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Press Release

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New insights into Glioblastoma invasiveness

Luxembourg Institute of Health (LIH) identifies protein that activates genes involved in malignant brain tumour growth and expansion

*Researchers from the [NORLUX Neuro-Oncology Laboratory](#) at the LIH Department of Oncology (DONC) explored the molecular mechanisms responsible for the ability of Glioblastoma (GBM) to infiltrate and spread to healthy brain tissue. They brought forward the novel role of protein ZFAND3 in activating several genes that stimulate the adhesion and penetration of GBM cells in the surrounding parenchyma, the functional tissue in the brain. The findings, which carry significant implications for the development of novel therapeutic strategies against GBM, were published in the prestigious international journal *Nature Communications*.*

One of the hallmarks of Glioblastoma (GBM), the most aggressive type of brain cancer, is its high invasive capacity, which leads to its expansion into the neighbouring normal brain tissue. GBM cells insinuate themselves in the space of the neural tissue and migrate along blood vessels to more distant locations where they then metastasise. 'Stray' cancer cells can therefore escape surgical resection, radio- and chemotherapy, thereby accounting for the limited success of current treatment approaches and for the poor patient prognosis observed. Novel molecular targets that regulate invasion and that can be leveraged during drug development are therefore a priority in modern-day oncology.



The NORLUX Neuro-Oncology Laboratory team at the LIH Department of Oncology (DONC)

"In this context, we sought to elucidate the genes responsible for GBM invasiveness and the specific molecules that 'switch' them on", says Prof Simone Niclou, Director of the LIH Department of Oncology and corresponding author of the publication.

Using a molecular biology technique commonly used to uncover the function of a gene and its effects on the functioning of the cell, the scientists found a set of genes associated with GBM proliferation, some of which previously known to be involved in invasion and metastasis. This selection was further narrowed down by analysing the differences in their expression in non-invasive versus invasive GBM cells. The team found the gene coding for the AN1-Type Zinc Finger protein 3 (ZFAND3) to be significantly more active in invasive cells compared

non-invasive cells. Invasive cells located in the periphery of the tumours consequently presented higher amounts of the resulting ZFAND3 protein.

“When we deactivated the ZFAND3 gene in highly invasive GBM cells, we observed that colonisation of healthy tissue was significantly impaired, indicating that ZFAND3 plays a key role in promoting GBM invasiveness”, explains Dr Anne Schuster, first author of the publication. “Similarly, when we over-activated the ZFAND3 gene in non-invasive GBM cells in mice, we noticed that the tumour lost the well-defined growth pattern typical of non-invasive tumours, and that the number of cells escaping the primary tumour increased considerably, further confirming that ZFAND3 confers invasion potential to GBM cells even if they were initially non-invasive”, adds Eliane Klein, second author of the study.

The team went a step further and sought to unravel the precise mechanism behind the ability of ZFAND3 to induce infiltration. They noted that ZFAND3 acts directly in the nucleus of the cell, where it interacts closely with several other proteins to stimulate the activation of a series of invasion-related genes, thereby resulting in the aggressive behaviour that characterises highly invasive GBM cells.

“In essence, our work has brought forward ZFAND3 as a novel key regulator involved in the malignancy of GBM, thereby providing a new and much needed potential target against which future drugs may be directed”, concludes Prof Niclou.

The findings were published in December 2020 in the renowned journal Nature Communications, with the full title “AN1-type zinc finger protein 3 (ZFAND3) is a transcriptional regulator that drives Glioblastoma invasion”.

Funding and collaborations

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The study was performed in close collaboration with national and international partners, and involved LIH’s Department of Oncology, including NORLUX Neuro-Oncology Laboratory and the Functional Tumor Genetics group, LIH’s Quantitative Biology Unit, the National Center of Genetics of the Laboratoire National de Santé (LNS), the University of Heidelberg (Germany), the University of Bergen (Norway), Odense University Hospital (Denmark) and the University of Southern Denmark (Denmark).

About the Luxembourg Institute of Health: Research dedicated to life

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