IDO

Indoleamine 2,3-dioxygenase (IDO), a key enzyme of tryptophan (Trp) metabolism, is involved in tumor-derived immune suppression through depletion of Trp and accumulation of the metabolite kynurenine, resulting in inactivation of natural killer cells and generation of regulatory T cells (Tregs).

It has been reported that high expression of IDO in cancer cells is associated with suppression of the antitumor immune response and is consistent with a poor prognosis. Thus, IDO may be a therapeutic target for malignant cancer.

Hanihara et al. showed that IDO expression is markedly increased in human glioblastoma and secondary glioblastoma with malignant change, suggesting that IDO targeting may also have therapeutic potential for patients with glioma. The aim of this study was to investigate the antitumor effect of IDO inhibition and to examine the synergistic function of IDO inhibitor and temozolomide (TMZ) in a murine glioma model.

Murine glioma GL261 cells and human glioma U87 cells were included in this study. The authors used 3 mouse models to study glioma cell growth: 1) a subcutaneous ectopic model, 2) a syngeneic intracranial orthotopic model, and 3) an allogenic intracranial orthotopic model. IDO inhibition was achieved via knockdown of IDO in GL261 cells using short hairpin RNA (shRNA) and through oral administration of the IDO inhibitor, 1-methyl-l-tryptophan (1-MT). Tumor volume in the subcutaneous model and survival time in the intracranial model were evaluated.

In the subcutaneous model, oral administration of 1-MT significantly suppressed tumor growth, and synergistic antitumor effects of 1-MT and TMZ were observed ($p < 0.01$). Mice containing intracranially inoculated IDO knockdown cells had a significantly longer survival period as compared with control mice ($p < 0.01$).

These results suggest that IDO expression is implicated in immunosuppression and tumor progression in glioma cells. Therefore, combining IDO inhibition with standard TMZ treatment could be an encouraging therapeutic strategy for patients with malignant glioma [1)].

1)
Hanihara M, Kawataki T, Oh-Oka K, Mitsuka K, Nakao A, Kinouchi H. Synergistic antitumor effect with indoleamine 2,3-dioxygenase inhibition and temozolomide in a murine glioma model. J Neurosurg. 2016 Jun;124(6):1594-601. doi: 10.3171/2015.5.JNS141901. Epub 2015 Dec 4. PubMed PMID: 26636389.