Cleavage of growth differentiation factor 15 (GDF15) by membrane type 1-matrix metalloproteinase abrogates GDF15-mediated suppression of tumor cell growth.

S.H. Abd El-Aziz, Y. Endo, H. Miyamori, T. Takino and H. Sato

Growth Differentiation Factor 15 (GDF15), a TGF- β superfamily member, has been cloned from placenta cDNA library as a gene product that promoted activation of pro-MMP2 mediated by MT1-MMP. Expression of MT1-MMP in HEK293T cells caused cleavage of GDF15 mature form at N^{252}-M^{253} to produce 6-kD C-terminal fragment. Treatment of MCF7 cells with GDF15 induced activation of p53 and enhanced expression of p21, which was abrogated by MT1-MMP expression. Treatment of MCF7 cells with GDF15 caused suppression of cell proliferation. However, proliferation of MCF7 cells trasnfected with MT1-MMP gene was not affected by GDF15 treatment, but was suppressed in the presence of MMP inhibitor BB94. HT1080 cells transfected with GDF15 gene, which endogenously express MT1-MMP, synthesize a high level GDF15 precursor form and a low level mature form, and treatment of cells with BB94 enhanced production of GDF15 mature form. In consistent with GDF15 production, HT1080 cells transfected with GDF15 gene proliferated almost equally with control cells, and addition of BB94 effectively suppressed growth of HT1080 cells transfected with GDF15 gene but not control cells. These results suggest that MT1-MMP contributes to tumor cell proliferation through the cleavage of GDF15 which down-regulates cell proliferation by inducing activation of p53 and p21 synthesis.

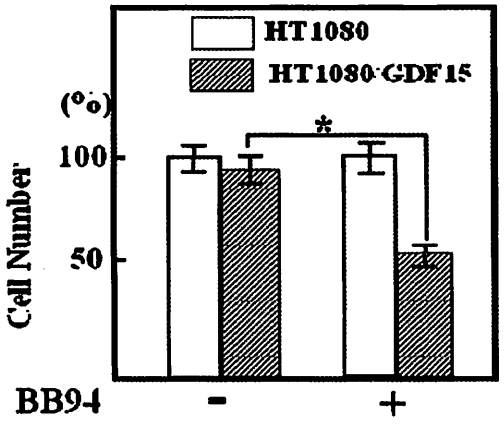

Fig. 1. HT1080 cells stably transfected with control plasmid or GDF15 plasmid were cultured in the presence or absence of BB94 for 24 h, and the cell number was compared. *, P<0.001. Note that inhibition of endogenous MT1-MMP by BB94 induced accumulation of GDF15, which in turn caused growth suppression.

Reference: S.H. Abd El-Aziz et al., Cancer Sci., 98, 1330-1335 (2007).