Research on the Development of a Drug Delivery System Using Nanoparticles and Inhibitors Targeting the PI3k/mTOR and Braf/Mnk Signaling Pathways in BRAF-mutant and PTEN-deficient Melanoma

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Abstract:

Accumulation of genetic and epigenetic alterations allows for activation of multiple signaling pathways that promote growth, proliferation, and survival of melanoma. Mutations such as BRAF V600E, K, NRAS, KIT, and downstream effectors in the MAPK pathway drive tumor growth and resistance to conventional therapies so no targeted therapies are fully effective. Inhibition of one signaling pathway in cancer promotes development of the escape mechanisms by activating parallel pathways. We hypothesized that coordinating inhibition of PI3K/mTOR and inhibition of phosphorylation of eIF4E would lead to a better anticancer effect. Study was carried out on human melanoma cell lines with similar genomic alteration (BRAFV600E and PTEN loss). We used a highly specific PI3K/mTOR inhibitor, dactolisib (NVP-BEZ235), and Mnk inhibitor - CGP57380 alone and in combination. Expression of cell signaling proteins was monitored by phospho-specific antibodies, was analyzed using Western Blot. The proliferation of cells was assessed with the crystal violet test, wound healing model was used to compare the migration of melanoma cell lines, images of acridine orange staining was used for monitoring of autophagy. We want to use our preliminary research on the effects of inhibitors to develop a nanoparticle drug delivery system.

Keywords:

Melanoma, Mnk, PI3K/mTOR, SPION.