Poster

[P26-9] P26-9: Oncologic drugs (5): Pharmacokinetics, TDM practice

Chair: Kiyoshi Mihara, Japan

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[P26-9-5] Metformin inhibit tumor progression by nickel chloride via p-AKT related autophagy

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Keywords: Metformin, Nickel chloride, AKT, Autophagy

Background

mTOR, the Akt and AMPK downstream effector, plays a critical role in cell proliferation, growth and survival. Activated mTOR promotes protein translation by phosphorylating its substrates. The molecular basis of nickel carcinogenicity has proven complex, as many chronic inflammation and stress response pathways are activated in nickel-specific toxicology profiles. The aim of the study investigates effects of metformin on $NiCl_2$ -induced autophagy-related signaling pathway.

Methods

To quantify the acidic vesicular organelle (AVO) after nickel and metformin treatment, flow cytometric analysis was performed in autophagic cells. ELISA was performed using Human LCN2/NGAL DuoSet ELISA Kit. VZV-G pseudotyped lentivirus-shRNA system, Western blot and Real-time PCR were investigated the gene signaling.

Results

Treatment with metformin blunted AVO formation in a dose-dependent manner in $NiCl_2$-treated cells with acridine orange staining and flow cytometric analysis. Metformin did not affect $NiCl_2$-activated fluorescence, indicating that metformin does not contribute to blockage of nickel ions into cells with Ni^{2+}-selective fluorescence dye Newport GreenTM DCF. Metformin treatment revived the Akt-Ser473 phosphorylated expression, but reduced NiCl2-mediated autophagy, perhaps through AKT-dependent but mTOR-independent pathway. In BEAS-2B shHK2 cells, $NiCl_2$-elicited LC3B-II and cleaved caspase-7 expressions were significantly diminished.

Conclusions

Metformin decreases nickel-induced autophagy and activation of apoptosis through restoration of p-AKT and inhibition of its downstream HK2 gene, protein and activity.