complex human osteosarcoma into biologically and clinically relevant molecular subtypes. This in turn may enhance prognosis and prediction, and identify relevant therapeutic targets.

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