DANA-FARBER CANCER INSTITUTE

CENTER FOR SARCOMA AND BONE ONCOLOGY

LIPOSARCOMA

RESEARCH DESCRIPTION

Reliable research models of liposarcoma are acutely needed for preclinical investigation of the disease and potential treatments. Such models help scientists identify the precise junctions where complex cellular pathways shift from normal to malignant function, and suggest potential targets for therapeutic intervention. Until recently, liposarcoma had not been effectively modeled. However, investigators at the Center for Sarcoma and Bone Oncology, led by Andrew Wagner, MD, PhD, collaborated with the laboratory of Ewa Sicinska, MD, to develop a panel of liposarcoma models that are a valuable resource for preclinical testing.

For many cancers, xenograft models – the transplant of tumor tissue into mice – are superior to other research approaches. Xenografts faithfully replicate an important genetic hallmark of liposarcoma – an anomaly in a portion of chromosome 12 that compromises tumor-suppressing programs through two different pathways, CDK4 and MDM2. Having both of these pathways activated at once exacerbates the cancer-driving effect. Since about 95 percent of liposarcomas have this trait, experimental treatments to disrupt this activation are being designed for patients with liposarcoma and other cancers driven by the same pathways.

The process through which cells grow and divide is controlled in part by the gene CDK4. When CDK4 is amplified, cells endlessly replicate and form a tumor. Dr. Wagner has tested an inhibitor of CDK4 activity in cell lines and in xenograft models, observing encouraging results in both. The inhibitor restored normal function to the cell growth cycle, and the tumor cells stopped growing. Dr. Wagner confirmed this finding with sophisticated imaging techniques that showed cancer cells were no longer using glucose, a necessary fuel for growth. Back in the clinical setting, Geoffrey Shapiro, MD, PhD, director of the Early Drug Development Center at Dana-Farber, is leading a phase I clinical trial of this CDK4 inhibitor as an experimental treatment for liposarcoma and a variety of other tumor types.

Another critical “brake” that normally prevents tumor formation by halting the cell cycle, initiating DNA repair, and regulating cell death, can be eliminated by amplification of the gene MDM2. Dr. Wagner’s preclinical tests with different MDM2 inhibitors have restored proper cell function. In xenograft models, when the mice stopped receiving treatment, their tumors did not grow back.

Dr. Wagner’s experiments are, to date, the most robust proof of principle for MDM2 inhibition against liposarcoma. On the basis of this data, Dr. Wagner is now leading a number of clinical trials testing different MDM2 inhibitors. The Center for Sarcoma and Bone Oncology’s leadership in clinical trials is based on the expertise of Dana-Farber’s physician-scientists and, in the case of liposarcoma, on research models that are not available elsewhere.