Identification and functional characterization of *BRIT1/MCPH1* synthetic lethal genes to treat breast cancer

Abstract

This study aims to identify synthetic lethal (SL) genes to improve treatment for *MCPH1/BRIT1* deficient breast cancer patients. The tumour suppressor gene *MCPH1/BRIT1* regulates the cell cycle and DNA repair and has reduced expression in a third of breast cancers. In order to identify *MCPH1/BRT1* SL genes two high throughput siRNA screens were performed in U2OS cells, which were transfected with 7,752 genes with and without *MCPH1/BRIT1* siRNA knockdown.

Potential SL genes were then prioritized based on six filtering criteria 1) percentage differences in cell viability between the two siRNA screens, 2) gene expression in the U2OS cell line in which the SL screen was performed and 3) normal breast tissue, 4) the impact of the gene's expression on breast cancer patients' survival, 5) availability of inhibitors and 6) similarity of function with *MCPH1/BRIT1*. The *BRD4* gene showed a 40% differences in cell viability between the *BRD4* and *MCPH1/BRIT1* and *BRD4* siRNA screens. According to the Human Protein Atlas *BRD4* was expressed at the RNA level in the U20S cell line and normal breast tissue at 14.9 and 20.4, respectively. In addition, a BRD4 inhibitor JQ1 is available. Moreover, BRD4 displays similar functions to MCPH1/BRIT1 including DNA repair, cell cycle regulation, transcription and telomere regulation, and chromosome condensation.

Next colony formation assays (CFA) were performed to determine the optimal BRD4 inhibitor range for breast cancer cell lines MDA-MB-468, MCF7, MDA-MB-231 and T47D. Then, the BRD4 inhibitor CFA were performed on siControl and *siMCPH1/BRIT1* knockdown MDA-MB-468 cells. This study confirmed the growth inhibition of *siMCPH1/BRIT1* knockdown cells compared with the siControl in the MDA-MB-468 cell line. Furthermore, real-time PCR analysis identified reduced *BRD4* expression after si*MCPH1/BRIT1* knockdown compared with siControl in all four breast cancer cell lines, suggesting a potential transcriptional link between these genes. Consequently, *BRD4* represents a potential SL gene for *MCPH1/BRIT1*.