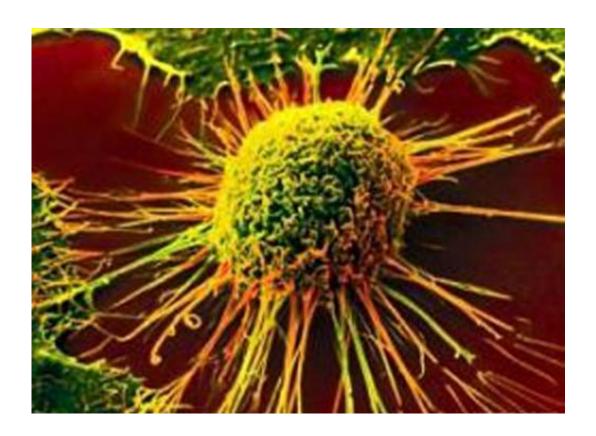# 'Dark matter' in cancer genome prompts immune response

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Researchers at the Icahn School of Medicine at Mount Sinai have discovered a group of non-coding RNA molecules in cancer cells that sets off an immune response because they appear to have features similar to those of pathogens. As a result of these molecules being expressed and amplified in cancer, the immune response they generate

may be influencing the cancer's growth, investigators say in their study, published in the *PNAS* early edition this month.

Their finding comes from probing the part of the genome's "dark matter"—an area known as satellite DNA—which produces large quantities of non-coding RNA (ncRNA) set apart from coding genes and mRNA. These largely mysterious RNA molecules do not produce proteins, but can have important regulatory roles.

"These ncRNAs are found in both human and mice cancer cells," said the study's senior investigator, Benjamin Greenbaum, PhD, an assistant professor at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai. "These areas were called 'junk DNA', but over the last five years researchers have come to understand this is the home of a number of functionally important ncRNAs."

Nina Bhardwaj, MD, PhD, Director of Immunotherapy and professor of Hematology and Medical Oncology at The Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai and co-senior investigator on this research, added, "Cancer appears to use these ncRNAs to stimulate an immune response that could encourage tumor growth and survival, although much remains unknown about their role."

"If further research defines these molecules as helping cancer grow it may be possible to either target and inhibit these molecules or use them as a marker to look for cancer development," she said. "On the other hand, research may show that they are mounting some sort of immune fight against cancer. In that case, we could try to boost that effort."

The multinational team used mathematical tools derived from theoretical physics to shine some light on ncRNA dark matter.

"We searched a large database of ncRNA for patterns of nucleotides that

were unusual," said Dr. Greenbaum, a computational biologist. "Think of the genome's sequence of nucleotides as words. In the human genome, some of the words are typically over- and under-represented. We wanted to know how these patterns differed in the RNA transcribed in cancers, such as those from satellite regions. The methods we used allowed us to analyze this big dataset much faster."

The team found that in several cancers where odd RNAs were being activated and transcribed, these unusual RNAs were substantially amplified —that is, many copies of them existed than were found in normal cells.

"These ncRNAs had unusual patterns that were similar to some pathogens and this causes them to stimulate an innate immune response," said Dr. Bhardwaj.

"All in all, we believe these ncRNAs may play a significant role in mediating immune responses against cancer," said Dr. Greenbaum. "But much work remains to describe their precise interactions."

More information: Antoine Tanne et al. Distinguishing the immunostimulatory properties of noncoding RNAs expressed in cancer cells, *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1517584112

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