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Fibroblast growth factor-7 facilitates osteogenic differentiation of embryonic stem cells through the activation of ERK/Runx2 signaling

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Abstract Fibroblast growth factor-7 (FGF7) is known to regulate proliferation and differentiation of cells; however, little information is available on how FGF7 affects the differentiation of embryonic stem cells (ESCs). We examined the effects of FGF7 on proliferation and osteogenic differentiation of mouse ESCs. Exogenous FGF7 addition did not change the proliferation rate of mouse ESCs. In contrast, the addition of FGF7 facilitated the dexamethasone, ascorbic acid, and β-glycerophosphate (DAG)-induced increases in bone-like nodule formation and calcium accumulation. FGF7 also augmented mRNA expression of runt-related transcription factor-2 (Runx2), osterix, bone sialoprotein (BSP), and osteocalcin (OC) in the presence of DAG. FGF7-mediated increases in the mineralization and bone-specific gene expression were almost completely attenuated by pretreating with anti-FGF7 antibody. FGF7 treatment accelerated the DAG-induced activation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) in the cells. A pharmacological inhibitor specific to ERK, but not to JNK or p38 kinase, dramatically suppressed FGF7-mediated mineralization and accumulation of collagen and OC in the presence of DAG. This suppression was accompanied by the reduction in Runx2, osterix, BSP, and OC mRNA levels, which were increased by FGF7 in the presence of DAG. Collectively, our results suggest that FGF7 stimulates osteogenic differentiation, but not proliferation, in ESCs, by activating ERK/Runx2 signaling.

Keywords FGF7 · Osteogenic differentiation · Mouse embryonic stem cells · MAPK · Runx2

Introduction

Fibroblast growth factors (FGFs) play critical roles in multiple biological processes including cellular proliferation, differentiation, and survival [1, 2]. Approximately 23 members of the FGF family have been identified and their functions differ according to the FGF family, the cell types in which they are expressed, and the stages of development [3, 4]. Among the FGFs, FGF7, also known as keratinocyte growth factor-1, is a specific paracrine mediator of epithelial cell growth and is required for normal epithelial homeostasis [5]. The expression of FGF7 is up-regulated during wound heading, chronic inflammatory bowel diseases, and psoriasis [6–8].

Fibroblast growth factors control differentiation of stem cells into osteoblasts, osteoclasts, cementoblasts, and adipocytes [9–12]. Especially, FGF7 is produced in osteogenically differentiated cells [13] and it also stimulated oocyte growth via stem cell factor-related signaling [14]. FGF7 is known as a dermal papilla signal that induces hair follicles to proliferate and initiate the new hair cycle [15]. These findings suggest that FGF7 acts as paracrine and/or

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