学位の種類	博士（医学）
報告番号	甲第１６２１号
学位記番号	第１１５６号
氏名	藤田　和彦
授与年月日	平成 30 年 3 月 26 日
学位論文の題名	HSP90 inhibitors potentiate PGF2α-induced IL-6 synthesis via p38 MAP kinase in osteoblasts （骨芽細胞において HSP90 阻害剤は p38 MAP kinase を介して PGF2α による IL-6 産生を促進する） PLoS One Vol.12: e0177878, 2017
論文審査担当者	主査：　和田 郁雄 副査：　岡本 尚，大塚 隆信

Abstract

Heat shock proteins (HSPs) are induced in response to biological stress such as heat stress and chemical stress. Heat shock protein 90 (HSP90) that is ubiquitously expressed in various tissues, is recognized to be a major molecular chaperone. We have previously reported that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a potent bone remodeling mediator, stimulates the synthesis of interleukin-6 (IL-6) through p44/p42 mitogen-activated protein (MAP) kinase and p38 MAP kinase in osteoblast-like MC3T3-E1 cells, and that Rho-kinase acts at a point upstream of p38 MAP kinase. In the present study, we investigated the involvement of HSP90 in the $PGF_{2\alpha}$-stimulated IL-6 synthesis and the underlying mechanism in MC3T3-E1 cells. Geldanamycin, an inhibitor of HSP90, significantly amplified both the $PGF_{2\alpha}$-stimulated IL-6 release and the mRNA expression levels. In addition, other HSP90 inhibitors, 17-allylamino-17demethoxy-geldanamycin (17-AAG) and 17-dimethylamino-ethylamino-17-demethoxy-geldanamycin (17-DMAG) and onalespib, enhanced the $PGF_{2\alpha}$-stimulated IL-6 release. Geldanamycin, 17-AAG and onalespib markedly strengthened the $PGF_{2\alpha}$-induced phosphorylation of p38 MAP kinase. Geldanamycin and 17-AAG did not affect the $PGF_{2\alpha}$-induced phosphorylation of p44/p42 MAP kinase and myosin phosphatase targeting subunit (MYPT-1), a substrate of Rho-kinase, and the protein levels of RhoA and Rho-kinase. In addition, HSP90-siRNA enhanced the $PGF_{2\alpha}$-induced phosphorylation of p38 MAP kinase. Furthermore, SB203580, an inhibitor of p38 MAP kinase, significantly suppressed the amplification by geldanamycin, 17-AAG or 17-DMAG of the $PGF_{2\alpha}$-stimulated IL-6 release. Our results strongly suggest that HSP90 negatively regulates the $PGF_{2\alpha}$-stimulated IL-6 synthesis in osteoblasts, and that the effect of HSP90 is exerted through regulating p38 MAP kinase activation. Therefore, HSP90 inhibitors might lead a new therapeutic strategy for acceleration of fracture healing and bone metabolic

diseases such as osteoporosis. Further investigations would be required to clarify the details underlying the effects of HSP90 on bone metabolism.