Session III: Genetic Basis and Pathogenesis

of WM and IgM Related Disorders

Abstract 115

Presenter: L. Xu

5-Azacytidine inhibits the mammalian target of rapamycin complex 1 signal and induces apoptosis in Waldenström's macroglobulinemia. Lian Xu, B. Ciccarelli, E. Hatjiharissi, S. Adamia, Y. Zhou, J. Sun, G. Yang, H. Tseng, X. Liu, Z. Hunter, L. Ioakimidis, R. Manning, C. Patterson and S.P. Treon. Bing Center for Waldenström's Macroglobulinemia, Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts USA.

5-Azacytidine (5-AzaC) is a potent DNA methyltransferase inhibitor and has been proved by the FDA for treating myelodysplastic syndrom. Potential efficacy of 5-AzaC on a number of myeloid and lymphoid proliferative disorders, including acute and chronic myeloid leukemia, chronic lymphothetic leukemia, and multiple myeloma, has been reported in the preclinical studies. We investigated the cytotoxic effect and the mechanism of action of 5-AzaC in Waldenström's macroglobulinemia (WM). 5-AzaC exhibited significant dose-dependent cytotoxicity against the WM cell line BCWM1. Treatment of BCWM1 cells with 2 uM of 5-AzaC rapidly induced cell cycle arrest at G1. More than 40% of BCWM1 cells underwent to apoptosis in 48 hours. 5-AzaC also induced significant apoptosis in primary samples of WM but no significant cytotoxic effect was seen in peripheral blood mononuclear cells from healthy donors. Cleavage of caspase 3, 7, 8 and 9 and PARP-1 were associated with the 5-AzaC induced apoptosis, suggesting that both the mitochondrial and the death receptor pathways were involved in the apoptotic process. While treatment of BCWM1 cells with 5-AzaC did not result in significant changes of PTEN expression and phosphorylation of Akt and mTOR, 5-AzaC rapidly induced down-regulation of raptor which is a key component of the mammalian target of rapamycin complex 1 (mTORC1), and consequently inhibited phosphorylation of S6 kinase 1 (S6K1) which is a down-stream target of mTORC1 and an important regulator of protein translation. Rapamycin, a potent mTORC1 inhibitor via disrupting the association of mTOR and raptor, also induced G1 arrest of BCWM1 cells. Moreover, an enhanced inhibition of cell growth was observed when 5-AzaC was combined with rapamycin in the treatment. These data suggest that down-regulation of raptor contributed to the 5-AzaC induced cytotoxicity in WM cells. In conclusion, 5-AzaC inhibited the mTORC1 activity via down-regulating raptor in WM cells. 5-AzaC alone or combined with mTOR inhibitors represent a novel and potentially important platform for the treatment of WM.