# Cerebrospinal Fluid Liquid Biopsy

The correct characterisation of central nervous system (CNS) malignancies is crucial for accurate diagnosis and prognosis and also the identification of actionable genomic alterations that can guide the therapeutic strategy. Surgical biopsies are performed to characterise the tumour; however, these procedures are invasive and are not always feasible for all patients. Moreover, they only provide a static snapshot and can miss tumour heterogeneity. Currently, monitoring of CNS cancer is performed by conventional imaging techniques and, in some cases, cytology analysis of the cerebrospinal fluid (CSF); however, these techniques have limited sensitivity. To overcome these limitations, a liquid biopsy of the CSF can be used to obtain information about the tumour in a less invasive manner. The CSF is a source of cell-free circulating tumour DNA (ctDNA), and the analysis of this biomarker can characterise and monitor brain cancer. Recent studies have shown that ctDNA is more abundant in the CSF than plasma for CNS malignancies and that it can be sequenced to reveal tumour heterogeneity and provide diagnostic and prognostic information. Furthermore, analysis of longitudinal samples can aid patient monitoring by detecting residual disease or even tracking tumour evolution at relapse and, therefore, tailoring the therapeutic strategy [1)].

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Liquid biopsy of the CSF is a less invasive, non-surgical method that can be used for diagnosing CNS lymphoma. In this study, we established a clinically applicable protocol for determining mutations in MYD88 in the CSF of patients with CNS lymphoma. CSF was collected prior to the start of chemotherapy from 42 patients with CNS lymphoma and matched tumor specimens. Mutations in MYD88 in 33 tumor samples were identified using pyrosequencing. Using 10 ng each of cellular DNA and cell-free DNA (cfDNA) extracted from the CSF, the MYD88 L265P mutation was detected using digital PCR. The conditions to judge mutation were rigorously determined. The median Target/Total value of cases with MYD88 mutations in the tumors was 5.1% in cellular DNA and 22.0% in cfDNA. The criteria to judge mutation were then determined, with a Target/Total value of 0.25% as the cutoff. When MYD88 mutations were determined based on these criteria, the sensitivity and specificity were 92.2% and 100%, respectively, with cellular DNA; and the sensitivity and specificity were 100% with cfDNA. Therefore, the DNA yield, mutated allele fraction, and accuracy were significantly higher in cfDNA compared with that in cellular DNA. Taken together, this study highlights the importance of detecting the MYD88 L265P mutation in cfDNA of the CSF for diagnosing CNS lymphoma using digital PCR, a highly accurate and clinically applicable method [2)].

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The contents of cerebrospinal fluid (CSF) exosomes could reflect glioma status. Hence, sampling exosomes from CSF is a means of liquid biopsy for glioma. However, few studies have focused on the function of microRNAs in CSF exosomes. In this study, we found that miR-3184-3p was enriched in CSF exosomes in glioma patients and was downregulated after tumour resection. We found that MiR-3184 facilitates glioma progression in two ways. On the one hand, miR-3184 directly promotes proliferation, migration and invasion while inhibiting apoptosis in glioma. On the other hand, miR-3184 in glioma-derived exosomes polarizes macrophages to an M2-like phenotype, which further aggravates tumour progression. Overall, the current findings uncovered a new mechanism and highlighted the significant role of miR-3184 in glioma progression. Furthermore, exosomal miR-3184 could be a considerable factor with potential applications in glioma diagnosis and treatment in the future [3)].

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