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Targeting MEK/MELK in atypical teratoid rhabdoid tumor: a treatment approach aimed at exploiting blood–brain barrier deficiencies

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See the article by Meel et al. in this issue, pp. 58–69.

Atypical teratoid rhabdoid tumors (ATRT) are highly aggressive pediatric tumors that arise in the brain and central nervous system. Current treatment strategies consist of an intense multimodal approach leading to moderate improvement in survival at the cost of toxicity-related morbidity.[1] The primary mutation observed in ATRT is loss of SMARCB1, a core subunit of the SWItch/sucrose nonfermentable DNA remodeling complex, with no additional recurrent mutations observed.[2] The apparent genetic homogeneity is in stark contrast to the heterogeneous phenotypes that present in the clinic.[3] Recent large genomic and epigenomic studies have identified 3 distinct ATRT subtypes with unique clinical phenotypes, epigenomic landscapes, and drug susceptibility despite the shared genetic loss of SMARCB1.[4,5] Indeed, further examination of the molecular pathways implicated in the pathogenesis of each distinct subgroup point to aberrant epigenetic signatures across the 3 subgroups providing initial evidence of subgroup-specific dependencies. The extent of the underlying oncogenic drivers of each subgroup and the ability to develop effective therapeutic treatments tailored to the genetic drivers of each subgroup remain to be elucidated.

ATRT have demonstrated a propensity to express LIN28, an inhibitory RNA protein that represses let-7 miRNA expression, at high levels leading to transcriptional activation of oncogenic drivers.[6] Studies have linked the overexpression of LIN28 to aberrant activation of mitogen-activated protein kinase (MAPK) to promote tumor growth and proliferation.[6] An important downstream mediator of the MAPK signaling pathway is maternal embryonic leucine zipper kinase (MELK), which regulates the cell cycle, stem cell renewal, and apoptosis and has been implicated in the maintenance of cancer stem cell–like states, providing an attractive therapeutic target.[7,8] The strong initial implication of dysregulated MAPK/MELK activity led Meel et al to confirm that ATRT possess high levels of MELK compared with normal brain tissue and proposed therapeutically targeting MEK and MELK in ATRT preclinical models.[9]

Meel et al first investigated the use of MEK/MELK agents in VUMC-AT/RT-01 and VUMC-AT/RT-01R, a primary/recurrent neurosphere culture of a Group 1/sonic hedgehog (SHH) ATRT derived from a patient tumor arising in the parietal/occipital region. These lines were further supported by the additional use of ATRT cell lines CHLA-02 and CHLA-04 (SHH) and compared with the Group 2B/MYC line CHLA-06 to evaluate the efficacy of a MEK/MELK treatment regime. Examination of transcriptional and protein expression upon treatment with OTSSP167, a small-molecule MELK inhibitor, and trametinib, an established MEK inhibitor, as single agents and in combination, revealed a potent anti-proliferative effect of both compounds that was further enhanced when utilized in combination with strong synergism observed in all lines. Of note, however, was that treatment with single or combination agents in Group 2B/MYC did not produce the desired reduction of MELK protein expression as was observed in the other Group 1/SHH lines despite a strong highest single agent synergistic score implicating off-target effects in Group 2B/MYC cells demonstrative of the hallmark heterogeneous molecular mechanisms that underpin each subgroup in ATRT. Nevertheless, Meel et al provide initial evidence, albeit tentative, of differential sensitivity and dependency of the MEK/MELK signaling axis that requires further validation in additional preclinical models in order to verify this exciting initial observation.

Following on from the in vitro neurosphere observations, Meel et al proceed to evaluate the combination therapy in a

patient-derived xenograft (PDX) model of the VUMC-AT/RT-01 neurosphere line. The single agent treatment regimens of OTSSP167 and trametinib produced no significant effect; however, combination therapy produced a modest increase in overall survival. Unfortunately, an inability to engraft the recurrent VUMC AT/RT-01R, a more robust responder in vitro to MEK-MELK inhibition, prevented the ability to assess if these in vitro models were recapitulated in a similar vein in vivo. Additionally, the question remains if such a treatment approach is restricted to on-target therapeutic response to Group 1/SHH ATRT subgroups or if such survival increases would occur in Group 2A/TYR or Group 2B/MYC in vivo, albeit through potentially alternate molecular mechanisms. Nevertheless, further evaluation of additional ATRT in vivo models to ascertain the precise nuances of targeting the MEK/MELK signaling axis with this particular treatment combination requires further interrogation.

Despite the promising preclinical data presented by Meel et al, neither OTSSP167 nor trametinib are known to effectively cross the blood–brain barrier (BBB). To ensure that a combined MEK/MELK treatment strategy possesses translational potential, Meel et al proceeded to evaluate the integrity of the BBB in PDX models of ATRT. The authors were able to demonstrate irregular vascularization with fewer blood vessels observed, and those present demonstrated significantly larger diameters in PDX models of ATRT disease compared with the wild-type counterparts. Analyzing Cldn5, a marker of tight junctions, revealed disorganized junction points between epithelial cells. The authors noted that these phenotypic characteristics bear strong resemblance to the WNT subgroup of medulloblastoma, which has been shown to contain an impaired BBB that provides an avenue for therapeutic agents to act on the tumor. However, it is important to note that in this initial study, the tumor injection site for the SHH patient primary cells was in the cerebellum, while the primary tumor site in the patient most likely originated in the parietal lobe and then spread to the occipital lobe, perhaps suggesting that the location of the tumor is a factor in loss of BBB integrity. While the authors do in fact demonstrate that striatal injected CHLA-06 cells produce BBB deficiencies and bear some of the listed hallmarks of a disrupted BBB, it remains to be seen how closely the striatal site recapitulates what is observed in WNT medulloblastoma.

Meel et al provide compelling initial evidence of a novel therapeutic strategy to utilize MEK and MELK inhibitors in the treatment of ATRT to potentially uncover an effective novel treatment strategy for ATRT. The challenge remains in acquiring a sufficient number of preclinical models that accurately reflect the disease to definitively inform on the translational potential of such a treatment approach in ATRT.

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