Jumping Genes and the Dark Genome: a study with the collaboration of BSC offers a new insight into childhood cancers

This discovery has opened the path to a deeper study, currently taking place at BSC by the group led by David Torrents, to decipher the impact and the mechanism behind these rearrangements in cancer.

A new discovery published in the journal ***Nature Genetics*** identifies a mechanism for the triggering of solid tumors — including most types of cancers that affect children and young adults. Memorial Sloan Kettering (MSK) led the study with the collaboration of **Barcelona Supercomputing Center (BSC)**, New York Genome Center, University of Cambridge, among others.

Cancer is primarily a disease of the aged. A person's risk rises throughout the years as genetic mutations pile up, due either to copying mistakes when cells replicate or to ongoing exposure to certain environmental factors. Researchers have long been puzzled by why tumors develop in children, who presumably haven't had enough time for large numbers of random mutations to accumulate. This study points to a surprising cause: a gene called **PGBD5** that becomes abnormally activated during childhood. An enzyme made by the gene snips out DNA segments and flips them or moves them to a different location within the genome. This DNA transfer can drastically alter normal gene function and trigger cancer.

This landmark discovery suggests a cause behind the development of solid tumors, including most types of cancer that affect children and young adults. Rather than normal cells becoming cancerous as a result of random mutations, the PGBD5 gene itself produces the mutations and turns cells malignant. ***"This explains a long-standing conundrum as to how pediatric tumors develop and provides a whole new category of human cancers that result from this process,"*** says MSK cancer biologist and pediatric oncologist Alex Kentsis, who led the study. ***"We suspect similar mechanisms will be identified by future research, and their study should open new avenues of treatment."*** As further proof of PGDB5's effect, they found that expressing PGDB5 in normal human cells could turn them cancerous both in a lab dish and in mouse models.

The research team made its discovery by analyzing the genes of cells from human rhabdoid tumors. These rare childhood cancers are aggressive and can arise in many different organs, including the brain, kidneys, and liver.

The Dark Genome

PGBD5 was already understood to be a type of enzyme called a DNA transposase. A wide range of multicellular organisms use DNA transposases to control gene expression. They rearrange DNA segments known as transposons. This phenomenon was first uncovered in the 1940s and '50s by Barbara McClintock. In her studies of corn, she revealed that DNA segments can sometimes move, or transpose, from one site on a chromosome to another. This explains why corn can produce many colors of kernels on a single ear: The transposons alter the expression of pigment-controlling genes. This discovery about transposons — also called "jumping genes" — and how they affect gene expression brought Dr. McClintock the Nobel Prize.

Since then, similar DNA sequences have been found in most living organisms. Although it is now known that almost 50% of the human genome is derived from transposons, very few instances of their functions are known. Rather, they were considered artifacts of evolution, lying within the "dark genome" — the portion of DNA that doesn't code for proteins. But in recent years, scientists have come to understand that the dark genome, also referred to as junk DNA, actually serves important functions.

The role of BSC

The Computational Genomics group at BSC led by David Torrents is focused in the understanding of the role of genome rearrangements in the development and progression of tumors. Within this study, this group has analyzed the genomic rearrangements generated by *PGBD5*, identifying concrete deletions and loses of parts of the genome, as well as the associated sequence signatures that will make their identification much more direct. These results support and confirm the effect of this gene in turning normal cells into cancerous ones. This analysis was done using SMuFin, one of the tools generated by this group to find and classify genomic rearrangements in cancer genomes. This discovery has opened the path to a deeper study, currently taking place at BSC, to decipher the impact and the mechanism behind these rearrangements in cancer.

Reference:

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