
Conference or Workshop Item:
Bruns, A-F, Rippaus, N, Droop, A et al. (8 more authors) (2019) Chromatin remodelling to facilitate treatment resistance in glioblastoma. In: British Neuro-Oncology Society Annual Meeting 2019 (BNOS 2019), 03-05 Jul 2019, London, UK.

https://doi.org/10.1093/neuonc/noz167.027

Chromatin remodelling of adult glioblastoma through standard treatment

Recent findings from our group, and the wider community, show that standard treatment does not impose an apparent bottleneck on the clonal evolution of adult glioblastoma (GBM), implying a lack of direct therapeutic opportunity. This does not negate the possibility that multiple treatment-resistance mechanisms co-exist in tumours, repeated across patients, making a combination of targeted therapies a potentially effective approach. We investigated whether treatment resistance may be driven by selection of cellular properties conferred above the level of the genome. Differential expression analysis was performed on 23 pairs of primary and recurrent tumours from patients who received standard treatment and had a local recurrence treated by surgery and second line chemotherapy. This revealed a treatment-induced shift in cell states linked to normal neurodevelopment. The latter is orchestrated by cascades of transcription factors. We, therefore, applied a bespoke gene set enrichment analysis to our paired expression data to investigate whether any factors were implicated in co-regulation of the genes that were altered through therapy. This identified a specific chromatin remodelling machinery, instrumental in normal neurogenesis. We validated our results in an independent cohort of 22 paired GBM samples. Our results suggest that the chromatin remodelling machinery is responsible for determining transcriptional hierarchies in GBM, shown elsewhere to have different treatment sensitivities such that their relative abundances are altered through treatment.