Mapping the Epigenetic Landscape of Glioblastoma Progression

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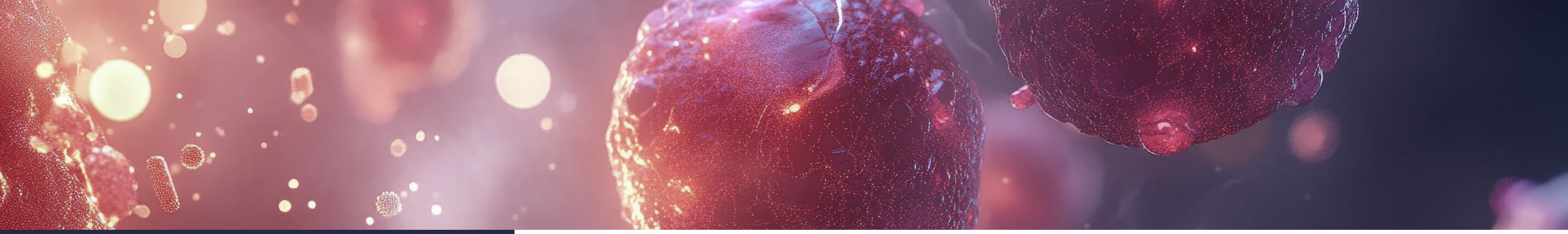


Mapping the Epigenetic Landscape of Glioblastoma Progression

Glioblastoma, the most aggressive form of brain cancer, continues to challenge medical professionals with its poor survival rates. Recent groundbreaking research by Dr Silvia Remeseiro and her colleagues at Umeå University in Sweden has shed light on the complex epigenetic and chromatin-related mechanisms underlying the communication between neurons and glioma cells. This research opens new avenues for understanding and potentially treating this formidable disease.

The Epigenetic Frontier of Glioblastoma

Glioblastomas stand out as the most aggressive and common type of brain tumour in adults. Despite significant research efforts, clinical outcomes have remained stubbornly poor, with only 4% of patients surviving five years post-diagnosis. The complexity of glioblastoma lies not only in its genetic makeup but also in its ability to hijack normal cellular processes for its own growth and spread.

Dr Silvia Remeseiro's team has made significant strides in unravelling the epigenetic intricacies that drive glioblastoma progression. Their research, published in Nature Communications, reveals how the three-dimensional organisation of DNA influences the development and aggression of glioblastoma tumours. At the heart of glioblastoma's aggressive nature lies a complex interplay between gene promoters and enhancers – specific regions of DNA that control gene expression.

The research team mapped out these regulatory systems using advanced laboratory techniques, comparing samples from glioblastoma patients with non-cancerous controls. Their findings revealed significant alterations in the 3D structure of DNA within glioblastoma cells. These changes disrupt the delicate balance of enhancer-promoter interactions, leading to aberrant gene expression. Specifically, they observed a loss of long-range enhancer interactions coupled with a gain of promoter-promoter interactions. This restructuring was accompanied by increased promoter activation, resulting in the dysregulation of genes critical for normal brain function and development, paving the way for tumour growth and invasion.

The Epigenetic Basis of Neuron-Glioma Communication

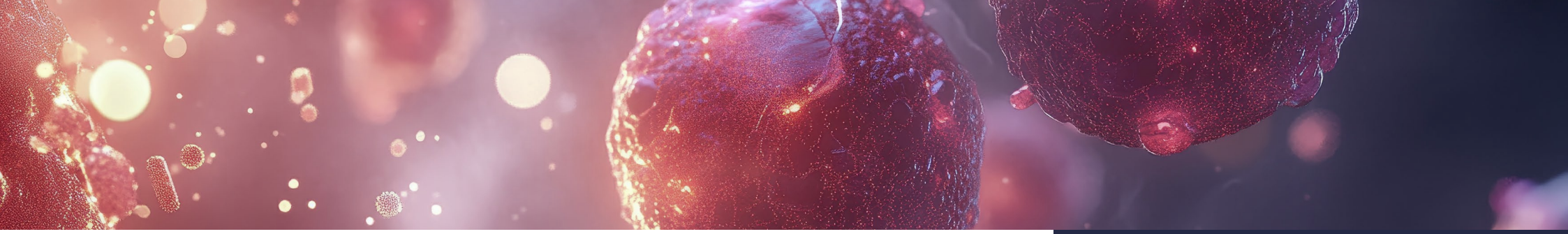
One of the most striking discoveries is the role of epigenetic factors in facilitating communication between neurons and glioma cells. The research team identified key players in this process, including the proteins SMAD3 and PITX1. These proteins bind to and control enhancers whose activity is altered in glioma cells, promoting the expression of genes mediating nerve-to-tumour communication.

Furthermore, the acquisition of super-enhancers by cancer cells drives the expression of oncogenes, further fuelling tumour progression. Changes in chromatin accessibility and histone modifications around enhancers and promoters contribute to the altered gene expression profile of glioblastoma cells, creating a perfect storm for tumour growth.

Neurogliomal Synapses – The Epigenetic Bridge

The formation of neurogliomal synapses – true synaptic connections between neurons and glioma cells – represents a paradigm shift in our understanding of glioblastoma progression. Dr Remeseiro's work reveals how epigenetic changes underpin this process. Epigenetic alterations drive the expression of synaptic proteins in glioma cells, enabling them to form functional synapses with neurons. The team found evidence of epigenetic control over the expression of multiple genes encoding proteins crucial for receiving synaptic signals from neurons.

Moreover, epigenetic changes facilitate the formation of a glioma network that amplifies and synchronises calcium signals, promoting tumour growth. This intricate web of epigenetic modifications creates a conducive environment for the aggressive spread of glioblastoma. The discovery that neurogliomal synapses transmit electrical signals to tumour cells and drive tumour progression has revolutionised brain cancer research in recent years.



The Role of Neuronal Activity in Glioma Progression

In the central nervous system, cancer development is influenced by interactions between neurons and tumour cells. Neuronal activity promotes glioma progression through activity-regulated secretion of paracrine growth factors, including NLGN3, IGF-1, and BDNF, and electrochemical communication mediated by synapses between neurons and glioma cells. These neurogliomal synapses provide glutamatergic synaptic signalling between neurons and glioma cells, promoting both tumour cell proliferation and invasion.

The electrochemical signals are amplified in a glioma network that spreads calcium signals. In this network, glioma cells are connected to each other through microtubes with 'gap junctions'. Among other functions, the glioma network can amplify and synchronise depolarising currents in the tumour cell network via central pacemaker cells. This results in a rhythm of periodic depolarisation similar to a heartbeat within the tumour, which is crucial for tumour growth. Membrane depolarisation is a phenomenon that promotes glioma cell proliferation through mechanisms that remain to be fully understood.

Glioma cells can, in turn, release synaptogenic proteins that promote neuronal hyperexcitability and functional remodelling of neural circuits, increasing neuronal activity in the tumour environment and promoting glioma progression. Understanding these critical interactions between neurons and glioma cells will be essential for improving the prognosis of such a difficult-to-treat cancer as glioblastoma.

Beyond Gene Mutations: The Importance of Enhancers

In cancer genomics, the focus has traditionally been on searching for mutations in key cancer-related genes. However, Genome-Wide Association Studies (GWAS) have shown that most mutations that increase cancer risk are found in DNA regions that do not contain genes but can influence how genes function. This is because DNA contains so-called enhancers or 'switches' that ensure the right genes are activated in the right cells at the right time. Precise control of gene expression is crucial for normal cell function. Errors in these enhancers can lead to changes in gene expression, which, over time, can result in cancer or other diseases.

The three-dimensional organisation of DNA is crucial for mediating physical contact between distant enhancers and gene promoters, necessary for normal gene expression. Abnormalities in how enhancers interact with gene promoters can also lead to changes in gene expression and, ultimately, cancer. Various mechanisms – including structural and epigenetic changes, as well as mutations – can lead to the acquisition of oncogenic enhancers that drive the expression of key cancer-related genes.

Therapeutic Implications and Future Directions

The elucidation of these epigenetic mechanisms opens up exciting new possibilities for glioblastoma treatment. Targeting specific enhancer-promoter interactions could potentially slow tumour growth and increase sensitivity to existing treatments. The identification of key epigenetic regulators like SMAD3 and PITX1 provides new targets for drug development, paving the way for more targeted therapies.

Integrating epigenetic-targeted therapies with existing treatments like temozolomide could improve efficacy and patient outcomes. Furthermore, developing strategies to interrupt the epigenetic processes underlying neurogliomal synapse formation could significantly impede tumour progression. Similarly, epigenomic disruption of *EGFR* enhancers has been found to reduce the proliferation and migration of glioblastoma cells and make them more sensitive to temozolomide, the current drug used clinically to treat glioblastoma patients.

Dr Remeseiro's groundbreaking work has unveiled the critical role of epigenetics in the aggressive nature of glioblastoma.

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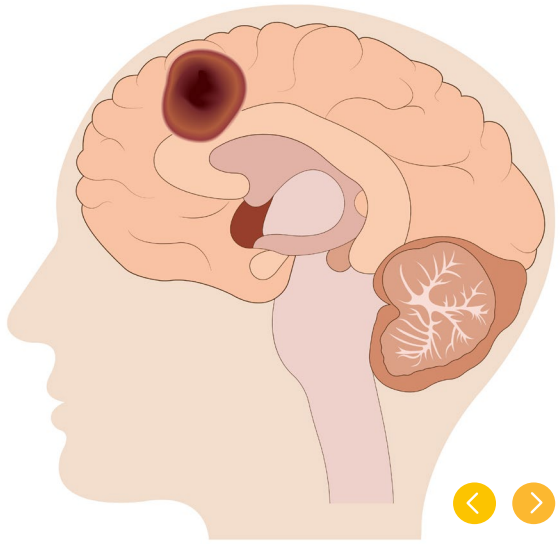

By elucidating the chromatin-level changes that facilitate neuron-glioma communication, this research paves the way for novel therapeutic approaches. While continuing to unravel the epigenetic landscape of glioblastoma, hope grows for more effective treatments and improved outcomes for patients facing this formidable disease. The discovery could lead to a paradigm shift in the treatment of glioblastoma, potentially allowing to combat the disease by controlling the proteins that regulate key genes and thereby blocking the communication between nerve cells and brain tumours.

MEET THE RESEARCHER

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Dr Silvia Remeseiro obtained her PhD at one of Europe's leading cancer research facilities, the Spanish National Cancer Research Center (CNIO) in Madrid. Following this, she was awarded a Marie Curie/EIPOD postdoctoral fellowship and joined the prestigious European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. Presently, Dr Remeseiro leads her own laboratory at the Department of Medical and Translational Biology, is a Wallenberg Fellow in Molecular Medicine, and holds the position of Associate Professor in the Umeå University Faculty of Medicine. Whilst Dr Remeseiro has conducted extensive research on the role of genetics in cancer, her current research focuses specifically on studying the interplay between long-range gene regulation and the 3D chromatin organisation in glioblastoma. Dr Remeseiro is the recipient of significant funding grants from the Swedish Research Council, Cancerfonden and Knut and Alice Wallenberg Foundation, among others, has been at the helm of several long-standing research projects, and has authored numerous publications in highly regarded journals.

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FURTHER READING

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