Project Details	
Project Code	NMH27Ca Siebzehnrubl
Title	From Multi-OMICs to mechanism: understanding the links between protein turnover and therapy resistance in glioblastoma stem cells
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	How do glioblastoma stem cells evade therapy and drive tumour recurrence? This project will address this question by investigating how FGF2-FGFR1 signalling regulates protein homeostasis in these highly aggressive cells. Using patient-derived models, multi-OMICs datasets, proteomics and functional laboratory assays, you will identify novel molecular mechanisms underlying stemness and treatment resistance. The project combines computational and experimental approaches, providing broad training in cancer biology, bioinformatics and molecular techniques. You will have the opportunity to develop your own analytical strategies, help prioritise candidate genes for validation, and contribute directly to discovering new therapeutic opportunities for brain cancer.
Description	Background Brain cancer affects almost 10.000 patients/year in the UK. The most frequent of these cancers in adults is glioblastoma (GBM), which is invariably lethal. GBMs are highly heterogeneous cancers, which constitutes a tremendous obstacle to the development of effective therapies. GBM cancer stem-like cells (GSCs) are key to the formation, maintenance, recurrence, and resistance of GBM tumours. Therefore, our overall aim is to increase understanding of functionally relevant molecular mechanisms which define GSCs and to develop new tools to identify this subpopulation in experimental settings and human patient datasets. In previous work funded by 2 MRC project grants, we identified the FGF2-FGFR1 signalling axis as an important regulator of GBM stemness and showed that GSCs can be distinguished from other GBM cells based on high FGFR1 status. FGF2-FGFR1 signalling constitutes an Achilles' heel of GBM, but to leverage this for improved therapy we first need to better understand how this signalling cascade controls stemness in GBM. The stem cell-associated transcription factor ZEB1 is an essential downstream effector of FGF2-FGFR1 signalling, and pilot data indicates that ZEB1 regulates expression of the E3 ubiquitin ligase HECTD4. This links FGF2-FGFR1 signalling directly to proteostasis and suggests a potential GSC-specific mechanism for controlling protein turnover. Pilot data support that protein levels in GSC are different from other GBM cells, which may enable GSCs to resist anti-cancer therapies. Better understanding of the molecular mechanisms acting to maintain GBM stemness will allow identifying new targets to overcome therapy resistance. Key research question This project will evaluate how proteostasis is controlled in GSCs compared to other GBM cells, and specifically how FGF2-FGFR1-ZEB1-HECTD4 signalling affects the GSC proteome. We will address this question using multi-OMICs data generated in a previous MRC-funded project, state-of-the-art experimental models, as well as with new proteomic analysis.

	The specific objectives of the project are: Objective 1) Define targets of FGF2-FGFR1 signalling in GSCs. In previous work, we have already identified ZEB1 as transcription factor induced by FGF2-FGFR1 signalling. Pilot data indicate HECTD4 as additional downstream effector. In this objective, we will take an unbiased approach to identify additional downstream targets of FGF2-FGFR1 signalling using comparative analysis of existing single cell and bulk sequencing as well as kinome profiling datasets from experimental in vitro and in vivo GBM models. Objective 2) Evaluate functions of HECTD4 in GBM. In this objective, we will determine the molecular functions of HECTD4 using genetic targeting in human patient-derived GBM cell lines and explore the impact of HECTD4 depletion on the whole proteome of GSCs, and on cancer stemness using functional cell-based assays. This will identify protein targets controlled by FGF2-FGFR1-ZEB1-HECTD4 signalling linked to cancer stemness and therapy resistance. Objective 3) Validate downstream targets of FGF2-FGFR1 signalling. We will validate candidates from Objective 1 and Objective 2 in public human patient OMICs datasets (e.g. single cell, spatial transcriptomics, proteomics). From the candidates validated in human datasets, we will select key targets linked to stemness and therapy resistance and further validate these using genetic targeting in human patient-derived GBM cell lines and functional assays. The student will be able to take ownership and steer the project during the data analysis work packages, e.g. by providing input into the comparative analysis and/or computational methods for analysing the data. Similarly, the student will be able to steer the process of identifying and selecting candidate molecules for validation.
Can be completed part time?	Yes
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