Oncogenic effects of activated beta-catenin in desmoid fibromatosis

Aimee Crago, MD, PhD, Assistant Attending Surgeon, Memorial Sloan Kettering Cancer Center

Desmoid tumors are rare cancers that develop in the soft tissues. Desmoids do not metastasize, but local recurrence is observed in over 30% of patients following surgical resection. Local recurrence can be associated with significant pain, impaired joint function or, when recurrence is in the abdomen, with bowel perforation, infection, and death. Unfortunately, chemotherapy is not effective against this disease and the side effects associated with radiation can be prohibitive. For this reason, it is essential that we search for new ways to treat patients with advanced desmoid tumors. This project seeks to identify potential novel therapies by improving our understanding of the molecular events associated with desmoid formation.

In most cases, desmoid tumors are associated with a change in the gene that encodes beta-catenin. This event activates beta-catenin, which is an oncoprotein, and induces growth of desmoid cells. The exact mechanisms by which beta-catenin does this are not understood. We plan to characterize genes and signaling pathways which beta-catenin mutation can alter in the desmoid precursor cell, particularly the mitogen activate protein kinases, known to cause cancer in many tumors. We believe that beta-catenin causes the desmoid cell to secrete growth factors that signal mitogen activated kinases to make the desmoid cell grow. By understanding this pathway, we hope to determine which of the changes beta-catenin induces in the cell are important for formation of the cancer and test whether modulating affected pathways can provide a mechanism for treating desmoid tumors. We will also search for ways to predict which tumors will recur after surgery.

This research has important implications for not only patients with desmoid tumors but for those with a wide range of cancers. Beta-catenin pathways are often altered in other forms of soft tissue sarcoma as well as more common diseases such as colorectal cancer and pancreatic cancer, yet its effects on the cell have been difficult to target with drugs. Novel mechanisms, which are identified in this study as having potential benefit for treatment of desmoid tumors, may also be useful for the management of these more common lesions