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EV packing allows meningioma tracking in blood

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Liquid biopsies which detect tumor-derived material in blood or other body fluids have enormous potential in cancer diagnosis and monitoring and are already in clinical use in many solid tumors. The minimally invasive nature of sampling enables multiple-time point tracking to monitor response and inform management decisions, for example, by assaying circulating tumor DNA (ctDNA) in the setting of de novo or treatment-induced mutation.[1] Blood based sampling has also been implemented for personalized medicine in early phase clinical studies and is increasingly being explored as a screening approach.

In brain tumors the approaches that have been used in other malignancies, relying on detection of circulating tumor cells or tumor DNA are more challenging since shedding of relevant material into blood is much less common, presumably due to restricted passage across the tumor/blood barrier. Studies examining the use of circulating tumor cells or ctDNA in blood in glioma patients have confirmed that sensitivity is low.[2] Sampling CSF improves sensitivity and has promising utility in pediatric tumors, but is more invasive and unlikely to be appropriate in the majority of patients in most settings.[3] These challenges have forced the neuro oncology research community to investigate alternative assays to improve sensitivity for detection of tumor genomic material as well as to explore completely different approaches, which have opened a fascinating window into cellular cargo trafficking in cancer patients. One of these is the identification of endosome derived extracellular vesicles (EVs) as a source of tumor-derived material that can be isolated from blood. These EVs include exosomes, microvesicles, and oncosomes that carry cargoes including DNA, RNA, lipids, and proteins. Carriage within EV protects ctDNA and RNA from degradation, thereby providing an advantage in terms of half-life of tumor genomic material in blood. Previously published data have confirmed raised levels compared to healthy controls and suggested utility as circulating biomarkers in range of solid tumours.[4]

In this edition, Ricklefs et al. demonstrate for the first time that this approach of isolating ctDNA through circulating EVs may also have potential as a biomarker in meningioma.[5] The authors used data from 46 patients with grade 1–3 meningioma undergoing surgery and 18 matched healthy controls to show that plasma EV levels are higher in meningioma patients than in healthy controls. Interestingly absolute EV levels were not associated with tumor size but there was an association with tumor grade and with edema, suggesting changes in the blood-tumor barrier and/or the tumor microenvironment are relevant variables in driving EV levels in plasma. In this context it is worth noting that the interaction between meningioma and the local brain environment is still poorly understood but there are suggestions that the brain-meningioma interface in benign tumors is demarcated by pial–glial basement membrane which is absent in higher grade variants.[6]

In their study, Ricklefs et al. also show that EV levels fall at early time points (Day 1–6) post op, and go on to assess the correlation with postsurgical residuum. The extent of resection appears relevant in that the most marked reduction of EVs occurred in patients with completely resected tumors (Simpson grade I) but the series contained only small numbers of patients who underwent more limited resections (Simpson grade II and above), so the sensitivity of the assay in these patients could not be demonstrated.

The researchers then used meningioma cells maintained ex vivo to compare EV DNA with data from cultured parental cells and the respective tumors. They exploit data confirming the utility of methylome analysis in classifying meningioma[7] and show that this classification is recapitulated in the majority of EV-DNA from ex vivo cell cultures. The mutational profile of parental tumors was also mainly faithfully copied in EVs. They went on to use proteomic profiling but were unable to demonstrate a tumor specific proteome that reflected that of the original tumor. However exploratory analysis of spectroscopy data defined proteins specific to meningioma-derived EVs, that were also found in meningioma tissue samples and which were distinct from those found in EVs secreted by GBM cells, providing a potential means of enriching for meningioma EVs in plasma samples.

These data provide a further example of the potential utility of a liquid biopsy approach applied to a tumor type in which immediate treatment is not always required but where a specific

molecular pathology profile may inform the decision to treat. Although the great majority of meningiomas are benign, a noninvasive assay that could select the 20% of cases that need early intervention would be extremely valuable. This approach could also be complementary to the evolving understanding of the molecular pathology of these tumors at specific sites and at different ages and could provide the means to better select and stratify these patients within clinical studies.[8]

Future application of this approach will rely on further optimization of the assay and validation in larger prospective cohorts at the time of surgery and through long-term follow-up. For this liquid biopsy to be clinically useful it will also have to pass the tests of standardization, which is a major hurdle in EV biology, applicability to clinical diagnostic time frames and demonstration of cost effectiveness.

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Author contribution

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Declaration

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