Study of “Exceptional Responders” Yields Clues to Cancer and Potential Treatments

A genomic study has uncovered molecular changes in tumors that may lead to dramatic and long-lasting responses to cancer therapy.

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In a comprehensive analysis of patients with cancer who had exceptional responses to therapy, researchers have identified molecular changes in the patients’ tumors that may explain some of the exceptional responses. The results demonstrate that genomic characterizations of cancer can uncover genetic alterations that may contribute to unexpected and long-lasting responses to treatment, according to the researchers.

The results appeared in Cancer Cell on Nov. 19. Researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, conducted the study in collaboration with investigators from other institutions, including NCI-designated Cancer Centers.

“The majority of patients in this study had metastatic cancers that are typically difficult to treat, yet some of the patient responses lasted for many years,” said Louis Staudt, M.D., Ph.D., director of NCI’s Center for Cancer Genomics, who co-led the study. “Researchers and the doctors who treat these patients have long been curious about the mechanisms underlying these rare responses to treatment. Using modern genomic tools, we can now start to solve these fascinating puzzles.”

“As clinical researchers, we have a lot to learn from these patients, and they have a lot to teach us,” said Percy Ivy, M.D., of NCI’s Division of Cancer Treatment and Diagnosis, who co-led the research. “The knowledge gained from studying exceptional responders can help inform how we take care of patients in the future and will help move us closer to the goal of precision oncology.”

The retrospective study, which is now closed to accrual, included detailed medical histories and tumor samples from 111 patients with various types of cancer who had received standard treatments, such as chemotherapy. The patients had been identified by NCI’s Exceptional Responders Initiative, a national project launched in 2014 to explore the feasibility of collecting and analyzing the data and biospecimens needed to better understand the biological basis of exceptional responses in cancer.

For 26 of the 111 (23.4%) patients, the researchers were able to identify molecular features that could potentially explain exceptional responses to treatment, such as the co-occurrence of multiple rare genetic changes in the tumor genome or the infiltration of the tumor with certain types of immune cells.

The study defined an exceptional responder as someone who had a partial or complete response to a treatment that would be effective in less than 10% of similar patients. The duration of an exceptional response is one that lasts at least three times longer than the median response time.

To analyze the tumor tissue (and normal tissue, when available) from patients in the study, the researchers used multiple genomic approaches—including analysis of DNA mutations, RNA expression levels, DNA copy number alterations, and DNA methylation—as well as analysis of the immune cells in the tumor microenvironment.

The mechanisms underlying exceptional responses in the study fit into several broad categories, including the body's ability to repair DNA damage and the immune system's response to tumors. Another category described rare combinations of genomic alterations that resulted in the death of tumor cells during treatment—a concept known as synthetic lethality.

For example, the researchers identified mutations in the BRCA1 or BRCA2 genes in two patients with cancers that rarely involve alterations in these genes, which help repair DNA. But in these patients, the researchers suggested, the mutations may have impaired the tumor's ability to fix damaged DNA, thereby increasing the effectiveness of treatments such as platinum-based chemotherapy that harm DNA.

"Our findings demonstrate the importance of testing patient tumors for alterations that may point to available treatments," Dr. Staudt said. "There is a need for a shift towards molecular diagnosis of cancer that provides information that cannot be gleaned from looking at tumors through a microscope."

The study also adds to the growing body of evidence highlighting the ability of the immune system to "kick in" and help eradicate tumors. In some patients in the study, increased levels of B lymphocytes, a type of immune cell, in tumors were associated with exceptional responses.

Results and hypotheses developed during this retrospective analysis will need to be confirmed by larger studies, according to the researchers. But if confirmed, the findings could potentially provide leads for investigators trying to develop treatments that exploit the vulnerabilities of tumor cells like those found in some exceptional responders, they noted.

For example, in two patients treated with the DNA-damaging drug temozolomide, the researchers identified two DNA-repair pathways that needed to be simultaneously inactivated to achieve an exceptional response. This finding supports the development of drugs that block these DNA repair mechanisms, which might generally improve the responses of patients with cancer to temozolomide.

“This proof-of-concept study demonstrates that the analysis of the tumors of exceptional responders is not only possible but necessary to learn as much as we can from these patients,” said Dr. Ivy. “We are immensely grateful to the many generous patients who participated in this study, even though they had nothing to gain personally from doing so, and to our many collaborators across the country, without whom this work would not have been possible.”

Since the Exceptional Responders Initiative began, researchers have reviewed the medical histories of more than 500 patients who had been recommended to the initiative by a physician. Chemotherapy is among the most widely used treatments for cancer, and the vast majority of the patients considered for enrollment in the initiative had exceptional responses to chemotherapy agents.

For the majority of the patients in the analysis, multiple genomic approaches were needed to characterize the tumor samples. Focusing on DNA mutations alone would not have provided the clues the investigators needed to develop hypotheses about the biological underpinnings of the responses, the researchers said.

More research and additional analytical approaches are needed to describe the molecular underpinnings of the unsolved cases of unexceptional responders, they noted. To encourage participation in this effort by investigators around the world, the NCI team and their colleagues have made their molecular profiling results and clinical information publicly available in the NCI Genomic Data Commons.

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