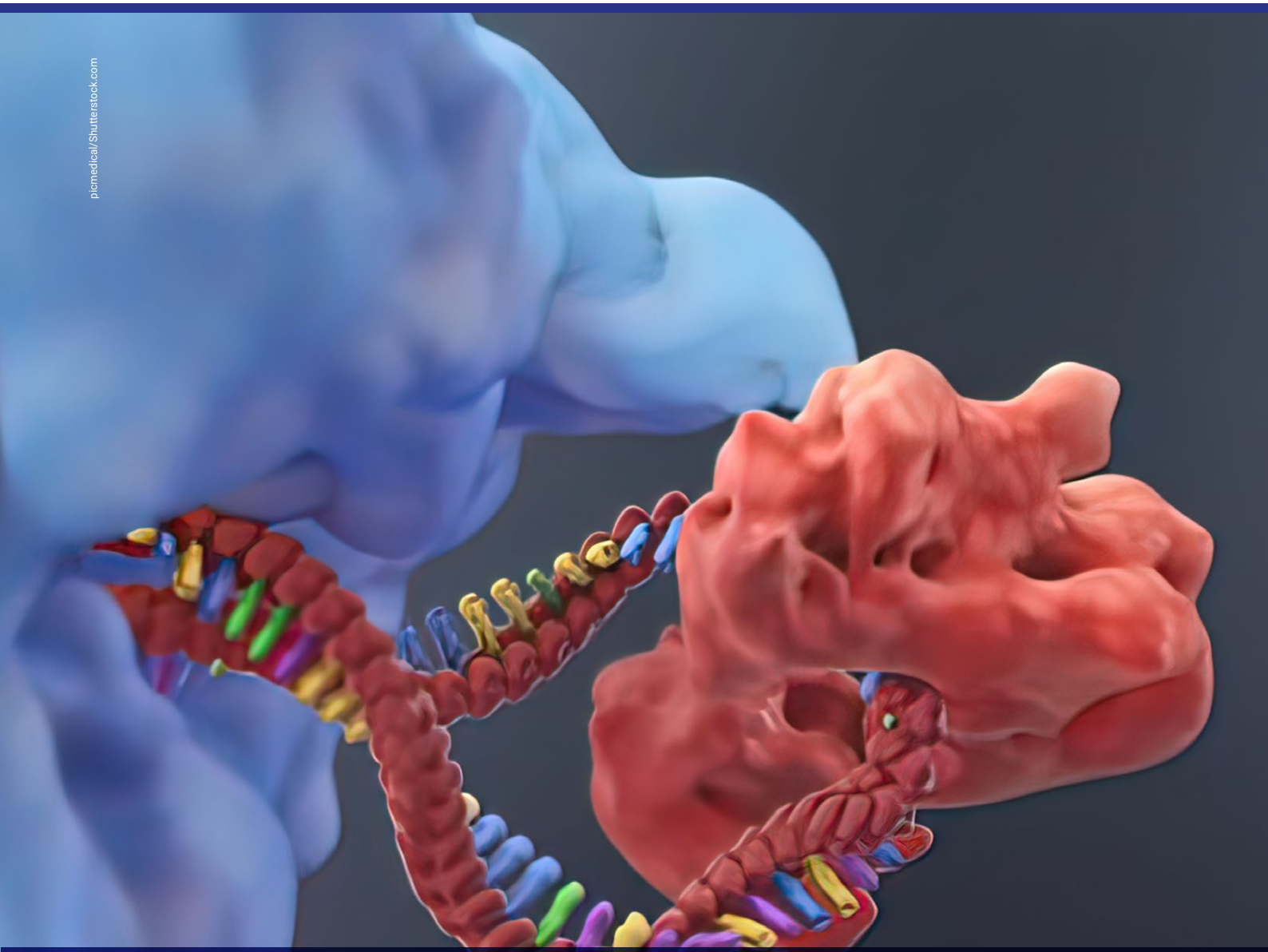

Adding structure to biology's central dogma for potential new cancer treatments

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Further reading

Sanghi, A, et al, (2021) Chromatin accessibility associates with protein-RNA correlation in human cancer. *Nature Communications*, 12, Article 5732.

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Adding structure to biology's central dogma for potential new cancer treatments

- Cancer alters chromatin, the structure of DNA, making it hard to detect and treat.
- Akshay Sanghi and colleagues at Stanford University, USA, have created a chromatin-based model that predicts protein creation in metastatic thyroid cancer.
- Their model can identify problematic proteins that establish the cancer's behaviour and, in doing so, reveal potential new approaches to treatment.

The 'central dogma' process is fundamental to biology and human life. Simply put, it is the process by which DNA codes for RNA (transcription) and RNA is translated into proteins (translation). Proteins are vital to the function of cells in our body. The process from DNA to RNA to proteins is, however, more complex, and changes in associated processes can lead to alterations in protein expression in disease. To understand these alterations in cancer, Akshay Sanghi and researchers at Stanford University, USA, built a predictive model using large-scale DNA, RNA, and protein data.

Their innovative genomics study demonstrates that protein expression is related to how accessible DNA is to the molecules (transcription factors) that read the DNA sequence to make RNA. Furthermore, the location of the accessible regions most predictive of protein expression are revealed to be inside or central to the gene body (proximal enhancer regions) and not in the distant regions as previous studies had indicated.

We know that cancer causes significant changes in chromatin, the structure of DNA – leading to reprogramming of a cell's growth and migratory abilities. Additionally, such reprogramming can enable a cancerous cell to fly under the radar, evading detection by the body's immune system. Cancer evolution is the process whereby tumours evolve and may develop characteristics that the original tumour did not possess. Such characteristics may include drug resistance and the ability to further adapt. Understanding how a tumour evolves may therefore help us develop new cancer therapies.

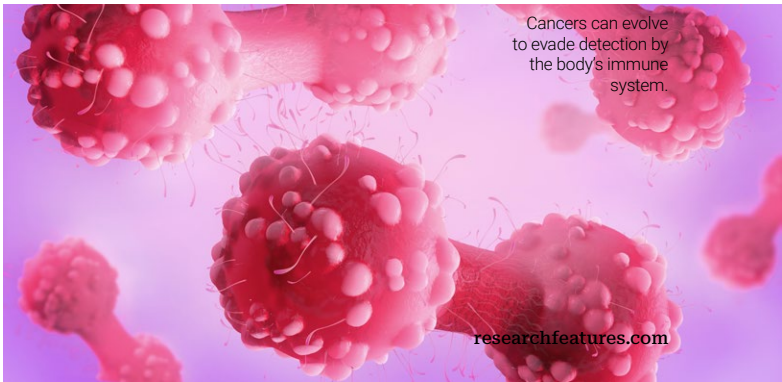
Chromatin consists of DNA strands, histones, and nucleosomes, tightly packaged into a condensed structure. Gene expression is regulated by the organisation of this structure and how easily proteins can access the DNA strands needed for transcription into RNA. DNA consists of a chain of nucleotide sequences which code for a particular messenger RNA (mRNA) which in turn codes for the building blocks of proteins (amino acids). Chromatin accessibility refers to the physical availability of DNA regions to participate and influence gene regulation (regions not blocked by molecules). Components such as enhancers, promoters, insulators, and chromatin-binding factors work together in a complex interplay to regulate gene expression. However, outside influences and stimuli can cause accessibility changes in our genome, altering gene regulation and leading to a pathogenic state.

Using an integration of proteomics and epigenomics, the researchers identified a group of proteins implicated in the progression of thyroid cancer.

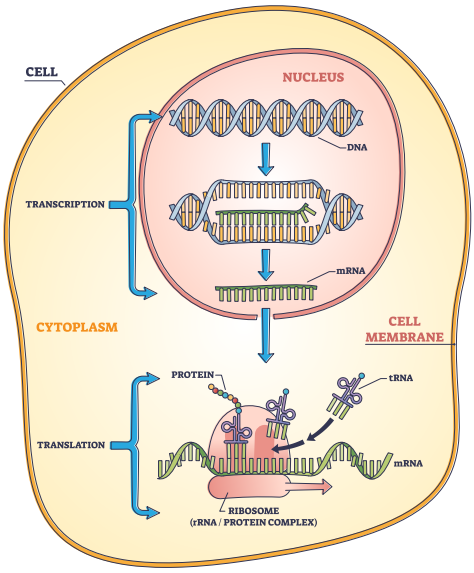
This recent study aimed to understand how cancer alters chromatic accessibility and subsequently the expression of proteins involved in its pathogenesis. Furthermore, it aimed to deepen our knowledge of the gene regulatory molecular mechanisms involved in the progression from normal tissue to tumour, and the divergence of tumours into different subtypes.

Using advanced multi-omics techniques to build a predictive model

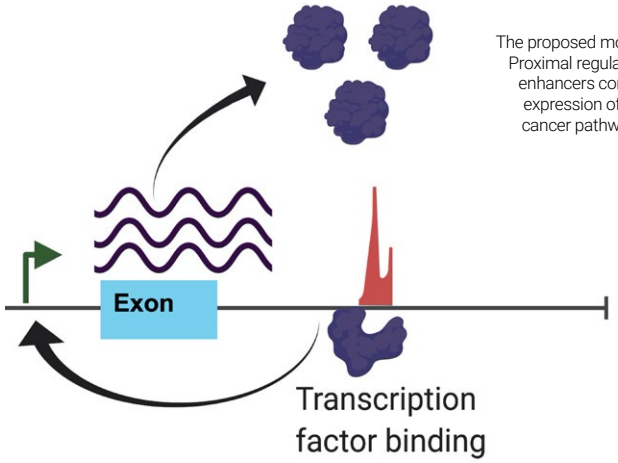
Recent advances in high-throughput technologies allow examination of vast quantities of molecules, including chromatin (epigenomics), RNA (transcriptomics), and proteins (proteomics). Because RNA is translated into proteins, the amount of RNA present (RNA abundance) is thought to relate to the amount of protein. However, studies have shown that this is not always the case and, depending on the context and condition, protein–RNA correlation can be low. Much like DNA accessibility, RNA abundance contributes to the regulation of gene expression, so to truly understand the strongest predictors of gene expression, markers of both DNA accessibility and RNA abundance were included in an integrated model to predict protein expression.



Cancers can evolve to evade detection by the body's immune system.



Gene expression: Cellular structure with nucleus transcription and protein translation stages.



The proposed model: Proximal regulatory enhancers control expression of key cancer pathways.

Through gaining such an understanding of the relationship between the chromatin landscape and gene regulation, epigenetic targets for treatment are revealed.

The model was then evaluated in thyroid cancer tissue and patient matched healthy tissues enabling better understanding of tumour regulatory mechanisms. The model was further validated in samples from human breast cancer patients. Using an integration of epigenomics, transcriptomics, and proteomics (epigenoproteomics), the researchers identified a connected group of proteins implicated in the progression of thyroid cancer. These proteins are genes that have correlated RNA-protein, indicating they are active in thyroid cancer. The results are the first to show that enhancer regions located within the gene body most notably influence gene expression in thyroid cancer. Specifically, these enhancers are predicted to initiate the transcription and translation processes required in gene regulation.

Implications for cancer research

So, how does this study contribute to cancer research and what could this mean for thyroid cancer patients? Firstly, by successfully building a predictive model, the study confirms the benefit and utility of employing multi-omics techniques to gain understanding of disease mechanisms. Through gaining such an understanding of the relationship between the chromatin landscape and gene regulation, epigenetic targets for treatment are revealed. Vitally, it bridges the process of gene expression and tumour phenotypes, expanding our understanding of the molecular mechanisms leading to tumour phenotypes.

This research also gives vital information about the molecular mechanisms of tumour phenotypes and has immense potential to enable the study and understanding of aggressive cancer biology. The creation of this multi-omics model and identification of gene regulatory mechanisms implicated in two types of cancer gives promise that treatments targeted at the relevant molecules could be developed and tested. It is hoped that this scientific finding one day translates into real-world benefit for cancer sufferers worldwide.

Personal response

How will you advance the understanding of epigenoproteomics established in this study?

The canonical thinking about cancer evolution is mutations drive cancer phenotypes, but our lab is conducting further investigation to prove that our predictive model is independent of mutational signature. Thyroid cancer is an exciting model to assess this question as it has the lowest mutational burden of all adult tumours. Using bulk data, we have identified key epigenoproteomic links that are ubiquitous and independent of thyroid mutational drivers. We are currently assessing whether these epigenoproteomics can drive cancer phenotypes, which would suggest a big shift in our understanding of cancer drivers.

To take epigenoproteomics to a more microscopic level, we are assessing the heterogeneity of the key epigenetic-protein links at the single cell level. Using inference strategies that consider bulk and single-cell data from the same thyroid cancer samples, we can assess whether epigenetic-protein links are maintained at the single cell level.

Can you apply this epigenoproteomic framework to other cancers?

This study provides a framework for how to link dynamic epigenetic states to protein expression. We show that cancer tissues gain proximal enhancers that are predicted to drive protein expression. Our findings support a model that can be leveraged to dissect epigenetic-driven evolution in cancer phenotypes. Our lab has been doing large-scale bulk and single multi-omics on other cancers besides thyroid cancer. We are generating ATAC-seq, RNA-seq, and proteomics data such that we can apply the epigenoproteomic framework in other phenotypes. A main interest is applying epigenoproteomics to pre-cancer tissue, and multiple regions within a disease-burdened tissue. These studies aim to assess whether the framework proposed in this study is preserved throughout the cancer evolution process.

What technology is needed to advance investigations in epigenoproteomics?

Another interesting question is can we detect epigenetic-protein links at the single-cell level? Our data so far has shown that a bulk system (such as a tumour) links proximal enhancers to protein expression. However, a single-cell system is much more susceptible to stochastic processes that could scramble such a direct link. To assess whether our framework applies to the smallest scale, we are interested in developing single-cell tools that can quantify chromatin occupancy in tandem with RNA and protein abundance. Currently, the technology is limited to only measuring chromatin states and RNA abundance in an individual cell but adding the protein data would be a game-changer. Semi-quantitative approaches to measuring protein in single cells exist, and current approaches have yet to truly achieve quantitative DNA, RNA, and protein data from a single cell. Such a technology would propel the field in understanding how individual cells utilise epigenetic states for protein expression.

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