学位の種類	博士（医学）
報告番号	甲第１６１７号
学位記番号	第１１５２号
氏名	川端　哲
授与年月日	平成 30 年 3 月 26 日
学位論文の題名	Resveratrol inhibits the epidermal growth factor-induced migration of osteoblasts : the suppression of SAPK/JNK and Akt （Resveratrol は SAPK/JNK と Akt を介して epidermal growth factor による骨芽細胞の遊走を抑制する） Cellular Physiology and Biochemistry Vol. 43: P.1025-1036, 2017.
論文審査担当者	主査：　和田 郁雄 副査：　岡本 尚，大塚 隆信

Abstract

The migration of osteoblasts is recognized as important for many processes essential to physiological bone metabolism, including bone remodeling and responses to mechanical loading. Numerous humoral factors, such as epidermal growth factor (EGF), play essential roles in bone metabolism. However, the details of the mechanism underlying EGF-induced migration of osteoblasts remain to be clarified. Resveratrol is a polyphenol enriched in the skins of grapes and berries, that shows various beneficial effects for human health. In the present study, we investigated the mechanism behind the epidermal growth factor (EGF)-induced migration of osteoblast-like MC3T3-E1 cells, and the effect of resveratrol on this cell migration. The EGF-induced migration was suppressed by PD98059, an inhibitor of MEK1/2, as well as SB203580, an inhibitor of p38 MAP kinase, SP600125, an inhibitor of SAPK/JNK, and deguelin, an inhibitor of Akt. Meanwhile, rapamycin, an inhibitor of upstream kinase of p70 S6 kinase, and fasudil, an inhibitor of Rho-kinase, hardly affected the migration. Resveratrol significantly reduced the EGF-induced migration in a dose-dependent manner. SRT1720, an SIRT1 activator, suppressed the migration by EGF. Additionally, resveratrol markedly attenuated the EGF-induced phosphorylation of SAPK/JNK and Akt without affecting the phosphorylation of p44/p42 MAP kinase or p38 MAP kinase. The phosphorylation of SAPK/JNK and Akt induced by EGF was supressed by SRT1720. Our results strongly suggest that resveratrol reduces the EGF-stimulated migration of osteoblasts via suppression of SAPK and Akt, and that the inhibitory effect of resveratrol is mediated in part via SIRT1.