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Gene sequencing project finds family of drugs with promise for treating childhood tumor

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Drugs that enhance a process called oxidative stress were found to kill rhabdomyosarcoma tumor cells growing in the laboratory and possibly bolstered the effectiveness of chemotherapy against this aggressive tumor of muscle and other soft tissue. The findings are the latest from the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project and appear in the December 9 edition of the scientific journal *Cancer Cell*.

Oxidative stress is caused when oxygen-free radicals and other byproducts of cell metabolism build up in cells. This study offers the first evidence that rhabdomyosarcoma patients might benefit from drugs that harness the mechanism to kill cancer cells, including medications that are on the market or in development.

The results followed next generation, whole genome sequencing of the tumor and normal genomes of 16 tumors from 13 rhabdomyosarcoma patients. The findings were validated with more focused sequencing of tumors from an additional 37 patients. The analysis also provided new clues about why tumors recur.

"Overall, survival for patients with recurrent rhabdomyosarcoma is just 17 percent, and until now nothing was known about how tumors evolve in response to therapy," said corresponding author Michael Dyer, Ph.D., a member of the St. Jude Department of Developmental Neurobiology

and a Howard Hughes Medical Institute Investigator. "Clinically, we know that chemotherapy will kill the vast majority of tumor cells. This analysis suggests that a rare subset of tumor cells harbor different genetic alterations and that those cells serve as the seeds for the recurrence of rhabdomyosarcoma."

Based on the results, St. Jude plans to expand biopsies to include recurrent rhabdomyosarcoma tumors and possibly other solid tumors. Researchers said the importance of collecting tissue samples from recurrent tumors will grow as more targeted therapies become available.

"Studies like the current one involving rhabdomyosarcoma are giving us a close-up look at the way cancer evolves in response to treatment," said study co-author Richard K. Wilson, Ph.D., director of The Genome Institute at Washington University School of Medicine in St. Louis, where scientists have extensive expertise analyzing tumor recurrence using whole-genome sequencing. "When cancer comes back, it's genetically very similar to the original tumor but often with additional mutations that may give cancer cells new strategies to survive attack by whatever drugs are thrown at them. This makes a lot of sense but it's been hard to prove without whole-genome sequencing."

The study was part of the Pediatric Cancer Genome Project. Since its launch in 2010, the project has sequenced the complete normal and cancer genomes of 700 young cancer patients with some of the most aggressive and least understood cancers. The project has advanced understanding of the genetic origins of childhood cancers and helped to build a foundation for the next generation of cancer diagnostic and treatment tools.

About 350 new cases of rhabdomyosarcoma are identified each year in the U.S., making it the most common soft tissue tumor in children. Current therapies cure more than 75 percent of patients whose tumors

have not spread widely. The prognosis is worse, however, for other patients, including those with recurrent disease.

About 60 percent of rhabdomyosarcoma patients have tumors of the embryonal subtype, and about 25 percent have the alveolar subtype. This study showed the two subtypes have different genetic origins and involve a dramatically different number of chromosomal rearrangements, mutations and other gene variations.

Embryonal rhabdomyosarcoma included far more genomic alterations than alveolar subtype tumors. The results support the hypothesis that alveolar rhabdomyosarcoma is driven by a single chromosomal rearrangement. The result is a new gene created by fusing part of the FOXO1 gene with either the PAX3 or the PAX7 genes.

In this study, 58 percent of patients with intermediate or high-risk embryonal subtype tumors had mutations in genes, including NRAS, KRAS and HRAS, that make up the RAS pathway. The pathway helps to regulate cell division and is often deregulated in cancer cells. No RAS pathway mutations were found in alveolar rhabdomyosarcoma.

RAS pathway mutations were not the only changes that distinguished the normal and embryonal tumor genomes. "Based on mutations we found in the genome, there is evidence of high levels of oxidative stress in the tumors," Dyer said.

When researchers screened a library of more than 200 drugs and related compounds for activity against embryonal subtype tumor cells from three patients, the most promising results involved drugs that increased oxidative stress in tumor cells. The drugs killed cancer cells and also enhanced the effectiveness of chemotherapy. Drugs that targeted the RAS pathway showed little activity against the tumor cells.

"This suggests that altering the ability of tumor cells to handle that stress or increasing the stress just a bit is enough to push the cell over the edge and it dies," Dyer said. "This gives us novel and exciting new therapeutic options to pursue based on results from drug screenings of primary tumor samples from patients."

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