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Stroma-derived secreted factors increase desmoid tumor cell proliferation

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The tumor stroma, consisting mainly of mesenchymal cells, are known to support the maintenance of neoplastic cells. However, their role in soft tissue neoplasms, such as desmoid tumors, has been underexplored in part due to the difficulty in distinguishing between the mutant and non-mutant mesenchymal cells. Specifically, the lack of known reliable surface markers hinders our ability to compare, and study the interaction of, the tumor and stromal fibroblastic populations. First, we isolated and expanded single cells derived from desmoid tumor patient samples and used Sanger sequencing to identify mutant and non-mutant colonies. We then compared the expression of over 300 proteins known to be expressed on the cell surface by a high throughput flow cytometry-based screen. From this screen, we identified CD142 as a surface marker that is highly expressed by the mutant desmoid tumor cells. Next, we hypothesized that the non-mutant, CD142-low, population expresses soluble factors that can modulate the proliferation of the mutant desmoid tumor cells. Indeed, conditioned media derived from the non-mutant population increased the proliferation rate of tumor cells as measured by BrdU incorporation. To identify candidate soluble factors, we analyzed the secretome of non-mutant cells with a multiplex antibody array which detects over 100 known cytokines. We identified CCL2, CXCL12, and PTX3 to be secreted by the non-mutant population. Treatment of mutant tumor cells with these recombinant proteins increased their proliferation rate. Finally, we investigated downstream signaling components that may mediate the effect of these cytokines on tumor cell behavior. A multiplex phospho-kinase antibody array detected the activation of STAT6 upon mutant cell exposure to the non-mutant conditioned media. Treatment of tumor cells with the STAT6 inhibitor AS 1517499 counteracted the pro-proliferative effect of stroma-derived factors. In summary, we propose that non-mutant stromal cells can maintain the proliferation of mutant desmoid tumor cells via secreted factors and activation of downstream signaling components such as STAT6. Our increased understanding of the composition of desmoid tumors, and the cell-cell communication found within, highlights the complexity of this disease and identifies potential targets for future therapy.