Where DNA copying into RNA starts could determine whether cancer cells are receptive to treatment

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In research published in Nature Structural & Molecular Biology, researchers from the University of Birmingham have found that

transcription start sites (TSS) have a significant role in determining cancer cell behavior.

The team observed that cancer cells may be more vulnerable to radiotherapy when the point where they begin the process of DNA copying into RNA, known as transcription, using the less common 'YC' first-base-cytosine site rather than the more usual 'YR' adenine or guanine start sites.

The findings will enable researchers to further understand the process in which cancer cells proliferate and look for targets that could ensure that those cells are as vulnerable to lines of treatment as possible.

Dr. Joseph Wragg from the Institute of Cancer and Genomic Sciences at the University of Birmingham and a lead author of the study said, "These findings are hugely exciting for our understanding of gene regulation in cancers. The discovery of a significant difference in how a cancer cell behaves depending on this small detail in the replication process may lead to the ability to target these changes ourselves."

"This is especially exciting where we could potentially 'switch on' a vulnerability to radiotherapy or chemotherapy and it could make treatments quicker and more effective."

Dual initiating promoters

The team has previously looked at a key process involved in transcription in which a core promoter that supports the earliest stages of cell replication can have two different results.

The discovery of dual initiating promoters (DIPs) enabled the team to study how a small messenger RNA signal can lead to the significant change in cell behavior. Furthermore, the team found that up to 40% of

gene studies were capable of dual initiation.

Ferenc Mueller, Professor in Developmental Genetics in the Institute of Cancer and Genomic Sciences at the University of Birmingham and a co-lead author of the paper said, "Identifying the role that the start of a gene has in gene regulation has the potential to rewrite our understanding of how transcription and translation are coordinated in cancer, with implications for cell behavior, metabolism and treatment response."

"Future research will look at how different sites that we've identified that affect cell behavior are decided, including these dual initiating promoters. We will be looking specifically at how DIPs affect site selection across a range of contexts with a view to define how they determine where the transcription process begins."

More information: Joseph W. Wragg et al, Intra-promoter switch of transcription initiation sites in proliferation signaling-dependent RNA metabolism, *Nature Structural & Molecular Biology* (2023). DOI: 10.1038/s41594-023-01156-8

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