

Outside Influence: How Extrachromosomal DNA Fuels Cancer

Cancer cells store genes in circular pieces of DNA, known as extrachromosomal DNA or ecDNA, that defy the laws of genetics.

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Research has uncovered many strategies that cancer cells use to survive and proliferate in the body, from rewiring their metabolism to recruiting neighboring healthy cells to suppress the immune system. Recently, Damon Runyon alumnus and current Innovation Award Committee Member Howard Y. Chang, MD, PhD, and his colleagues at Stanford University, including Damon Runyon Fellow Xiaowei Yan, PhD, unveiled yet another strategy. Cancer cells store genes in circular pieces of DNA, known as extrachromosomal DNA or ecDNA, that defy the laws of genetics.

Scientists have known about ecDNA since the 1960s, but it was thought to be found in only a small percentage of tumors. By tracing oncogene after oncogene to its origin, Dr. Chang and his team have overturned this assumption: ecDNA is found in nearly a fifth of tumors, and contains many of the instructions cancer cells need to thrive.

Unfortunately for us, ecDNA has several advantages over chromosomes when it comes to passing on genetic material. For one, genes contained in these rings are transcribed four times more than equivalent sequences on chromosomes, a feat accomplished by the ecDNAs clumping together so that gene-enhancing proteins can promote gene expression on multiple rings at once.

Even more surprising, ecDNAs break the laws of inheritance outlined by Gregor Mendel over a century ago. According to the law of independent assortment, genes on different chromosomes are distributed between daughter cells independently of one another; inheriting gene A on chromosome X makes you no more likely to inherit gene B on chromosome Y. But ecDNAs, the team found, tend to be inherited together. If an offspring's cells have ecDNA A, they likely also have ecDNA B. Sometimes they even receive more copies of an oncogene than their parent possessed.

Plainly, this anomalous system of inheritance works to cancer's advantage. But its discovery is the first step toward targeting ecDNA as a form of cancer treatment. Dr. Chang and his team have homed in on an enzyme called CHK1, which coordinates the processes of DNA transcription and replication so that they don't interfere with each other. By administering a CHK1 inhibitor along with another cancer drug, the team was able to selectively kill ecDNA-containing cancer cells.

“Perhaps the most exciting finding is that oncogene expression from ecDNA hubs may present a new therapeutic vulnerability of cancer cells,” wrote Dr. Chang’s mentee, King L. Hung, PhD. “We are now working really hard to pinpoint this vulnerability. Stay tuned!”

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