G protein-coupled receptor GPR160 is associated with apoptosis and cell cycle arrest of prostate cancer cells

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ABSTRACT

G protein-coupled receptors (GPCRs) represent the largest membrane protein family implicated in the therapeutic intervention of a variety of diseases including cancer. Exploration of biological actions of orphan GPCRs may lead to the identification of new targets for drug discovery. This study investigates potential roles of GPR160, an orphan GPCR, in the pathogenesis of prostate cancer. The transcription levels of GPR160 in the prostate cancer tissue samples and cell lines, such as PC-3, LNCaP, DU145 and 22Rv1 cells, were significantly higher than that seen in normal prostate tissue and cells. Knockdown of GPR160 by lentivirus-mediated short hairpin RNA constructs targeting human GPR160 gene (ShGPR160) resulted in prostate cancer cell apoptosis and growth arrest both in vitro and in athymic mice. Differential gene expression patterns in PC-3 cells infected with ShGPR160 or scramble lentivirus showed that 815 genes were activated and 1193 repressed. Functional annotation of differentially expressed genes (DEGs) revealed that microtubule cytoskeleton, cytokine activity, cell cycle phase and mitosis are the most evident functions enriched by the repressed genes, while regulation of programmed cell death, apoptosis and chemotaxis are enriched significantly by the activated genes. Treatment of cells with GPR160-targeting shRNA lentiviruses or duplex siRNA oligos increased the transcription of IL6 and CASP1 gene significantly. Our data suggest that the expression level of endogenous GPR160 is associated with the pathogenesis of prostate cancer.

INTRODUCTION

G protein-coupled receptors (GPCRs) are cell-surface molecules that transduce extracellular signals into intracellular effector pathways through the activation of heterotrimeric G proteins [1]. Owing to their special structural features, signal transduction pathways and extensive physiological functions, GPCRs rank the highest success rate among all drug target categories in pharmaceutical development [2]. About 40% clinically approved drugs target GPCRs [3]. There are more than 800 members of GPCRs, but only a small number of them are targeted by current drugs [4]. A tremendous amount of efforts have been made so far aiming at exploiting therapeutic applications of the remaining family members, including more than 140 orphan GPCRs whose endogenous ligands have yet to be unmasked [5].

Since the first identification of MAS gene, which encodes a functional GPCR, as an oncogene [6], an increasing body of evidence links GPCR expression and activation to human primary and metastatic tumors [7, 8]. GPCRs, G proteins and their downstream signaling affect different facets of human malignancies, including cancer initiation and progression, cell invasion and metastasis, angiogenesis, as well as the establishment and maintenance of a permissive microenvironment [8]. Widespread mutations of G proteins and GPCRs were also found in common cancer cells, such as activating mutations of GNAS (encoding Gαs) in 28% of growth hormone-secreting