구두발표-3

Inhibitors of AKT Signaling Pathway and their Application

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The AKT signaling pathway is a highly regulated cell signaling system that forms a network with other cell signaling pathways. Hence, the AKT signaling pathway mediates several important cellular functions that include cell survival, proliferation, cell migration, and et cetera. Irregularities that led overactive AKT signaling have been linked to many diseases such as cancer and metabolic-associated diseases. Hence, modulating the overactive AKT signaling pathway via inhibitor is a tantalizing prospect for treatment of cancer and metabolic-associated diseases. Two inhibitors of the AKT signaling pathway will be presented in this symposium: 1) Bisleuconothine A (BisA), a bisindole alkaloid that inhibit autophagy and 2) Ceramicine B (CerB), a limonoid that inhibit adipogenesis. The first topic is on a bisindole alkaloid, BisA and its mechanism in inducing autophagosome formation in lung cancer cell line, A549.(1) Since most autophagy inducing agents generally induce apoptosis, we found that BisA does not induce apoptosis even in high dose. BisA up-regulation of LC3 lipidation is achieved through mTOR inactivation. The phosphorylation of PRAS40, a mTOR repressor was suppressed by BisA. This observation suggested that BisA inactivates mTOR via suppression of PRAS40 phosphorylation. Interestingly, the phosphorylation of AKT, an upstream regulator of PRAS40 phosphorylation was also down-regulated by BisA. These findings suggested that Bis-A induces autophagosomes formation by interfering with the AKT-mTOR signaling pathway. The second topic is on CerB and its mechanism in inhibiting adipogenesis in preadipocytes cell line, MC3T3-G2/PA6.(2,3) CerB inhibits the phosphorylation of protein kinase B (AKT) at the Thr308 position but not the Ser473. Consequently, the phosphorylation of FOXO3 which is located downstream of AKT is also inhibited. Considering that FOXO3 is an important regulator of PPARγ which is a key factor in adipogenesis, CerB may inhibit adipogenesis via the AKT-FOXO3 signaling pathway. Taken together, both BisA and CerB highlighted the potential of AKT signaling pathway modulation as an approach to induce autophagy and inhibit the formation of fat cells, respectively.

References

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