HDAC 억제제가 저산소성 간암세포의 생존에 미치는 영향

Enhanced histone deacetylase inhibitor-induced growth suppression in hypoxic hepatocellular carcinoma cells

Backgrounds/Aims: Mass-forming hepatocellular carcinomas (HCCs) are characteristically hypervascular. However, infiltrative types of HCCs rarely show hypervascularity, though they are frequently growing more rapidly than mass-forming types. Therefore, hypoxia is most likely to activate survival signals in these hypoxic HCC cells. Since hypoxia may also increase histone deacetylase (HDAC) activity, we postulated that HDAC inhibition may suppress cell growth more efficiently in hypoxic HCC cells than in normoxic cells. Methods: Human HCC cells were cultured either in a normoxic or hypoxic condition. Cell growth was assessed using the MTS assay and apoptotic signals were explored using immunoblot analysis. HDAC inhibitor, trichostatin A (TSA), and JNK inhibitor, SP600125, were used in this study. Results: TSA suppressed HCC cell growth by inducing cellular apoptosis, which was mediated by mitochondrial apoptotic signals. TSA induced apoptosis more efficiently in hypoxic HCC cells than in normoxic cells. This enhancement of apoptosis in hypoxic cells was due to more augmented induction of Bax and Noxa in these cells as compared to normoxic cells. TSA induced JNK activation more potently in hypoxic cells than in normoxic cells, and this was responsible for differential induction of Bax and Noxa in hypoxic cells. Indeed, JNK inhibitor pretreatment partially prevented TSA-induced growth suppression in hypoxic HCC cells. Conclusions: These results demonstrate that HDAC inhibitor suppresses cell growth more efficiently in hypoxic HCC cells than in normoxic cells through differential induction of JNK-dependent Bax and Noxa. Therefore, HDAC inhibitors may therapeutically be useful in HCCs, especially in advanced infiltrative type of tumors which are exposed to hypoxic environment.