AKT1

AKT1 is involved in regulating PI3K/AKT/mTOR, a tumor-generating pathway. Ipatasertib, a highly selective inhibitor of AKT1, is widely used in the treatment of tumors. In a study, many structural and biochemical methods were used to find better AKT1(Serine/threonine-specific protein kinase 1) inhibitors, which laid a foundation for the further development of AKT1 inhibitors and provided new drugs for the treatment of tumors. ZINC15 database and Discovery Studio 4.5, a computer-aided drug screening software with many modules (LibDock for virtual screening, ADME (Absorption, Distribution, Metabolism, Excretion), and TOPKAT (toxicity prediction module) for the toxicity and properties analysis, and MD simulation for stability prediction), were employed. CCK8 assay, ELISA assay genicity, and higher tolerance to cytochrome P4502D6. MD simulations indicated they could bind with AKT1 stably in the natural environment. The cell experiment and specific assay for AKT1 inhibition showed they could inhibit the proliferation and AKT1 expression of MG63 cells (Osteosarcoma cells). Moreover, these novel compounds with structural modifications can be potential contributors that lead to further rational drug design for targeting AKT1 [1].

Genetic aberrations (TRAF7, KLF4, AKT1, and SMO) and the effects of genetic aberrations on the expression of inhibitory immune checkpoint molecules (PD-L1, IDO, and TDO2) in skull base meningiomas are still unclear.

Genetic alterations in the four genes were identified in 92 skull base meningiomas by Sanger sequencing. The expression differences in immune checkpoints between mutant and wild-type (WT) tumors were determined by immunohistochemistry (IHC) and Western blot (WB).

The four mutations were not concurrently detected in the patients with skull base meningiomas. Among the tumors from the KLF4-mutated group, almost half were petroclival meningiomas. KLF4- and TRAF7-mutated tumors were predominantly secretory meningiomas. SMO-mutated tumors exhibited higher calcification, and half of these tumors were observed in the brain midline. Receiver operating characteristic curve analysis indicated that tumor volume can predict KLF4 and TRAF7 mutation status with high sensitivity and specificity, respectively. The IHC and WB analyses indicated that PD-L1, IDO, and TDO2 levels in tumors with TRAF7 mutations were significantly higher than those in WT tumors. Meanwhile, there was a significant difference in TDO2 between tumors with AKT1 mutations and WT tumors. Specifically, TRAF7 mutations could play a key role in skull base meningiomas by regulating the expression of inhibitory immune checkpoints and thus suppressing immune responses.

Checkpoint inhibitors may be potential strategies for targeted immunotherapies of these mutant meningiomas [2].

1)
Zhong S, Zhang Z, Guo Z, Yang W, Dou G, Lv X, Wang X, Ge J, Wu B, Pan X, Wang H, Mou Y. Identification of novel natural inhibitors targeting AKT Serine/Threonine Kinase 1 (AKT1) by computational study. Bioengineered. 2022 May;13(5):12003-12020. doi: 10.1080/21655979.2021.2011631. PMID: 35603567.
2)
Hao S, Huang G, Feng J, Li D, Wang K, Wang L, Wu Z, Wan H, Zhang L, Zhang J. Non-NF2 mutations have a key effect on inhibitory immune checkpoints and tumor pathogenesis in skull base meningiomas. J Neurooncol. 2019 Jun 8. doi: 10.1007/s11060-019-03198-9. [Epub ahead of print]

PubMed PMID: 31177425.