with over an estimated 26,000 cancer deaths annually. Presently, androgen deprivation therapy (ADT) with antiandrogens to suppress androgen synthesis or prevent androgens from binding to the androgen receptor (AR) are the standard treatments for metastatic PCa. Unfortunately, most ADT, including the recently developed potent antiandrogen enzalutamide (Enz), eventually fails. Results from clinical studies revealed that monoamine oxidase (MAO) might play key roles for the progression of some neuron disorders, including depression, Parkinson’s disease, or Alzheimer’s disease. The connection of MAO-A to the development of Enz resistance in CRPC, however, has not been investigated.

METHODS: MTT assay was used to detect cell proliferation. Lentivirus packaging and cell transfection was used to construct MAO-A shRNA. qRT-PCR, RNAseq and Western blot were used to detect MAO-A levels. MAO-Glo assay was used to detect MAO-A activity. Luciferase reporter and Chromatin immunoprecipitation (ChIP) assays were performed to clarify how AR alters MAO-A. Nude mice xenograft model was established for in vivo study. CTC samples used for MAO-A expression analysis were excess “left-over” cDNA samples from an ongoing prospective blood-based CTC ARv7 study in men with metastatic CRPC.

RESULTS: We illustrated that elevated MAO-A expression was increased in the Enz resistant cells. Consistently, after treated with Enz, elevated MAO-A level was detected in CTCs from patients. We also found phenelzine or clorgyline can reverse Enz resistance and clorgyline delays the development of Enz resistance. Enz can function via increasing ARv7 to increase MAO-A expression during the development of Enz resistance. Enz-increased ARv7 expression may lead to increase MAO-A expression by transcriptional regulation via direct binding to the ARE on the MAO-A 5’ promoter region. Also, ARv7 can increase the MAO-A protein stability. Targeting the MAO-A suppressed hypoxia signals to overcome Enz resistance. Targeting MAO-A signaling suppressed EnzR tumor growth in vivo.

CONCLUSIONS: Here we report that high expression of MAO-A is associated with positive ARv7 detection in CRPC patients following Enz treatment. Targeting MAO-A with phenelzine or clorgyline, the FDA-approved drugs for antidepression, re-sensitize the Enz resistant (EnzR) cells to Enz treatment and further suppress EnzR cell growth in vitro and in vivo. Our findings suggest that Enz-increased ARv7 expression can transcriptionally enhance MAO-A expression resulting in Enz resistance via altering the hypoxia (HIF-1α) signals. Together, our results show that targeting the Enz/ARv7/MAO-A signaling with the antidepressants phenelzine or clorgyline can restore Enz sensitivity to suppress EnzR cell growth, which may indicate that these antidepression drugs can overcome the Enz resistance to further suppress the EnzR CRPC.

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MP33-06
MACROPHAGE INHIBITORY CYTOKINE-1 INDUCED BY A HIGH-FAT DIET PROMOTES PROSTATE CANCER PROGRESSION BY STIMULATING TUMOR-PROMOTING CYTOKINE PRODUCTION FROM TUMOR STROMAL CELLS

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INTRODUCTION AND OBJECTIVE: Recent studies have indicated that a high-fat diet (HFD) and/or HFD-induced obesity may influence prostate cancer (PCa) progression, but the role of HFD in PCa microenvironment is unclear. This study aimed to delineate the molecular mechanisms of PCa progression under HFD milieu and define the stromal microenvironment focusing on macrophage inhibitory cytokine-1 (MIC-1) activation.

METHODS: We investigated the effects of HFD on PCa stromal microenvironment and MIC-1 signaling activation using PC-3M-luc-C6 PCa model mice fed with HFD or control diet. Further, we explored the effect of periprostatic adipocytes derived from primary PCa patients on activation and cytokine secretion of prostate stromal fibroblasts. Expression patterns and roles of MIC-1 signaling on human PCa stroma activation and progression were also investigated.

RESULTS: HFD stimulated PCa cell growth and invasion as a result of upregulated MIC-1 signaling and subsequently increased the secretion of interleukin (IL)-8 and IL-6 from prostate stromal fibroblasts in PC-3M-luc-C6 PCa mouse model. In addition, periprostatic adipocytes directly stimulated MIC-1 production from PC-3 cells and IL-8 secretion in prostate stromal fibroblasts through the upregulation of adipose lipolysis and free fatty acid release. The increased serum MIC-1 was significantly correlated with human PCa stroma activation, high serum IL-8, IL-6, and lipase activity, advanced PCa progression, and high body mass index of the patients. Glial-derived neurotrophic factor receptor α-like (GFRαL), a specific receptor of MIC-1, was highly expressed in both cytoplasm and membrane of PCa cells and surrounding stromal fibroblasts, and the expression level was decreased by androgen deprivation therapy and chemotherapy.

CONCLUSIONS: HFD-mediated activation of the PCa stromal microenvironment through metabolically upregulated MIC-1 signaling by increased available free fatty acids may be a critical mechanism of HFD and/or obesity-induced PCa progression.

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MP33-07
SERUM CHOLESTEROL-Lowering IN A PROSTATE CANCER MODEL ENHANCES ANTITUMOR IMMUNITY BY DECREASING MTOR2 SIGNALING IN CDS+ LYMPHOCYTES

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INTRODUCTION AND OBJECTIVE: Cholesterol-lowering (CL) therapies are widely and safely used to reduce cardiovascular disease. Epidemiology studies have shown an association between CL HMG-CoA-reductase inhibitors (i.e., statins) use and decreased risk of prostate cancer. Prior preclinical studies have shown that CL decreases the growth of prostate cancers. We evaluated an immune effect of CL.

METHODS: Statin do not reliably lower serum cholesterol in mice. Therefore, oral ezetimibe was used to inhibit intestinal cholesterol absorption. Ezetimibe remains in the gut and is not systemically absorbed. Therefore, it does not have any direct effects on the tumor or immunity. Mice were challenged with RM1 prostate adenocarcinoma cells. To monitor CD8+ T cell memory formation in vivo, Pmel-1 lymphocytes were harvested from Thy1.1+ transgenic mice and were adoptively transferred by tail vein injection into Thy1.2+ wild-type (WT) mice. Conditional knockout (KO) mice for mTORC2 were