The following abstract was submitted for the 2024 DTRF International Research Workshop.

"Multiomic profiling uncovers integral immune molecules that drive the pathogenic fibroblast milieu in desmoid tumors"

Cristabelle De Souza, PhD

Postdoctoral Fellow
Stanford University

ABSTRACT

Soft tissue sarcomas (STS) are rare and diverse mesenchymal cancers with limited treatment options. Desmoid tumor Fibromatosis (DTF), is a locally aggressive soft tissue sarcoma that harbors CTNNB1 mutations. While desmoid tumors do not metastasize, they can grow aggressively and become intertwined in surrounding tissue—making it difficult for surgical resection. These tumors arise from fibrotic connective tissue which drive the onset of aggressive fibromatosis. Current therapeutic modalities for DTF have solely focused on tumor monitoring, surgery, chemotherapy, and a few targeted therapeutics like sorafenib, pazopanib and nirogacestat but research on their mechanisms are still underway. However, targeting key signaling pathways like the WNT signaling pathway could have significant off-target and on-target effects that could be detrimental. We have used multiomic profiling by combining spatial transcriptomics technology with next-generation sequencing in > 30 desmoid patient samples to uncover important molecules that are significantly expressed both at the transcript and protein level within the pathogenic fibroblast populations of DTF tumors. In addition to several novel molecules, we identified a new cell-surface marker called CD63 to be significantly elevated in the cells of primary desmoid patients. Further, we have uncovered for the first-time that the innate immune system plays a key role in modulating the pathogenic progression of fibroblasts in patients with desmoid tumors. Using functional characterization, cell culture models and in vivo testing we have dissected key molecular pathways that drive the pathogenic transition of the fibroblast subpopulations in DTF. Moreover, CD63 can be efficiently targeted using monoclonal antibody therapy with minimal to no side effects and we have developed a therapeutic reagent that has a strong potential to be developed clinically for the treatment of patients. Finally, our studies have identified novel proteins and mechanistic strategies that can be targeted to revert the fibrotic phenotype in patients. We expect that this work will provide knowledge pertinent towards understanding the underlying pathological mechanisms that promote fibrosis and contribute to aggressive DTF tumors ultimately providing a promising therapeutic to block tumor growth.