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 研究課題名 (英文) Pre-clinical applications using PTEN-knockout prostate cancer mouse model
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研究成果の概要 (和文)：われわれは以前に PSA コンディショナル PTEN ノックアウトマウスを確立し、ヒト前立腺癌の発生・治療など多岐にわたる研究に対して有用であることを検証してきた。今回 PTEN flox/PSA-Cre マウス前立腺発癌モデルにおいて、抗アンドロゲン薬・分子標的薬の単剤およびコンビネーション療法にて Intervention 療法としての有効性について検討し、MEK 阻害剤 AZD6244 や JAK/STAT シグナル阻害剤 AZD1480 についても同様の研究を行い、有意な抗腫瘍効果を認めた。また、癌組織を用いた Adipokine profile の検討で発見した Leptin と CRPC モデルを用いて行った DNA マイクロアレイから得られた細胞外マトリックス蛋白である Lumican や HOXA10 についても検討し、予後を決定するバイオマーカーとして有用であると思われる。これらの結果については日本癌学会、泌尿器科学会、103 回アメリカ癌学会 (AACR) などにおいて報告した。

研究成果の概要 (英文)：To better understand the disease process of prostate cancer, we have developed a prostate-specific conditional knockout mouse model that targets the *PTEN* tumor suppressor gene. Our model is based on *PSA-Cre* recombinase driven inactivation of *Pten* to alter PI3K/Akt/mTOR signaling specific to the prostate, resulting in a stage-specific development and progression of cancer that mimics humans recapitulating various stages of disease progression ranging from precancerous PIN lesions to castration resistant prostate cancer. We performed several experiments that demonstrate the versatility and usefulness of this model for validation of preclinical targeted intervention, biomarker discovery (leptin, lumican and HOXA10) and characterizing lifestyle behavior effects on cancer progression.

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1. 研究開始当初の背景

Prostate cancer progression follows a series of defined states, which include prostatic intraepithelial neoplasia (PIN), prostate adenocarcinoma in situ, locally invasive adenocarcinoma and eventually metastatic cancer. *PTEN* is a key tumor suppressor commonly inactivated in human prostate cancer and is correlated with advanced disease. Currently, the mainstay for the treatment of advanced prostate cancer remains androgen deprivation therapy (ADT); however, resistance is inevitable and all patients eventually succumb to the disease. Furthermore, it has become clear that a number of non-androgen receptor

mediated pathways play significant roles in regulating tumor cell proliferation, survival, migration, and metabolism. A number of small molecule drugs have been developed to target specific pathways in hopes of attenuating the disease. However, cancer is a complex disease that involves the deregulation of a several molecular pathways. Moreover, crosstalk, compensatory signaling and salvage pathways contribute to ensure the survival tumors cells in the event of cellular stress.

Novel treatment strategies are currently being developed and explored, however, traditional xenograft models may be inadequate to explore this concept.

Genetically engineered mice have been developed to express or inhibit a particular gene function that leads to the development of prostate cancer. Driven by tissue specific promoters, deletion of tumor suppressors results in the generation of conditional transgenic mice that develop clinically relevant tumors that possess most of the clinicopathological and molecular features of human prostate cancer. In essence, these models provide a new tool for the characterization of prostate tumorigenesis process, drug target and biomarker discovery and preclinical efficacy evaluation.

We previously investigated the feasibility of this model to test the antitumor effects of the mTOR inhibitor, everolimus and the multi kinase inhibitor sorafenib. Based on our initial findings we will move to investigate the effects of targeted therapy on key signaling pathways associated with prostate cancer. Furthermore, we will use our data from genome-wide microarray analysis for novel biomarker discovery. Lastly we will also report our findings on the effects of long-term increased dietary fat and its effects on prostate cancer progression.

2. 研究の目的

To better understand the disease process of prostate cancer, we have developed a prostate-specific conditional knockout mouse model that targets the *Pten* tumor suppressor gene. Our model is based on *PSA-Cre* recombinase driven inactivation of *Pten* to alter PI3K/Akt/mTOR signaling specific to the prostate, resulting in a stage-specific development and progression of cancer that mimics humans recapitulating various stages of disease progression ranging from precancerous PIN lesions to castration resistant prostate cancer. We performed several experiments that demonstrate the versatility and usefulness of this model for validation of preclinical targeted intervention, biomarker discovery and characterizing lifestyle behavior effects on cancer progression.

3. 研究の方法

a. Preclinical target inhibition exp.

To evaluate the effects of targeted PI3K/Akt/mTOR, MAPK, and JAK/STAT3 signal inhibition we used recently obtained drugs from AstraZeneca, namely the: Akt inhibitor, AZD5363; MAPK inhibitor, AZD624; JAK2 inhibitor AZD1480; and from Chugai Pharmaceuticals, an anti-mouse IL-6 receptor (IL-6R) blocking antibody. We performed pharmacodynamic experiments to test the acute responses from a single dose of AZD5363, AZD6244, and AZD1480 in a dose- and time-dependent manner. Experimental endpoints included proliferation, apoptosis and target pathway downregulation. Endpoints were assessed by western blot and immunohistochemical (IHC) methods. We also examined the effects of chronic inhibition according to the

schedules shown in Figure 1. Experimental endpoints included toxicity, tumor burden, tumor proliferation and apoptosis, and target pathway inhibition. Toxicity and tolerability were assessed by changes in mouse body weights, appearance, demeanor and behavior. Tumor responses were measured by differences in genitourinary tract weight, 2D morphometric tumor area analysis, histology, proliferation and apoptosis. Target validation was assessed by evaluating inhibition of corresponding downstream target molecules by western blot and IHC methods.

To evaluate the possibility of upstream signal inhibition of STAT3 signal we first established the role of IL-6/IL-6R/STAT3 in our model by using standard western blot, IHC and ELISA methods. Upstream inhibition of the IL-6R was accomplished by using an anti-mouse IL-6R blocking antibody. In vivo effects of upstream STAT3 inhibition were measured by evaluating dose- and time-dependent changes in tumor cell proliferation and apoptosis as well as transcriptional activation of STAT3 by western blot and IHC in PTEN-mutant mice.

b. Biomarker discovery exp

We performed a comprehensive genome-wide microarray analysis of genes differentially up- or down-regulated in *PSACre;Pten^{loxP/loxP}* mutant mice and examined novel differentially expressed genes in to identify novel genes that could potentially serve as biomarkers for disease tumor characterization. Total RNAs were collected from the prostate glands of tumor bearing *PSACre;Pten^{loxP/loxP}* mutant and wild type mice. cDNAs were generated and were then hybridized onto Affymetrix microarray chips and analyzed with Agilent's Gene Spring software. Associated genes were identified by cDNA microarray analysis from a library of >45,000 genes. Because of the large amount of data generated and the complex nature of microarray analysis, we focused extensive analysis based on gene ontology, pathway databases and pathway-specific microarray annotations.

Expression of candidate genes was confirmed by measuring the levels mRNA and protein using qRT-PCR, western blot and immunohistochemistry in mouse PCa tissues at various points during tumor progression. Clinical significance was established by measuring the level of expression of candidate markers in matched normal and tumor human tissues from prostatectomy cases and from cancer-free human benign prostatic hyperplasia (BPH), and correlating the expression to clinico-pathological feature and biochemical recurrence.

4. 研究成果

a. Preclinical target inhibition

Inhibition of PI3K/AKT/mTOR signal activation. PI3K/Akt/mTOR signaling is commonly upregulated in prostate cancer as a result of *PTEN* inactivation. Bi-allelic inactivation of the tumor suppressor *PTEN* occurs at a high frequency in advanced prostate cancer and correlates with disease-specific mortality. The strong implication of *PTEN* in prostate cancer progression in humans has prompted us to develop a transgenic mouse model based on tissue-specific conditional inactivation of *PTEN*. As a result, we have generated homozygous *PTEN*-mutant mice that develop tumors in the prostate that mimic prostate cancer in humans. To investigate the potential of PI3K/Akt signal inhibition as a therapeutic option for *PTEN*-deficient tumors, we used our *PTEN*-mutant mouse model to assess the response of the Akt kinase inhibitor, AZD5363. Pharmacodynamic studies show that AZD5363 is a strong inhibitor of the PI3K/AKT signaling pathway as demonstrated by the inhibition of S6 phosphorylation (Fig. not shown). Inhibition of cellular proliferation, based on the expression of cyclin D1, coincided with decreased S6 phosphorylation (data not shown). Interestingly compensatory pathway activation of STAT3 signaling was observed after p-S6 downregulation (data not shown). We evaluated the antitumor efficacy of AZD5363 by measuring differences in tumor growth after 4 weeks of treatment. Chronic administration of AZD5363 was tolerable and prostate tumors from mice treated with AZD5363 showed a significant size reduction compared to controls (Fig. not shown). Treatment with AZD5363 also resulted in a significant reduction of tumor cell proliferation increase in the apoptotic index (Fig. not shown). We also showed that chronic administration of AZD5363 strongly inhibited phosphorylation of the PI3K/Akt downstream molecule, S6 (Fig. not shown). These findings provide preclinical evidence that targeting PI3K/AKT signaling in *PTEN* deficient tumor results in decreased tumor activity and may be potentially translated in the clinic.

Inhibition of MAPK signal activation.

The mitogen-activated protein kinase (MAPK) pathway is involved in a broad range of cellular processes that include proliferation, survival, apoptosis, and cellular differentiation. MAPK has also been shown to increase the transcription of androgen-dependent (AR) genes, independently of androgens by phosphorylation of the AR or its cofactors. Thus, MAPK signal inhibition has the potential to be a therapeutic target for prostate cancer. To determine the clinical benefit of MAPK inhibition, we used the highly selective MEK inhibitor, AZD6244, in a prostate-specific *PTEN*-conditional knockout mouse model of prostate cancer. In this model, prostate tumors from mice

exhibit increased levels of p-Erk1/2 expression that correlates with tumor progression. Acute pharmacodynamic responses, after a single dose of AZD6244, showed a strong inhibition of Erk1/2 phosphorylation that was maintained for at least 24 hours after drug administration (Fig. not shown). Levels of cellular proliferation decreased, and apoptosis was induced shortly after the administration of AZD6244, moreover, apoptosis was suppressed after 8 hours (data not shown). To further characterize the responses to MAPK signal inhibition, we examined the activity of downstream molecules of the PI3K/Akt and JAK/STAT3 signaling pathways. While PI3K/Akt activity decreased mildly, activation of JAK/STAT3 was transiently but strongly increased (data not shown). To determine tumor responses to chronic administration of AZD6244, *Pten*-mutant mice harboring prostate tumors were treated with AZD6244 for a period of 4 weeks. 2-D morphometric analysis of tumor surface area showed a significant reduction ($P < 0.001$, Fig. not shown) in treated mice. Histological analysis confirmed a reduction of tumor burden and cancer glands showed marked differences in cellular structure and organization (Fig. not shown). A significant of cancer cell proliferation accompanied by a significant increase in apoptosis was also observed (Fig. not shown). These findings provide preclinical evidence that inhibition of MAPK signaling can contribute to decreased tumor progression and may represent a promising therapeutic alternative.

Inhibition of JAK/STAT3 signaling by AZD1480

Signal transducers and activators of transcription (STAT) were originally identified as components of cytokine signal transduction pathways but are now also recognized as key regulators of apoptosis, proliferation, angiogenesis and immune responses in many malignant diseases. Activation of STAT3 occurs by the binding of various cytokines to its receptors leading to the activation of the JAK/STAT3 signaling pathway. Of these cytokines, interleukin-6 (IL-6) has been implicated in regulating growth of various malignant tumors. Activated IL-6 has also been shown to be elevated in the sera from patients with metastatic prostate cancer, and persistent activation of STAT3 is a common feature. To better characterize the potential role of JAK/STAT3 as a therapeutic target for advanced prostate cancer, we used the JAK1/2 inhibitor, AZD1480 to suppress the transcriptional activation of STAT3 in a *PTEN*-conditional knockout mouse model of prostate cancer. Prostate tumors from homozygous *PTEN*-mutant mice share many characteristics of human prostate cancer, including increased activation of the JAK/STAT3 signaling cascade. Our pharmacodynamic studies show that

AZD1480 elicited a strong inhibition of STAT3 signal activation leading to decreased tumor cell proliferation, and induction of apoptosis (data not shown). Our drug intervention studies show that persistent suppression of STAT3 by treatment with AZD1480 for 4 weeks results in a significant reduction tumor growth (Fig. not shown). This was characterized by significant decreases in tumor cell proliferation, induction of apoptosis (Fig. not shown). Inhibition of p-STAT3 pY705 was confirmed by western blot and IHC (Fig. not shown). Interestingly we also discovered that AZD1480 inhibited tumor angiogenesis in AZD1480-treated mice (Fig. not shown). Our findings show a strong antitumor effect for STAT3 signal inhibition and may thus represent a promising therapeutic option.

Inhibition of JAK/STAT3 signaling by MR-16

Interleukin-6 or IL-6 is a pleiotropic cytokine which is implicated in the regulation of immune response, but is also involved in regulating the growth of various malignant tumors. Mounting evidence suggests that IL-6 contributes to prostate cancer progression. Activated IL-6 has been shown to be elevated in the sera from patients with metastatic prostate cancer and it appears that the prostate tissue itself is a source of IL-6 and its receptor. Experimental data suggests that the IL-6/IL-6R signaling axis is an autocrine and paracrine growth factor in androgen independent prostate cancer cell lines and can activate a variety of signal transduction cascades, some of which may activate androgen receptor activity. In the present study we examined the role of IL6-induced Stat3 activation in the development and progression of prostate cancer and its possible role as a target for the treatment of prostate cancer using the prostate-specific conditional targeting PTEN knockout mouse model. In *PTEN*-mutant mice, elevated levels of IL6/IL-6R correlated with increased cellular proliferation in non-castrate and castrate prostate cancer (CRPC). Similar to human prostate cancer, mice with CRPC showed elevated levels of IL-6 and IL6-R in both serum and prostate tissue. To establish a therapeutic role for IL6/IL6R inhibition, we conducted a series of pharmacodynamic studies using an anti-mouse IL-6R antibody (MR-16) in tumor bearing homozygous *PTEN*-mutant mice. Our data shows that STAT3 activation was inhibited in a dose dependent manner during acute IL6-R blockade (Fig 4. not shown). Inhibition of STAT3 activity after chronic IL-6R blockade was transient. However, at day 45 of treatment, Levels of p-STAT3 and tumor cell proliferation were inhibited and apoptosis was induced (Fig 4. not shown). These findings show that this mouse model is relevant for the study of Stat3 signaling and tumor progression and inhibition of Stat3 transcriptional activation

by upstream signal blockade may be a promising approach for molecularly targeted therapeutic strategies in human prostate cancer. Thus this study will serve as the foundation for future drug intervention studies designed to assess the efficacy of targeting the JAK/STAT signal pathway using targeted monotherapy and combination drug therapy models.

b. Biomarker discovery

HOXA10 and Prostate Cancer

Drug target and biomarker discovery using human samples is difficult and is hampered by the amount of genetic variation among individuals as well as external factors that contribute to the pathogenesis. By interrogating the genome of a transgenic mouse model of prostate cancer, we identified *HOXA10* as candidate gene for further analysis and characterization. *HOXA10* is a member of the homeobox gene family and is a transcription factors primarily involved in embryonic development. Perturbed HOX gene expression has been identified in numerous cancers and thus suggests that these genes may play important roles in diagnosis and treatment of cancer. Protein levels of HOXA10 are highly expressed in the normal prostate glands from wildtype and PTEN-mutant mice and gradually decrease with tumor development and decreased differentiation (Fig. not shown). However, focal expression of HOXA10 is observed in poorly differentiated tumors and is highly expressed in metastases. To determine clinical significance, we examined HOXA10 immunohistochemical expression patterns in matched human normal and cancer specimens from prostatectomy cases. Characterization of HOXA10 expression was performed on human derived prostate cell lines and was found to be high in the benign prostatic hyperplasia BPH-1 human prostate cell line and low in malignant human prostate cancer cell lines PC3, DU145 and LNCaP. To determine clinical significance, we examined HOXA10 IHC expression patterns in matched human normal and cancer specimens from prostatectomy cases. We found that down-regulation of HOXA10 expression was significant in PCa compared to normal prostate tissue and its expression was significantly inversely correlated to Gleason pattern, differentiation, and clinical stage ($P < 0.001$, not shown). Furthermore, down-regulation of HOXA10 was significantly associated with an increased rate of biochemical recurrence (Fig. not shown). Our data shows that HOXA10 plays a significant role in normal prostate function and deregulation likely contributes to prostate cancer progression. Thus our findings suggest that HOXA10 may serve as a possible prognostic biomarker.

Lumican and Prostate Cancer

In order to identify potential biomarkers for

prostate cancer characterization, we performed comprehensive genome-wide microarray exploratory analysis in normal and cancer prostate samples from from *PSA^{Cre};Pten^{loxP/loxP}* mutant and wild type mice, to identify possible candidate biomarkers. This analysis revealed altered expression of lumican in tumor samples from *PTEN*-mutant mice. Lumican is a small leucine-rich extracellular matrix protein that has been shown to modulate cell migration and proliferation during embryonic development, and tissue repair. Expression and distinct glycosylation patterns of lumican in several tumor and stromal tissues has been shown to play important roles in vascular invasion, differentiation, proliferation, and invasion. In the present study, immunohistochemical analysis of lumican revealed a decrease in stromal expression and an increase in epithelial cancer cell expression in castrate-resistant tumors from homozygous *PTEN*-mutant mice. Western blot analysis also showed differences in lumican glycosylation. An increase in the proteoglycan form and decrease in glycoprotein form of lumican was observed in lysate samples collected from tumor bearing mice. Immunohistochemical analysis showed strong cytoplasmic expression in expression in benign and malignant human prostate cells lines. However, Western blot analysis showed that malignant (PC3, DU145, LNCaP and C4-2) but not benign (BPH-1) cells secreted the glycoprotein form of lumican. To determine clinical significance of lumican expression in humans, we performed immunohistochemical analysis in human normal and tumor prostate specimens. Stromal and epithelial expression decreased in tumors and was inversely correlated to Gleason grade, stage and differentiation. Together these data suggest that lumican may play a role in tumor progression however further work need to be performed to determine the functional role of lumican post-translational modifications and prostate cancer progression.

To determine a possible role for lumican as a prognostic biomarker for prostate cancer, we examined protein expression in normal and tumor specimens from prostatectomy cases. Tissue microarrays were constructed and immunostained for lumican. Slides were digitized and the expression levels of lumican were scored in both the stroma and epithelia. Expression scores were compared with clinicopathological features and disease progression, defined as death or biochemical recurrence. Stromal Lumican expression in tumor was negatively associated with Gleason score, differentiation, node/metastasis status and disease progression. Progression free survival was significantly longer for patients with high expression of stromal lumican (HR=0.25; P=0.005). Based on this set, stromal

expression of lumican correlated to good clinical outcome for patients with prostate cancer and thus appears to be a strong prognostic biomarker for disease progression.

5. 主な発表論文等

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6. 研究組織

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