Research Article

Transcriptional Regulation of Δ6-Desaturase by Peroxisome Proliferative-Activated Receptor δ Agonist in Human Pancreatic Cancer Cells: Role of MEK/ERK1/2 Pathway

Maryam Darabi,1 Shima Byagowi,2 Shabnam Fayezi,1,3 Masoud Darabi,1 Shahab Mirshahvaladi,4 and Mehdi Sahmani2

1 Department of Applied Research Center, Tabriz University of Medical Sciences, Tabriz 5166665811, Iran
2 Department of Clinical Biochemistry and Genetics, Cellular and Molecular Research Center, Faculty of Medicine, Qazvin University of Medical Sciences, Qazvin 341975981, Iran
3 Department of Anatomy and Cell Biology, Shahid Beheshti University of Medical Sciences, Tehran 193954719, Iran
4 Department of Biotechnology, Cellular and Molecular and Burns Research Centers, Iran University of Medical Sciences, Tehran 141556183, Iran

Correspondence should be addressed to Mehdi Sahmani; m.sahmani@gmail.com

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The Δ6-desaturase (Δ6D), also known as fatty acid desaturase 2, is a regulatory enzyme in de novo fatty acid synthesis, which has been linked to obesity and diabetes. The aim of the present study was to investigate the effect of peroxisome proliferative-activated receptor δ (PPARδ) agonist and MEK/ERK1/2-dependent pathway on the expression of Δ6D in human pancreatic carcinoma cell line PANC-1. PANC-1 cells cultured in RPMI-1640 were exposed to the commonly used ERK1/2 pathway inhibitor PD98059 and PPARδ agonist GW0742. Changes in mRNA and protein expression of Δ6D were then determined using real-time RT-PCR and Western blot, respectively. The expression of Δ6D (P < 0.01) increased following treatment with PPARδ agonist both at mRNA and protein levels, whereas no significant change was observed after treatment with MEK/ERK1/2 pathway inhibitor. It was also found that the increase in the expression of Δ6D in response to GW0742 was significantly inhibited by PD98059 (>40%, P < 0.05) or EGF receptor-selective inhibitor AG490 (>25%, P < 0.05) pretreatment. PPARδ and MEK/ERK1/2 signaling pathways affect differentially the expression of Δ6D in pancreatic cancer cells. Furthermore, there may be an inhibitory crosstalk between these two regulatory pathways on the mRNA expression of Δ6D and subsequently on Δ6D protein expression.

1. Introduction

Numerous in vitro and in vivo studies indicate the critical role of fatty acids in cell membrane fluidity, which in turn affect ligand binding and cellular signal transduction of surface receptors and G-proteins [1–3]. This role has been demonstrated by the fact that the altered levels of fatty acid desaturase enzymes are associated with various human diseases like diabetes and atherosclerosis [4, 5]. Studies have shown that lipotoxicity of human pancreatic islets, which is attributed to accumulation of saturated fatty acids, is one of the important causes of dysregulated insulin secretion and apoptosis of pancreatic β-cell [6, 7]. In contrast to saturated fatty acids, unsaturated fatty acids play a key role in survival of the pancreatic β-cell [8, 9]. The membrane-bound enzyme Δ6 fatty acid desaturase (Δ6D), encoded by the fatty acid desaturase 2 (FADS2) gene, is the first and rate-limiting enzyme in the synthesis of unsaturated fatty acids. FADS2-deficient mouse model has revealed that Δ6D is the main enzyme in in vivo production of n-6 polyunsaturated fatty acids (PUFA) [10].

The delta isoform of the peroxisome proliferator-activated receptor (PPAR) δ is a family of nuclear receptors regulating the expression of genes involved in fatty acid