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# Long-range gene regulation and 3D organization of the glioblastoma genome

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## Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till offentligt försvar i Aula Biologica, Biologihuset, torsdag den 30 januari 2025, kl. 09:00.

Avhandlingen kommer att försvaras på engelska.

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**Abstract**
Alterations in 3D chromatin organization and epigenetic regulation drive cancer progression. Here I use glioblastoma (GB) as a model to understand the broad impact of epigenetic changes on tumour biology. By mapping the promoter-enhancer interactome and chromatin states in GB, we uncovered extensive rewiring of chromatin architecture that leads to the activation of gene networks associated with synaptic communication, axonogenesis, axon guidance, and chromatin remodelling. Central to these networks are transcription factors (TFs) such as SMAD3 and PITX1, identified as key players in gene regulatory networks (GRNs) mediating neuron-to-glioma synaptic communication. Moreover, we showed that tumour growth can be affected by modulating the activity of TFs, such as SMAD3, which mediates neuron-to-glioma synapses. These findings highlight how epigenetic changes and reorganization of 3D genome topology enable GB cells to integrate neural signals and translate them into a proliferative response.

Through epigenetic perturbation of novel *EGFR (Epidermal Growth Factor Receptor*) enhancers, we observed a reduction in GB cell proliferation and invasion, alongside increased sensitivity to the chemotherapeutic agent temozolomide (TMZ). Therefore, targeting specific regulatory regions can also influence tumour cell behaviour, though to a lower extent than targeting complete GRNs via TF modulation.

Additionally, using Multi-Omics Binary Integration via Lasso Ensembles (MOBILE), a Machine Learning (ML)-based tool, we identified novel GRNs impacted by the rewiring of GB's epigenetic landscape and critical for GB pathogenesis. Among them, GABA signalling emerged as a previously unrecognized driver of GB tumour progression.

In summary, this work advances our understanding of how epigenetic regulation and 3D chromatin architecture shape the gene expression landscape of glioblastoma tumours. It paves the way for novel therapeutic strategies targeting chromatin regulators and GRNs to tackle difficult-to-treat cancers, such as glioblastoma.

**Keywords**
3D genome, enhancer, chromatin loops, epigenetics, gene regulation, glioblastoma, GRNs, neuron-to-glioma synapses, machine-learning.

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