

Novel integrative gene therapy for hormone refractory prostate cancer

メタデータ	言語: jpn 出版者: 公開日: 2021-11-08 キーワード (Ja): キーワード (En): 作成者: Konaka, Hiroyuki メールアドレス: 所属:
URL	https://doi.org/10.24517/00063091

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2005 Fiscal Year Final Research Report Summary

Novel integrative gene therapy for hormone refractory prostate cancer

Research Project

Project/Area Number

16591586

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

Urology

Research Institution

Kanazawa University

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Project Period (FY)

2004 – 2005

Keywords

gene therapy / promoter / dexamethasone / PSA / androgen receptor / glucocorticoid receptor

Research Abstract

Prostate specific antigen (PSA) is widely used as a diagnostic serum marker of prostate cancer, and the PSA promoter is also utilized as a prostate-specific vector for the delivery of therapeutic genes. The PSA promoter is regulated by androgen receptor (AR), as well as the other transcription factors. A recent study from our laboratory has demonstrated that NF- κ B down-regulates PSA transactivation and expression by binding to its cis-element, named XBE. In this study, we investigated the role of glucocorticoid receptor (GR) in regulating PSA promoter activity in androgen-independent DU145 or PC-3 prostate cancer cell lines. First, we demonstrated that GR-specific mRNA and protein were expressed in DU145 or PC-3 cells, not in androgen dependent LNCaP cells, and that dexamethasone (DEX), a synthetic glucocorticoid, induced markedly the promoter activity driven by tandem repeat of glucocorticoid responsive elements (GREs) in DU145 and PC-3 cells in a dose-dependent manner. Second, the results of transcription factor database search and gel shift assays identified two GREs (GREI and II) within the distal enhancer of the PSA promoter. Third, the mutation of GREs in the full-length and chimeric promoter reporters confirmed that GR could activate the PSA promoter by binding to GREs. Moreover, the deletion of XBE

in the chimeric PSA promoter constructs further enhanced the transcriptional activity of GR in AI DU145 or PC-3 cells, where NF- κ B constitutively active, and consistent with this observation, p65 subunit of NF- κ B inhibited GR function. Collectively, our data are the first physical evidence that DEX regulates the PSA promoter in AI PC-3 and DU145 cells through the intrinsic GR. These findings suggest that GR mediated-PSA promoter activation may be applicable for the expression of therapeutic genes in AI prostate cancers.

URL: https://kaken.nii.ac.jp/report/KAKENHI-PROJECT-16591586/165915862005kenkyu_seika_hokoku

Published: 2007-12-12