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Medulloblastoma (cross)talk through extracellular vesicles

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See the article by Albert et al in this issue pp. 586–598.

Over the past 10 years, medulloblastomas (MB) have been extensively characterized at the genomic level where it is now well accepted that they are comprised of at least 4 distinct molecular subgroups with unique demographics, genetics, and prognosis.[1] Further studies have shown additional heterogeneity within these four groups that may translate to the clinical setting.[2] Although the molecular understanding of this disease has increased extensively over the last 10-15 years, the clinical implementation through prognostic classification and translation into therapeutic strategies has lagged behind. Despite these major advances in classification, there has been little progress in discerning the tumor microenvironment (TME) and extracellular cues. As such, a major gap exists in our understanding of intratumoral heterogeneity, specifically the cell-cell interactions between MB and its TME.

The characterization of individual cells through the development of single-cell RNA sequencing (scRNA-seq) technologies has propelled the study of tumor heterogeneity and cell of origin of several malignancies. In the context of MB, scRNA-seq has been largely used as a tool to characterize cellular state, describe tumor heterogeneity and developmental origins.[3,4] Recent work applying scRNA-seq in MB has provided robust support that the four subgroups originate from distinct cells of origin, with specific developmental timings. The result of these studies has been to demonstrate that the cell of origin has influence on the biology and behavior of the developed tumor, thus expanding our understanding of the relationship of MB with normal developmental states.[4] Of the four subgroups, the sonic hedgehog (SHH) group present a unique opportunity for robust cross-species genomics due to the availability of several sporadic transgenic models. Indeed, the recent scRNA-seq papers have provided further evidence that SHH tumors have distinct transcriptomic profiles compatible with granule neuron precursors (GNP) in multiple stages of differentiation.[3,4] The ability to profile tumors at single-cell resolution provides an unprecedented ability to characterize cell-cell interactions and identify distinct cell populations as opposed to current bulk technologies. However, to date, there have been a paucity of studies using single-cell technologies to discern the interaction between MB and its TME.

To bridge this gap in knowledge, Albert et al. leverage scRNA-seq in a cross-species approach to study not only the SHH-MB developmental cellular state but to explore cellular communication in the TME mediated by extracellular vesicles (EVs). In addition, the authors identify an EV signature that correlates with prognosis in specific subgroups of MB (Figure 1).[5]

Herein, applying scRNA-seq, the authors characterize the cellular landscape of murine SHH-MB identifying tumor-specific clusters that showed close relationship to GNPs when compared to normal cerebellar cells (CB). In addition, lineage trajectory analysis showed a developmental block with tumor cells not reaching fully differentiated stages in accordance with previously published data establishing SHH precursors. The authors also described intratumoral heterogeneity with two major subpopulations. These findings and the potential therapeutic impact need to further be explored. Interestingly, two clusters of non-tumor cells were comprised of glial and immune cells with a prevalence of macrophages.[6] The transcriptomic profile of the tumor cells compared to CB cells found 75% of upregulated genes, most of which involved in gene regulatory elements. Interestingly, many of the upregulated genes from tumor cells were also found to be upregulated in the tumor-associated glial and immune cells, however, not in these same cell types in healthy tissue. This suggests there is considerable intracellular communication within the tumor niche, consistent with other tumor types such as high-grade gliomas.[7]

Based on the observation that EV-related genes were over-represented in their pathway analysis, the authors proceed to further investigate whether EVs mediate crosstalk between MB cells and their TME. EVs are small vesicles consisting of heterogeneous content including nucleic acids, proteins, and lipids which are cell of origin and tumor type-specific.[8] To test this hypothesis, they applied a co-culture experiment of MB cell lines with a murine oligodendrocyte cell line. They identified EVs in the

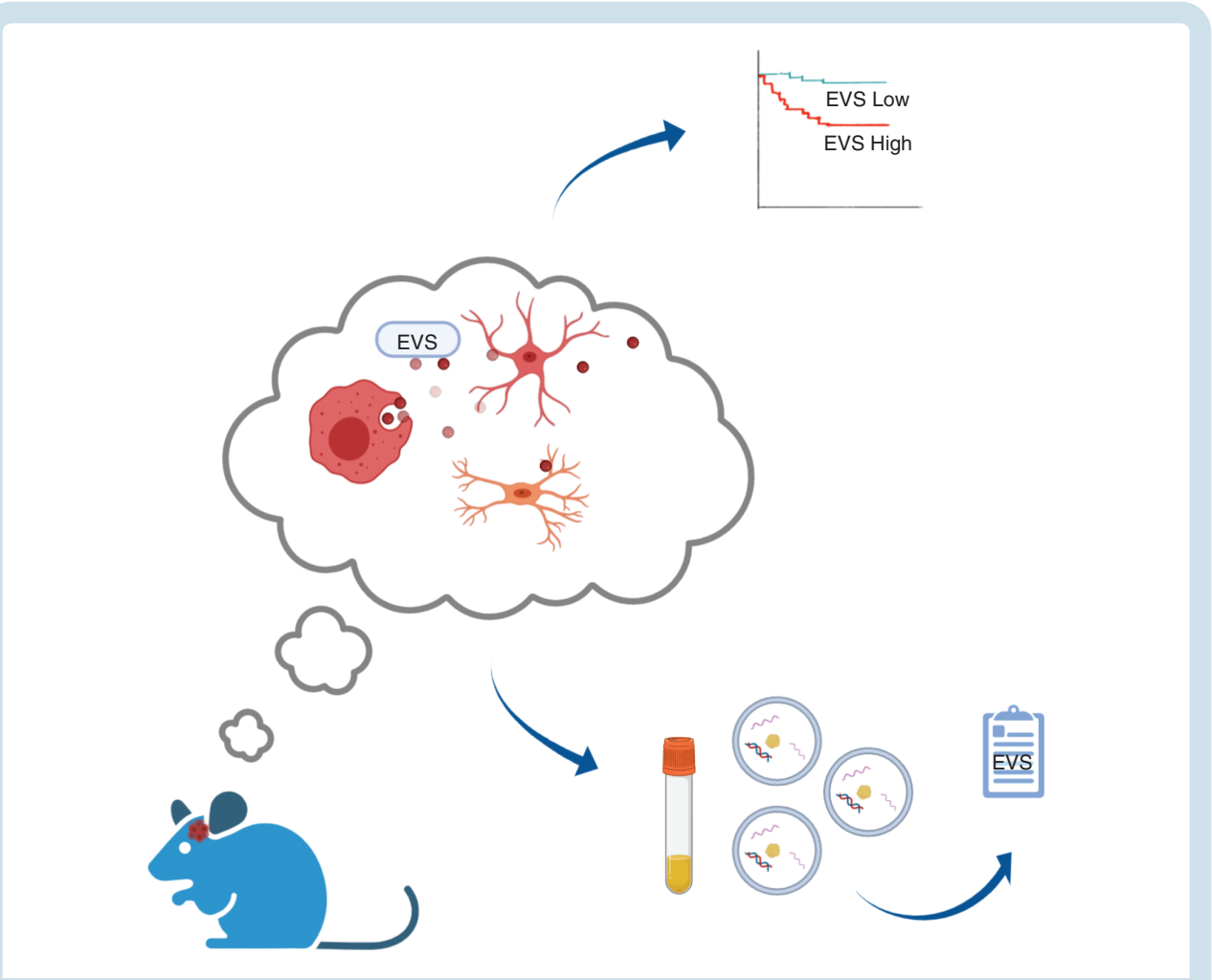

Fig. 1 Identification and potential applications for extracellular vesicles (EVs) in medulloblastoma. EVs facilitate intercellular communication, an EV signature identify prognostic groups, and in the future, can be explored as a tool in the context of liquid biopsy to monitor medulloblastoma treatment. This figure was created using BioRender.com.

culture media and a shared transcriptomic profile between these two cell types, which suggests that EVs play an important role in both MB and glial cell proliferation.[5] This shared transcriptomic profile is highly suggestive that secretion of EVs represents an essential aspect of cell-to-cell communication in MB, analogous to other cancer types.[9] These vesicles have additionally been implicated in signaling mechanisms that promote cancer progression and metastasis.[8] Indeed, further understanding of the role of EVs in MB has the potential to target metastasis, which represents the major cause of treatment failure, and a marker of high-risk disease.[10]

Another potential application of cancer-derived EVs is the potential to aid in cancer diagnosis, prognosis, and therapeutics specifically through the emerging field of liquid biopsy. Ultimately, the authors generated an EV signature and an associated score that was found to be prognostic in specific MB subgroups. Indeed, the finding that higher expression of the EV signature results in poorer outcome suggests that there is a higher level of tumor secreted EVs, hinting that the level of intercellular communication might influence treatment response. This represents a new concept in MB, where the interplay between the TME and therapeutic avenues needs to be further explored.

Applying EV transcriptomic signatures represents an exciting monitoring tool, and a raises the tantalizing prospect of using noninvasive monitoring for detection of early relapse. In addition to a potential role in liquid biopsies, the known role of EVs in mediating metastasis, and the propensity of MB to recur with dissemination, suggests that a deeper understanding of the content and role of EVs in MB might allow for prevention of metastatic relapse. This study furthers our understanding of the cell-cell interactions in MB, and provides additional support for the power of single-cell sequencing over traditional bulk RNA sequencing as the next frontier in

both risk stratification and deciphering how MB communicates with itself and its microenvironment.

Conflict of interest statement. The authors declare no conflicts of interest.

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