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RANK/RANKL expression in prostate cancer

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Bone is the most common metastatic site in patients with prostate cancer. Skeletal-related events consisting of pathological fracture, spinal cord compression, and intractable pain are causes of a reduced quality of life for patients [1,2]. Denosumab (XGEVA), a human monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), was found to be a new therapeutic option for bone metastasis [3–5].

Prostate cancer cells penetrate the bone marrow and induce osteoblasts to produce cytokines that promote the secretion of RANKL. RANKL expression acceleration induces osteoclast hyperplasia and facilitates bone resorption [1]. Denosumab controls these mechanisms by inhibiting RANK. A previous study demonstrated that primary prostate cancer cells expressed the *RANK* and *RANKL* genes, which was further elevated in bone metastasis lesions [6–10]. Therefore, denosumab is expected to exert its antitumor effect by inhibiting RANKL.

Abbreviations: RANK, receptor activator of nuclear factor kappa B; RANKL, receptor activator of nuclear factor kappa B ligand.

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cDNA was extracted from a total of 115 radical prostatectomy specimens obtained at Yokohama City University Hospital. *RANK/RANKL* gene expression was examined by real-time qPCR, using *RANK* and *RANKL* primers (Applied Biosystems, Foster City, CA, USA), as we previously described [11]. Overall, the expression levels of *RANK* ($p < 0.001$) and *RANKL* ($p = 0.008$) genes in prostate cancer tissues were significantly higher than those in non-cancerous tissues [Fig. 1]. Specifically, the levels of *RANK* and *RANKL* expression in tumor were higher than those in paired normal tissue in 70.9% and 78.1%, respectively. However, no correlations were observed between *RANK* or *RANKL* gene expression and Gleason score, pT stage, or lymph node metastasis. The median PSA recurrence free survival was 4517 days in lower *RANK* expression group and 3782 days in higher *RANK* expression group, but not significantly ($p = 0.172$). In *RANKL* expression, the median PSA recurrence free survival was 3702 in lower *RANKL* expression group and 2265 days in higher *RANKL* expression group ($p = 0.205$).

A correlation between *RANKL* gene expression and pathological features has been shown in renal cell carcinoma [12,13]. In the present study, we found overexpression of *RANK* and *RANKL* genes in prostate cancer compared with non-neoplastic prostate. However, there were no correlations between *RANK/RANKL* expression and pathological features, including pT stage and lymph node metastasis. Given that all of the specimens used in this study were obtained by radical prostatectomy, their similar characteristics might have obscured any differences.

A few studies have reported potential correlations between *RANK/RANKL* expression and oncologic outcomes. For instance, Ferreira et al. showed that *RANK* expression predicted disease-free survival and overall survival in breast cancer patients [14]. To the

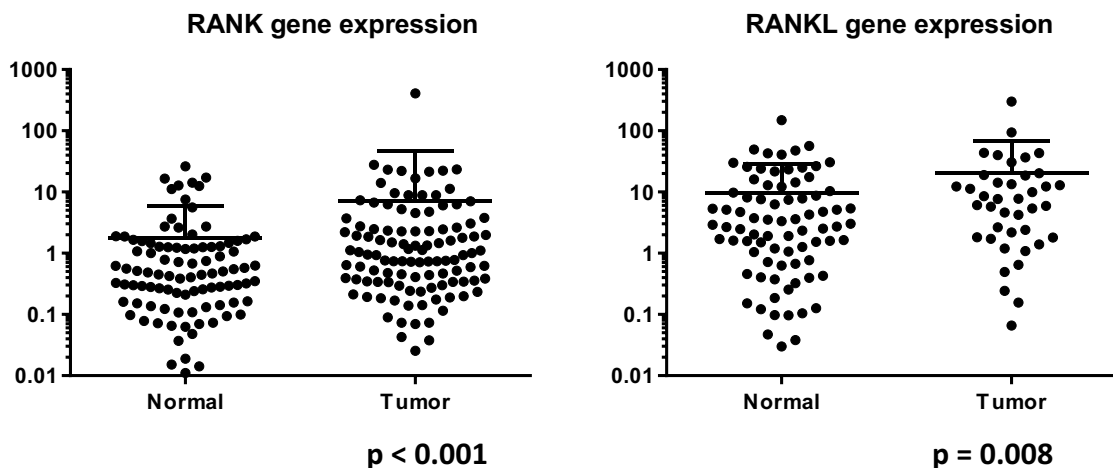


Fig. 1. RANK/RANKL gene expression in normal tissue vs. tumor tissue.

best of our knowledge, there have been no attempts to link between RANKL expression and the prognosis of prostate cancer patients. We found no significant correlation of RANK or RANKL expression with biochemical recurrence after radical prostatectomy.

Our study showed the increased expression of RANK and RANKL genes in prostate cancer, but its role was not proven. Further studies including a larger patient cohort are needed to validate the current results.

Conflict of interest

We declare no conflicts of interest.

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Authors contribution

KS and TK wrote the manuscript.
KS, TK, YH, ST, DT, TM, YH, JT, YM performed the operation.
YY, MY, HU wrote and checked the manuscript.

Ethical approval

Institutional review board of Yokohama City University Medical Center approved this study (D1507018).

Consent

We obtained written informed consent for publication. Institutional review board of Yokohama City University Medical Center approved this study (D1507018).

Guarantor

Takashi Kawahara.

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