INSIGHTS

A SHHecret target of relapsed medulloblastoma: Astrocytes

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In this issue of JEM, Guo et al. (2021. J. Exp. Med. https://doi.org/10.1084/jem.20202350) examine the importance of tumor-derived astrocytes in SHH-medulloblastoma recurrence. They show that tumor cells transdifferentiate to tumor-derived astrocytes via bone morphogenetic proteins and Sox9, which excitingly can be targeted by BMP inhibitors.

Medulloblastoma (MB) is the most common malignant central nervous system (CNS) tumor in children and typically develops in a back or posterior fossa of the brain, which contains the cerebellum and brainstem (Hovestadt et al., 2020). Survivors typically experience long-term sequelae caused both by the tumor and from aggressive multimodal therapies. Additionally, although aggressive treatments have generally improved outcomes, a 20–30% subset of MB patients relapse and ultimately succumb to the disease (Cacciotti et al., 2020). Thus, there is an imperative need to identify new approaches that target tumor over normal brain, sparing cognition and development. In this month’s issue of JEM, Guo and colleagues shed light on relapsed MB and identify tumor cells that have transdifferentiated to tumor-derived astrocytes (TAs; Guo et al., 2021). They reveal this mechanism as dependent on bone morphogenetic protein (BMP) signaling and phosphorylation of the transcription factor Sox9, which can be targeted pharmacologically.

Integration of genomic, clinical, and biological studies have revealed four genetically and epigenetically distinct MB subgroups (Wnt, Sonic Hedgehog [SHH], Group 3, and Group 4; Hovestadt et al., 2020). SHH MB accounts for ~30% of human MB and is distinguished by loss of function of the antagonizing receptor Patched1 (PtcH1) or gain of function of the activating receptor Smoothened. Cerebellar granule neurons compose the largest neuronal population of the CNS, and the SHH cascade is considered critical for proliferation of cerebellar granule neuron precursors (GNPs). Consistent with their responsiveness to Shh signaling, GNPs have been shown through several lines of evidence to be the cell of origin of SHH-MB in mice (Hovestadt et al., 2020).

MB recurrences are thought to be driven in part by a rare population of tumor-initiating or tumor stem cells resistant to conventional chemotherapies. These cells are considered heterogeneous and thus hard to target (Zhang et al., 2019). SHH-MB tumor recurrences are generally derived from stem- or glial-like progenitors (Liu et al., 2017; Yao et al., 2020). Astrocytes are specialized glial cells in the nervous system that provide support to neurons and regulate synaptic function (Hill et al., 2019). Recent work from this group and others supports a key role of TAs in promoting tumor growth and metastasis through distinct signaling and feedback loops. In mouse models, TAs can transdifferentiate from MB tumor cells and release cytokines that support the brain tumor microenvironment (Liu et al., 2017; Yao et al., 2020).

Using single cell RNA-sequencing and lineage tracing analyses, Guo et al. investigated cellular origin of TAs in a mouse model for relapsed SHH-MB driven by PtcH1 knockout (Guo et al., 2021). Interestingly, they found that transdifferentiated TAs were prevalent in both transplanted and relapsed MB, but not primary MB. Moreover, the transdifferentiated TAs had distinct expression profiles compared with lineage-independent TAs identified in the primary MB. They further identified Sox9 as a key transcription factor up-regulated in TAs from relapsed MB, and that Sox9 was phosphorylated via the BMP signaling cascade. Sox9 has been previously found to regulate astrocyte specification and has important functions in brain development as well as MB progression (Swartling et al., 2012; Suryo Rahmanto et al., 2016; Li et al., 2018). While Sox9 might have pleiotropic functions in MB development, the authors found that in this context, Sox9 expression was essential to tumor cell transdifferentiation, and expression was exclusive to tumor cells and astrocytes. Consistent with this finding, BMP signaling induced...
transdifferentiation of MB cells to TAs through phosphorylation and activation of Sox9.

Furthermore, the authors described a combination therapy of standard irradiation followed by inhibition of BMP signaling using tool BMP inhibitors LDN-193189 and LDN-214117 (Vogt et al., 2011; Mohedas et al., 2014). While these BMP inhibitors were ineffective in treating primary MB alone, they repressed MB cell transdifferentiation during relapse, as fewer TAs were detected in tumor tissue following the combined treatment. Importantly, these findings were validated using a human patient-derived xenograft (PDX) model for SHH-MB transplanted into the cerebellum of immunocompromised mice. Following injection, mice were irradiated and treated with BMP inhibitors. Those mice treated with inhibitors did not relapse. This suggests that tumor relapse was repressed after inhibition of the BMP pathway (see figure).

Overall, Guo and colleagues elegantly demonstrate distinct origins of TAs in a relapsed mouse model of SHH-MB. This has important implications for SHH-MB, as they elucidate further the tumor heterogeneity present in aggressive MB as well as present new therapeutic avenues to target subcompartments of cells residing in the tumor microenvironment (Guo et al., 2021). The authors revealed that tool BMP inhibitors could be used to target TAs and prevent MB recurrence. Clinical BMP inhibitors are just entering clinical trials (Sanchez-Duffhues et al., 2020), and they may have potential to target tumor subpopulations in combination with other therapies.

The work presented by Guo et al. brings forward new and compelling questions to explore in understanding MB recurrence. While the evidence presented along with previous work from other groups supports the key functions of TAs in MB recurrence (Liu et al., 2017; Yao et al., 2020), it is still unclear what drives these transdifferentiation events. It is important to further investigate beyond BMP signaling what intrinsic mechanisms regulate TAs. In particular, several studies have suggested that chemotherapy can lead to residual MB cells acquiring new mutations driving survival and chemoresistance (Zhang et al., 2019). Consequently, additional genomic analyses are needed to further delineate the key genes and pathways that activate transdifferentiation pathways to generate TAs in MB.

Further, an investigation of extrinsic mechanisms is critical to understanding how these TAs function in the tumor microenvironment in general. It would be important to probe through mouse models if there is cross-talk from microglia and whether it governs transdifferentiation of tumor cells to TAs. For example, are the microglia secreting chemokines that promote tumor cell fate decisions? Additionally, the complex interaction of astrocytes and microglia cells has been shown to promote an immunosuppressive environment in other brain tumors, such as glioblastoma (Henrik Heiland et al., 2019). It also would
be compelling to examine other functions of TAs, such as the potential cooperation of microglia and TAs in promoting the immune-suppressed state typical of MB, a "cold" tumor that is hard to target through immunotherapy. Finally, astrocytes are an integral part of supporting neuronal synapses and function (Hill et al., 2019), and MB is considered to be primarily comprised of undifferentiated neural stem or progenitor cells (Swartling et al., 2012; Zhang et al., 2019). Guo and colleagues’ studies raise the question whether TAs suppress MB cell neurogenesis to further promote tumor growth and recurrence. It would be intriguing to explore the signaling cascades that TAs harness to support MB tumor cells and the neural circuitry and target those pathways to promote neuronal differentiation and synapse.

While the authors focused on local recurrence, the paramount question from their work is how their findings apply to other models of MB recurrence. Of chief relevance, many patients succumb to MB metastases through leptomeningeal spread to the spinal cord, known as metastatic recurrence (Van Ommeren et al., 2020). It is imperative to understand if TAs are present and involved in more distal metastases in human PDXs from SHH-MB (including PDXs from relapsed tumors), and to test relevance to other MB subgroups. Metastases have genetic and epigenetic distinctions from their matched primary tumors and are likely derived from a subclone of cells from the primary lesion (Van Ommeren et al., 2020). It is important to validate if a TA component drives metastases in a similar model to local recurrence. In conclusion, Guo et al. reveal the importance of TAs in MB that will hopefully inspire more examinations, both in mouse and human PDX models, on whether these mechanisms are present and targetable in human SHH-MB and other MB subtypes.

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