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Targeting hyaluronic acid in desmoid tumors

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Desmoid tumors (DTs) are rare, mesenchymal tumors that exhibit features of an abundant wound healing process. Previously, we showed that mesenchymal stromal cells (MSCs) are constituents of DTs and may contribute to desmoid tumorigenesis via activities associated with wound healing. Hyaluronan (HA) is a long charged chain of repeating glucuronate and N-acetylglucosamine disaccharides that is synthesized by HA synthases (HAS) and degraded by hyaluronidases (HYAL). Hyaluronan is secreted into the extracellular matrix by injured stroma and is important for normal tissue repair and neoplastic progression. Here, we investigated the presence of HA in DTs and the anti-tumor effects of the HA inhibitor, 4-Methylumbelliferone (4-MU), on DT-derived mesenchymal cells. By immunohistochemistry and ELISA, we found abundant expression of HA in 29/30 DTs as well as >5-fold increased HA levels in DT-derived cell lines relative to controls. Immunohistochemistry also demonstrated high expression of HAS2 in DTs, and quantitative PCR analysis showed increased HAS2 upregulation in frozen DTs and DT-derived cells. 4-MU treatment of DT-derived cells significantly decreased proliferation as well as HA and HAS2 levels. Fluorescent immunohistochemistry showed that MSCs in DTs co-expressed HA, HAS2, HYAL2, as well as the major HA receptor CD44 and HA co-receptor TLR4. Taken together, our results suggest that paracrine regulation of HA signaling in DTs may contribute to MSC recruitment and tumor proliferation. Future studies investigating the role of HA in tumor-stroma crosstalk and inhibition of HA-MSC interactions as a novel therapeutic target in DTs and other solid tumors are warranted.