GDF15 propeptide promotes bone metastasis of castration-resistant prostate cancer by augmenting the bone microenvironment

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Abstract

We performed mass spectrometry on conditioned media from four prostate cancer cell lines and identified the GDF15 propeptide (GDPP) as a novel blood biomarker for castration-resistant prostate cancer (CRPC). GDPP was abundantly secreted from CRPC bone metastases and acted on the bone metastatic microenvironment to promote tumor progression, as shown in cell-based assays and a mouse bone-metastasis model. Clinically, in 185 patients treated at Osaka University Hospital, serum GDPP demonstrated superior diagnostic performance for bone metastasis compared with PSA and established bone metabolism markers (ALP, LDH, OC, BAP, PINP, TRACP-5b). GDPP also showed the strongest correlation with the Bone Scan Index (BSI) derived from bone scintigraphy, highlighting its potential as a robust bone metastasis of CRPC biomarker.

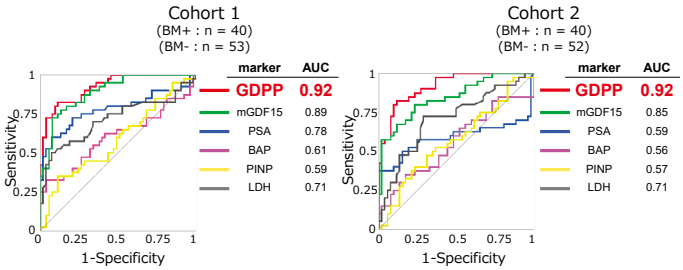
Background & Results

Prostate cancer is the most common cancer in men and often spreads to bone. Even after a diagnosis of bone metastasis, patients may live for almost three years, so careful management is essential. PSA is widely used to monitor disease status, but in CRPC patients, PSA often fails to reflect tumor burden. We identified the GDPP as a novel blood biomarker that tracks bone metastasis in both hormone-sensitive prostate cancer and CRPC. In patients with CRPC, GDPP showed stronger diagnostic performance for bone metastasis than existing markers and correlated more closely than others with BSI. During systemic therapy for CRPC, longitudinal changes in GDPP paralleled changes in BSI better than other biomarkers. Thus, plasma GDPP may aid both diagnosis and monitoring in real-world practice. Mechanistic studies further showed that GDPP promotes tumor progression and stimulates bone remodeling by increasing key transcriptional programs in osteoblasts (RUNX2, OSX, ALP) and osteoclasts (NFATc1, DC-STAMP, TRAP). Using a luciferase-tagged CRPC cell lines and bone metastasis mouse model, GDPP accelerated tumor growth, raised Ki-67 positivity in bone lesions, and increased mature osteoblast and osteoclast numbers. Together, these data suggest GDPP is a promising biomarker and mediator of CRPC with bone metastasis.

Significance of the research and Future perspective

We show that GDPP acts on the bone-metastatic microenvironment to drive CRPC bone lesions, indicating its promise as a novel biomarker. Because GDPP rises with bone metastasis, clinicians could detect progression earlier than with PSA alone and adjust therapy sooner, improving patient outcomes. Beyond discovery, we are evaluating GDPP as a tumor-agnostic biomarker for bone metastasis. A multicenter study is enrolling cancers with strong bone metastasis, including breast, kidney, and lung cancer. This work will test whether GDPP reliably reflects bone metastatic burden across tumor types and supports earlier, more precise treatment decisions. The Univeristy of Osaka will take the lead in initiating a clinical performance study in 2026, aiming to obtain regulatory approval and insurance reimbursement for its use as a diagnostic marker of bone metastasis.

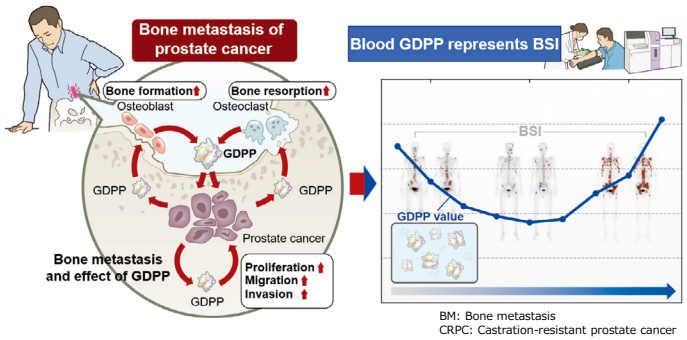
GDPP shows higher diagnostic accuracy for BM in CRPC patients than existing blood biomarkers



GDPP showed high diagnostic accuracy for BM (AUC = 0.92 in both cohorts)

BM: Bone metastasis
CRPC: Castration-resistant prostate cancer

GDPP is a novel blood biomarker of BM in CRPC patients



BM: Bone metastasis
CRPC: Castration-resistant prostate cancer

Patent	Japanese Patent Application No.2019-211488
Treatise	Yamamichi, Gaku; Kato, Taigo; Nonomura, Norio et al. Diagnostic and prognostic significance of tartrate-resistant acid phosphatase type 5b in newly diagnosed prostate cancer with bone metastasis: A real-world multi-institutional study. Int J Urol. 2023, 30(1), 70-76. doi: 10.1111/iju.15063 Yamamichi, Gaku; Kato, Taigo; Nonomura, Norio et al. GDF15 propeptide promotes bone metastasis of castration-resistant prostate cancer by augmenting the bone microenvironment. Biomark Res. 2024, 12(1), 147. doi: 10.1186/s40364-024-00695-6
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