N6-isopentenyladenosine Triggers Anti-Glioma Innate Immune Response through Induction of ULBP2 in a p53-Dependent Manner

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Failure of conventional cancer therapy renders glioblastoma (GBM) an attractive target for immunotherapy. Numerous evidences suggested that reactivation of p53, a key tumor suppressor, produces growth arrest, apoptosis or senescence in cancer cells. Moreover, it activates the innate immune response against cancer cells through the up-regulation of NKG2D ligands that activate Natural Killer (NK) cells. N6-isopentenyladenosine (i6A), a modified nucleoside founded in a free form or in transfer RNA (tRNA) of many eukaryotic and prokaryotic cells, is a promising isoprenoid-derived product with well-established pleiotropic biological effects, including a direct anti-tumor activity. Here we observed that i6A at concentrations of 0.1 and 1 µM was able to inhibit the growth of human glioblastoma cell lines and reactivate wild-type p53, but not mutant p53. This event also induced: 1) increase of mRNA expression of MICA/B, ULBP1, ULBP2, and ULBP3, constitutively expressed on glioblastoma cells, 2) a significant upregulation of cell surface expression of ULBP2, increasing the immunogenicity of i6A treated glioblastoma cells.

Indeed, this mechanism stimulated cytotoxicity of NK cells against co-cultured U343 GBM cells and mediated their recognition through NKG2D molecules.

We observed that the co-treatment of i6A-treated U343 GBM cells with pifithrin-α (PT-α) at 10 µM, a specific inhibitor of p53 activity, completely prevented the i6A action in restoring the immunogenicity of these cells.

This study could propose a new combinatorial strategy of NK cell–based immunochemotherapy in glioma cancer cells in which wild-type p53 function is preserved.