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Immunohistological Expression of Sclerostin in Metastatic Osteolytic Bone Tumors

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Abstract

Background/Aim: Metastatic osteolytic bone tumors represent a clinical challenge as their pathogenesis and progression involve complex interactions within the bone microenvironment. Sclerostin, a key inhibitor of the Wnt signaling pathway, is critical to bone metabolism; however, its involvement in metastatic bone tumors remains insufficiently characterized. This study investigated sclerostin's role in metastatic osteolytic tumors, specifically its relationship with other bone remodeling molecules, including DKK1, BMP6, and the proliferation marker Ki67.

Patients and Methods: Tumor specimens were collected from nine patients who underwent surgery for metastatic bone tumors in the femur or tibia. Sclerostin, DKK1, BMP6, and Ki67 expression was assessed using immunohistochemical staining. Positivity rates were determined for each protein. Correlations between their expression levels were examined using Pearson's correlation coefficient.

Results: All tumor samples demonstrated a certain degree of positivity for sclerostin, DKK1, BMP6, and Ki67. The mean proportion of sclerostin-positive cells was 7.3%. Sclerostin and DKK1 exhibited a moderately negative correlation (r=–0.45), suggesting their distinct roles in the tumor microenvironment. Sclerostin and BMP6A exhibited a weak positive correlation (r=0.25), while sclerostin and Ki67 showed no significant correlation. The cohort's one-year survival rate was 72.9%.

Conclusion: Sclerostin contributes to the bone formation processes within the osteolytic metastatic tumor microenvironment, possibly through interactions with BMP6 and modulation of Wnt signaling, thus highlighting its potential as a novel therapeutic target for the treatment of metastatic bone tumors. Further studies with larger, more homogeneous patient cohorts are warranted to validate these findings and elucidate the precise molecular mechanisms involved.

Keywords: Immunohistology, sclerostin, osteolytic, bone tumors.

Introduction

The Wingless protein (Wnt) signaling pathway is crucial for guiding the differentiation of mesenchymal stem cells into osteogenic lineages and is also essential for the maturation and sustained survival of osteoblasts, thereby playing a central role in bone formation and maintenance (1). The canonical Wnt signaling pathway in bone tissue is predominantly regulated by osteocytes, which serve as the principal source of two key inhibitory

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proteins: sclerostin (SOST) and Dickkopf-related protein 1 (DKK1) (2, 3). By secreting SOST and DKK1, osteocytes exert tight control over Wnt activity, thereby modulating bone formation and remodeling processes in response to physiological and pathological stimuli (2, 3). DKK, especially DKK1-4, are known to be major repressors of Wnt signaling (4). DKK proteins bind directly to the extracellular domain of low-density lipoprotein receptor-related protein (LRP) 5/6, physically interfering with the binding of Wnt protein to the receptor and thus strongly suppressing canonical Wnt signaling (5). Furthermore, when the membrane protein Kremen binds to the DKK and LRP5/6 complex, this complex is taken up into the cells by endocytosis, leading to reduced cell surface LRP5/6 and further suppression of Wnt signaling (6). In summary, DKK suppresses Wnt signaling by binding to the Wnt signaling co-receptor LRP5/6, which is involved in the regulation of development and tissue homeostasis, as well as in disease (*e.g.,* abnormal bone metabolism and cancer) (7). Interestingly, DKK1 and DKK2 have opposing roles in tumor angiogenesis as well as in vascular normalization and functional maintenance, suggesting their potential as new molecular targets in cancer therapy (8). In addition, DKK3 may have an additional oncogenic function other than tumor suppression (9). Furthermore, DKK4 is involved in tumor growth, invasion, metastasis, and chemotherapy resistance, as well as osteoblastogenesis and secondary hair and meibomian gland formation (10).

SOST has emerged as a novel target for anabolic bone-building therapies to treat certain bone diseases (11, 12). In osteoporosis, for example, anti-SOST antibodies exhibit a dual effect by activating Wnt signaling to promote bone formation while concurrently inhibiting its resorption (13). Interestingly, suppression of sclerostin has been reported to be a therapeutic target for postmenopausal osteoporosis (14). Blood levels of SOST are often elevated in patients with chronic kidney disease, contributing to the development of low-turnover bone lesions wherein both bone formation and resorption are suppressed (13). It is also believed to be effective in the treatment of conditions such as osteogenesis imperfecta and hypophosphatasia (15).

DKK1 is known as a potent antagonist of the Wnt/β-catenin signaling pathway (16-18). However, DKK1 plays an oncogenic role in many cancer types and is involved in multiple myeloma, bone lesions, tumors, and heart, head, and forelimb development (17, 19). Notably, recent studies have suggested that SOST may be involved in the pathogenesis of multiple myeloma, potentially serving as a biomarker for the malignancy (20).

Metastatic bone tumors vary in their sites of primary origin and progression and are often refractory to multiple treatment approaches (21). No treatments have yet been developed that can fully stop the progression of these malignancies. A recent study using mice showed that SOST may inhibit prostate cancer metastasis (22). Furthermore, it has been reported that Wnt signaling *via* DKK1 may be involved in bone metastasis of breast cancer (23). However, the involvement of SOST and DKK1 in malignancies that undergo osteolytic bone metastasis is unknown. In the present study, we used immunostaining techniques to elucidate the role of SOST in osteolytic metastatic bone tumors.

Patients and Methods

Patients and data collection. Nine patients with metastatic bone tumors who were being treated at our hospital were included in this study. Their clinical data were collected and retrospectively analyzed. All patients underwent surgical treatment for bone metastases in the proximal or trunk femur at our hospital between January 2016 and December 2022. Age, primary site, metastatic site, surgical procedure, postoperative outcome, and follow-up period (months) were extracted from the patients' electronic medical records. The follow-up period was defined as the period (in months) from the date of surgery until the date of the patient's final visit to our center or death.

Inclusion and exclusion criteria. The primary inclusion criterion was the ability to follow up each patient to obtain their medical treatment history. Patients who could not be followed up for this purpose were excluded.

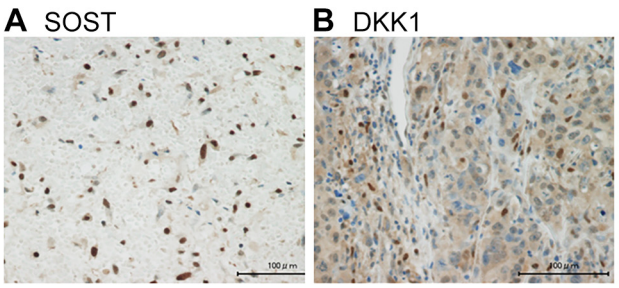

Figure 1. *Representative immunostaining images. (A) Sclerostin (SOST) immunostaining image showing tumor cells that tested positive for the protein. (B) Dickkopf-1 (DKK1) immunostaining image showing tumor cells that tested positive for the protein. Scale bar=100 µm.*

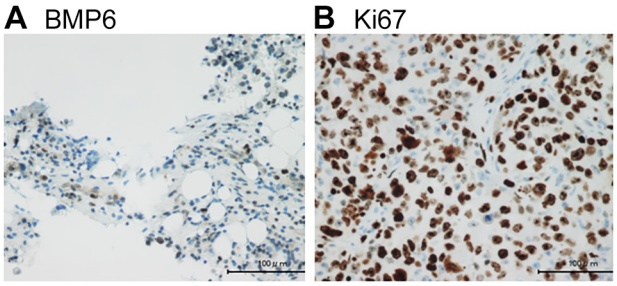

Figure 2. *Representative immunostaining images. (A) Bone morphogenetic protein 6 (BMP6) immunostaining image showing tumor cells that tested positive for the protein. (B) Ki67 immunostaining image showing tumor cells that tested positive for the protein. Scale bar=100 µm.*

The included patients comprised five males and four females. Their mean age was 65.5 (range=47-80) years. The primary cancer sites were gastric (two patients), unknown (two patients), breast (two patients), esophageal (two patients), and uterine (one patient). Six tumors were located in the proximal femur, two in the femoral diaphysis, and one in the tibia. The mean follow-up period was 11 months (range=1-24).

Pathological analyses. Pathological specimens obtained from biopsies performed on the patients were subjected to immunohistological staining using a goat polyclonal anti-SOST (1:100, ab194940; Abcam, Cambridge, MA, USA), rabbit polyclonal anti-DKK1 (21112-1-AP; Proteintech, Tokyo, Japan; 1:200 dilution in saline), rabbit polyclonal anti-BMP6 [1:100, PA5-75427; Thermo Fisher Scientific (Invitrogen), Waltham, MA, USA], and rabbit polyclonal anti-Ki67 (1:200, NB500-170SS; Funakoshi, Tokyo, Japan) antibodies diluted in saline.

The positive cellularity levels of the immunostaining procedures for the SOST, DKK1, BMP6, and Ki67 antibodies were calculated according to a previously described protocol, and the correlations between the respective positivity rates were also examined (19). This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our institution (approval no.: R03-247). Written informed consent has been obtained from the patients to publish this article.

Statistical analyses. One-way analysis of variance was used to compare differences between groups. The positivity rate of each molecule was plotted to generate a corresponding correlation diagrams. The correlation coefficient (r) was calculated by fitting a regression line to assess the correlation between the molecules. Pearson's correlation coefficient was used to assess the relationships between clinical parameters and the positivity rates for each molecule. Correlation strength was classified as follows: very strong ($|r|$=0.7-1.0), strong ($|r|$=0.5-0.7), moderate ($|r|$=0.4-0.5), weak ($|r|$=0.2-0.4), and no correlation ($|r|$ <0.2). The Kaplan–Meier method was used to calculate the 1-year survival rate after diagnosis. All statistical analyses were performed using Stat Mate 5.05 (ATMS, Tokyo, Japan) (24).

Results

All analyzed tumors exhibited some degree of positivity for each of the four proteins evaluated in the present study (Figure 1A and B, Figure 2A and B). Clinical characteristics and the positivity rate of each immunostained protein are summarized in Table I. The positive cell rates *via* immunostaining for SOST, DKK1, BMP6, and Ki67 were 7.3% (range=5.2-13.4%), 27.4% (0-58.5%), 27.6% (16-40.5%), and 31.3% (0.7-76.8%), respectively.

A moderately negative correlation was observed between SOST and DKK1 positivity (Figure 3A; r=–0.45). SOST and BMP6 positivity demonstrated a weak positive

Table I. *Clinical characteristics and immunohistochemical profiles of patients surgically treated for metastatic bone tumors.*

Age (years)	Primary tumor type	Site of bone metastasis	Nature of bone metastases	Surgery	Outcome	SOST (%)	DKK1 (%)	BMP-6 (%)	Ki67 (%)	
69	CUP	Proximal femur	Lytic	IM nail	AWD	17	5.2	35.8	23.1	0.75
57	Gastric	Proximal femur	Lytic	IM nail	AWD	3	12.3	25.9	28.2	48.1
71	Uterus	Proximal femur	Lytic	IM nail	AWD	22	13.4	18.4	37.3	0.7
70	Breast	Proximal femur	Combined	Bilateral IM nail	AWD	6	7.8	20.8	40.5	76.8
80	Gastric	Proximal femur	Lytic	BHA	DOD	5	1.1	40.8	31.4	1
65	Esophageal	Femoral shaft	Lytic	IM nail	DOD	1	7.3	58.5	20.8	47
47	Breast	Proximal femur	Lytic	IM nail	DOD	24	5.4	3	31.9	26.1
75	Esophageal	Tibia	Lytic	IM nail	DOD	6	2.7	44.3	16	45.8
56	CUP	Femoral shaft	Lytic	IM nail	DOD	15	10.8	0	19.5	36.1

CUP: Cancer of unknown primary; DKK1: dickkopf-1; BMP6: bone morphogenetic protein 6; IM nail: intermedullary nail; AWD: alive with disease; BHA: bilateral head arthroplasty; DOD: died from disease; SOST: sclerostin.

correlation (Figure 3B; r=0.25). Additionally, DDK1 and BMP6 positivity showed a moderately negative correlation (Figure 3C; r=–0.34). No relationship was observed between SOST and Ki67 positivity (Figure 3D; r=–0.14). DKK1 and Ki67 positivity exhibited a weak positive correlation (Figure 3E; r=0.24). The survival rate at one year after diagnosis was 72.9% (Figure 4).

Discussion

Serum SOST levels are often elevated in patients with osteolytic malignancies and thus may serve as predictive biomarkers for the potential efficacy of SOST-directed antibody treatments (25). However, the role of SOST in osteolytic metastatic bone tumors is currently not fully understood. Therefore, the present study used immunostaining to investigate the roles of SOST, DKK1, and BMP6 in metastatic bone tumors.

Both SOST and DKK1 inhibit bone formation by suppressing Wnt signaling (26). Specifically, SOST is expressed mainly in osteocytes and inhibits signaling by binding to Wnt co-receptors, such as LRP5/6 (27). DKK1 similarly binds to LRP5/6 as a target receptor but inhibits Wnt signaling *via* a Kremen-mediated, clathrin-dependent endocytic pathway (28). DKK1 also inhibits the formation of the Wnt-Frizzled complex, whereas SOST interferes with the nuclear translocation of β-catenin following its cytoplasmic accumulation (29).

Recent studies have reported increased SOST secretion by breast cancer cells and highlighted its potential as a therapeutic target for cancer-induced bone diseases (20, 30).

SOST is overexpressed in breast cancer cells and promotes tumor cell migration and invasion. This accelerates bone metastasis and osteolysis (31). However, serum SOST levels have not been shown to serve as reliable biomarkers for visceral or bone metastases originating from renal cancer (32). It has also been noted that SOST may promote bone invasion in some tumors, such as oral squamous cell carcinoma (33). These studies indicate that SOST is not only a diagnostic marker for bone tumors but also an important therapeutic target.

In the present study, the SOST- and DKK1-positive cell rates were 7.3% and 27.4%, respectively, with a moderately negative correlation observed between the two (r=–0.45). These findings suggest that SOST and DKK1 may play distinct roles in remodeling the bone microenvironment.

It has been suggested that SOST indirectly suppresses BMP signaling in general, including that of BMP6 (16). Specifically, it has been reported that SOST inhibits the Wnt pathway, thereby weakening BMP6-mediated effects on osteoblast differentiation and bone formation (34). In the present study, we observed a weak positive correlation between SOST and BMP6 positivity (r=0.25). A moderately negative correlation (r=–0.34) was also

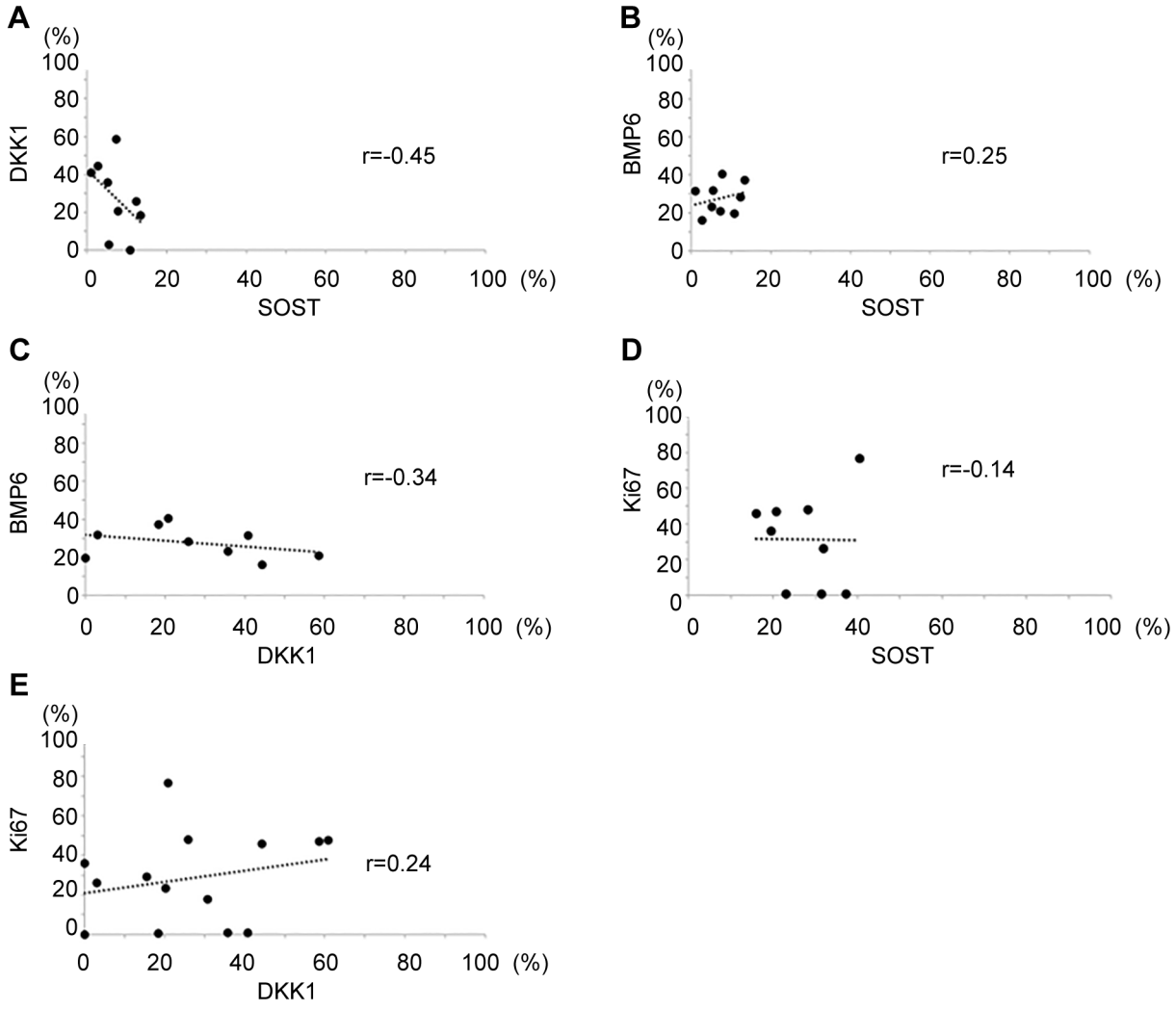

Figure 3. *Correlation between the positive rates of each molecule. (A) Moderate negative correlation is observed between sclerostin (SOST) and dickkopf-1 (DKK1) positivity rates (r=–0.45). (B) Weak positive correlation is observed between SOST and bone morphogenetic protein 6 (BMP6) positivity rates (r=0.25). (C) Moderately negative correlation is observed between DKK1 and BMP6 positivity rates (r=–0.34). (D) No correlation is observed between SOST and Ki67 positivity rates (r=–0.14). (E) Weak positive correlation is observed between DKK1 and Ki67 positivity rates (r=0.24).*

observed between DKK1 and BMP6. These findings suggest that SOST may stimulate the production of BMP6 in the local microenvironments of metastatic bone tumors, potentially promoting bone formation. Conversely, DKK1 may suppress BMP6 production and promote bone resorption.

Ki67 is a marker of cell proliferation, and previous reports suggest that tumor cells expressing high levels of both Ki67 and SOST may exhibit greater proliferative potential (35). However, in the present study, no correlation was found between SOST and Ki67 expression (r=–0.14). In contrast, a weak positive correlation was found between DKK1 and Ki67 (r=0.24). These findings suggest that DKK1 may be involved in tumor growth within the bone microenvironment of osteolytic metastatic bone tumors.

Typically, treatment for this condition is individually tailored, as these patients are in the terminal disease

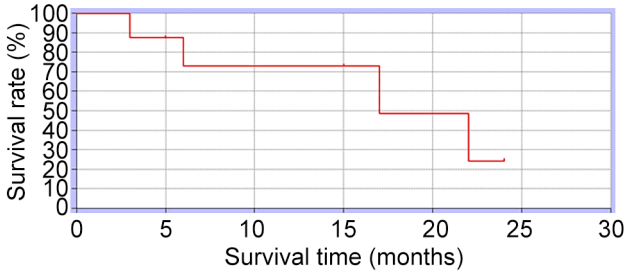

Figure 4. *Postoperative survival rates are shown using the Kaplan-Meier method. The one-year survival rate after surgery is 72.9%.*

stage (36, 37). In terms of overall patient survival, 1-year survival rates reported in the literature range from 42 to 75% (38, 39). Melanoma bone metastases are associated with a very poor 1-year survival rate of approximately 10%, with bone metastases significantly worsening overall prognosis (40). In contrast, prostate and breast cancers may allow relatively long-term survival even after bone metastasis, with 1-year survival rates varying substantially depending on the primary tumor type, treatment options, and overall disease status (41, 42). Recently, there was growing anticipation for early interventions utilizing immunotherapy, tumor microenvironment-targeted therapies, and novel technologies leveraging artificial intelligence (42).

We believe that the results of this study are in line with the findings of previous reports and can be applied to metastatic bone tumors in general.

Study limitations. First, the sample size was small, with only nine patients included, which limits the statistical power and generalizability of the findings. Second, the cohort was heterogeneous with regard to the primary tumor origin, as patients with metastatic bone tumors from various primary sites were analyzed together, potentially introducing confounding factors related to tumor biology. Third, the retrospective nature of the study may have introduced selection bias and limited the control over data collection and patient follow-up. Fourth, the immunohistochemical evaluation was performed using a semi-quantitative method, which may be subject to observer variability and may not fully capture subtle differences in protein expression levels. Fifth, the study did not investigate the relationships between the molecular findings (such as sclerostin, DKK1, and BMP6 expression) and detailed clinical parameters or patient outcomes, which restricts the ability to draw conclusions regarding the clinical significance of these biomarkers. Additionally, the relatively short and variable follow-up periods among patients may have impacted the assessment of long-term outcomes. Finally, as the study was conducted at a single institution, the results may not be broadly applicable to other populations or clinical settings.

To address the limitations of the present study, future research should focus on conducting prospective, multicenter studies with larger and more homogeneous patient cohorts to enhance the statistical power and generalizability of the findings. Standardizing the primary tumor types included in the analysis will help minimize heterogeneity and clarify the specific roles of sclerostin, DKK1, and BMP6 in different tumor backgrounds. Implementing fully quantitative and automated immunohistochemical evaluation methods can reduce observer bias and improve the accuracy and reproducibility of protein expression measurements. Furthermore, integrating detailed clinical data and longitudinal follow-up will enable the investigation of correlations between molecular findings and patient outcomes, such as response to therapy and survival. Expanding the analysis to include additional molecular markers and functional assays may also provide deeper insights into the underlying mechanisms of bone remodeling in metastatic bone tumors. Ultimately, such comprehensive approaches will facilitate the identification of novel therapeutic targets and the development of more effective, personalized treatment strategies for patients with osteolytic bone metastases.

Conclusion

Our findings suggest that SOST may play a role in bone formation within the bone microenvironments of

osteolytic metastatic bone tumors. The development of therapeutic strategies targeting this molecule may be crucial for the future treatment of metastatic bone tumors.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Conceptualization, K.H., S.N., H.T., and K.G.; methodology, K.H., S.N., and T.I.; software, K.H., T.I., and K.G.; validation, S.N., T.I., H.T., K.G., and K.H.; formal analysis, K.H., S.N., and T.I.; investigation, K.H., S.N., T.I., and K.G.; data curation, K.H., S.N., H.T., and K.G.; writing – original draft preparation, K.H., S.N., T.I., H.T., and K.G.; writing – review and editing, K.H., S.N., T.I., H.T., and K.G. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Rossini M, Gatti D, Adami S: Involvement of WNT/β-catenin signaling in the treatment of osteoporosis. Calcif Tissue Int 93(2): 121-132, 2013. DOI: 10.1007/s00223-013-9749-z
2 Spatz JM, Wein MN, Gooi JH, Qu Y, Garr JL, Liu S, Barry KJ, Uda Y, Lai F, Dedic C, Balcells-Camps M, Kronenberg HM, Babij P, Pajevic PD: The Wnt inhibitor sclerostin is up-regulated by mechanical unloading in osteocytes in vitro. J Biol Chem 290(27): 16744-16758, 2015. DOI: 10.1074/jbc.M114.628313
3 Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, Skonier JE, Zhao L, Sabo PJ, Fu Y, Alisch RS, Gillett L, Colbert T, Tacconi P, Galas D, Hamersma H, Beighton P, Mulligan J: Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet 68(3): 577-589, 2001. DOI: 10.1086/318811
4 Marini F, Giusti F, Palmini G, Brandi ML: Role of Wnt signaling and sclerostin in bone and as therapeutic targets in skeletal disorders. Osteoporos Int 34(2): 213-238, 2023. DOI: 10.1007/s00198-022-06523-7
5 Fujii Y, Hoshino T, Kumon H: Molecular simulation analysis of the structure complex of C2 domains of DKK family members and β-propeller domains of LRP5/6: explaining why DKK3 does not bind to LRP5/6. Acta Med Okayama 68(2): 63-78, 2014. DOI: 10.18926/AMO/52403
6 Wang K, Zhang Y, Li X, Chen L, Wang H, Wu J, Zheng J, Wu D: Characterization of the Kremen-binding site on Dkk1 and elucidation of the role of Kremen in Dkk-mediated Wnt antagonism. J Biol Chem 283(34): 23371-23375, 2008. DOI: 10.1074/jbc.M802376200
7 Davidson G: LRPs in WNT signalling. Handb Exp Pharmacol 69: 45-73, 2021. DOI: 10.1007/164_2021_526
8 Park H, Jung HY, Choi HJ, Kim DY, Yoo JY, Yun CO, Min JK, Kim YM, Kwon YG: Distinct roles of DKK1 and DKK2 in tumor angiogenesis. Angiogenesis 17(1): 221-234, 2014. DOI: 10.1007/s10456-013-9390-5
9 Katase N, Nagano K, Fujita S: DKK3 expression and function in head and neck squamous cell carcinoma and other cancers. J Oral Biosci 62(1): 9-15, 2020. DOI: 10.1016/j.job.2020.01.008
10 Cai X, Yao Z, Li L, Huang J: Role of DKK4 in tumorigenesis and tumor progression. Int J Biol Sci 14(6): 616-621, 2018. DOI: 10.7150/ijbs.24329
11 Sapir-Koren R, Livshits G: Osteocyte control of bone remodeling: is sclerostin a key molecular coordinator of the balanced bone resorption–formation cycles? Osteoporos Int 25(12): 2685-2700, 2014. DOI: 10.1007/s00198-014-2808-0
12 Xiaohui T, Wang L, Yang X, Jiang H, Zhang N, Zhang H, Li D, Li X, Zhang Y, Wang S, Zhong C, Yu S, Ren M, Sun M, Li N, Chen T, Ma Y, Li F, Liu J, Yu Y, Yue H, Zhang Z, Zhang G: Sclerostin inhibition in rare bone diseases: Molecular understanding and therapeutic perspectives. J Orthop Translat 47: 39-49, 2024. DOI: 10.1016/j.jot.2024.05.004
13 Aditya S, Rattan A: Sclerostin inhibition: a novel target for the treatment of postmenopausal osteoporosis. J Midlife Health 12(4): 267-275, 2021. DOI: 10.4103/jmh.JMH_106_20
14 Moysés RMA, Schiavi SC: Sclerostin, osteocytes, and chronic kidney disease – mineral bone disorder. Semin Dial 28(6): 578-586, 2015. DOI: 10.1111/sdi.12415
15 Liu DX, Wu KH, Zang XY, Lu JY, Liu MY, Li CM, Gao L: Dickkopf-related protein 1 as a biomarker of local immune status and worse prognosis of Oral squamous cell carcinoma. Technol Health Care 32(3): 1473-1488, 2024. DOI: 10.3233/THC-230527
16 Vasiliadis ES, Evangelopoulos DS, Kaspiris A, Benetos IS, Vlachos C, Pneumaticos SG: The role of sclerostin in bone

diseases. J Clin Med 11(3): 806, 2022. DOI: 10.3390/jcm11030806
17 Zhang M, Zheng J, Wu S, Chen H, Xiang L: Dynamic expression of IGFBP3 modulate dual actions of mineralization microenvironment during tooth development via Wnt/beta-catenin signaling pathway. Biol Direct 18(1): 34, 2023. DOI: 10.1186/s13062-023-00391-9
18 Tung CW, Hsu YC, Shih YH, Chang PJ, Lin CL: Glomerular mesangial cell and podocyte injuries in diabetic nephropathy. Nephrology (Carlton) 23 Suppl 23(S4): 32-37, 2018. DOI: 10.1111/nep.13451
19 Jiang H, Zhang Z, Yu Y, Chu HY, Yu S, Yao S, Zhang G, Zhang BT: Drug discovery of DKK1 inhibitors. Front Pharmacol 13: 847387, 2022. DOI: 10.3389/fphar.2022.847387
20 Gkotzamanidou M, Dimopoulos MA, Kastritis E, Christoulas D, Moulopoulos LA, Terpos E: Sclerostin: a possible target for the management of cancer-induced bone disease. Expert Opin Ther Targets 16(8): 761-769, 2012. DOI: 10.1517/14728222.2012.697154
21 Hashimoto K, Nishimura S, Ito T, Kakinoki R, Goto K: Treatment algorithm for metastatic malignancies in the lower extremities. Mol Clin Oncol 21(1): 51, 2024. DOI: 10.3892/mco.2024.2749
22 Hudson BD, Hum NR, Thomas CB, Kohlgruber A, Sebastian A, Collette NM, Coleman MA, Christiansen BA, Loots GG: SOST inhibits prostate cancer invasion. PLoS One 10(11): e0142058, 2015. DOI: 10.1371/journal.pone.0142058
23 Göbel A, Kuhlmann JD, Link T, Wimberger P, Browne AJ, Rauner M, Hofbauer LC, Rachner TD: Adjuvant tamoxifen but not aromatase inhibitor therapy decreases serum levels of the Wnt inhibitor dickkopf-1 while not affecting sclerostin in breast cancer patients. Breast Cancer Res Treat 164(3): 737-743, 2017. DOI: 10.1007/s10549-017-4296-3
24 Hashimoto K, Nishimura S, Ito T, Oka N, Kakinoki R, Akagi M: Clinicopathological assessment of cancer/testis antigens NYESO1 and MAGEA4 in osteosarcoma. Eur J Histochem 66(3): 3377, 2022. DOI: 10.4081/ejh.2022.3377
25 Dincel AS, Jørgensen NR, IOF-IFCC Joint Committee on Bone Metabolism (C-BM): New emerging biomarkers for bone disease: Sclerostin and Dickkopf-1 (DKK1). Calcif Tissue Int 112(2): 243-257, 2022. DOI: 10.1007/s00223-022-01020-9
26 Koide M, Kobayashi Y: Regulatory mechanisms of sclerostin expression during bone remodeling. J Bone Miner Metab 37(1): 9-17, 2019. DOI: 10.1007/s00774-018-0971-7
27 Thouverey C, Caverzasio J: Sclerostin inhibits osteoblast differentiation without affecting BMP2/SMAD1/5 or Wnt3a/β-catenin signaling but through activation of platelet-derived growth factor receptor signaling in vitro. Bonekey Rep 4: 757, 2015. DOI: 10.1038/bonekey.2015.126
28 van Dinther M, Zhang J, Weidauer SE, Boschert V, Muth EM, Knappik A, de Gorter DJ, van Kasteren PB, Frisch C, Mueller TD, ten Dijke P: Anti-Sclerostin antibody inhibits internalization of Sclerostin and Sclerostin-mediated antagonism of Wnt/LRP6 signaling. PLoS One 8(4): e62295, 2013. DOI: 10.1371/journal.pone.0062295
29 Starlinger J, Santol J, Kaiser G, Sarahrudi K: Close negative correlation of local and circulating Dickkopf-1 and Sclerostin levels during human fracture healing. Sci Rep 14(1): 6524, 2024. DOI: 10.1038/s41598-024-55756-5
30 Zhu M, Liu C, Li S, Zhang S, Yao Q, Song Q: Sclerostin induced tumor growth, bone metastasis and osteolysis in breast cancer. Sci Rep 7(1): 11399, 2017. DOI: 10.1038/s41598-017-11913-7
31 Hiraga T, Horibe K, Koide M, Yamashita T, Kobayashi Y: Sclerostin blockade promotes bone metastases of Wnt-responsive breast cancer cells. Cancer Sci 114(6): 2460-2470, 2023. DOI: 10.1111/cas.15765
32 Wibmer C, Amrein K, Fahrleitner-Pammer A, Gilg MM, Berghold A, Hutterer GC, Maurer-Ertl W, Gerger A, Leithner A, Pichler M, Szkandera J: Serum sclerostin levels in renal cell carcinoma patients with bone metastases. Sci Rep 6: 33551, 2016. DOI: 10.1038/srep33551
33 Schirmer U, Schneider SA, Khromov T, Bremmer F, Schminke B, Schliephake H, Liefeith K, Brockmeyer P: Sclerostin alters tumor cell characteristics of oral squamous cell carcinoma and may be a key player in local bone invasion. Cells 13(2): 137, 2024. DOI: 10.3390/cells13020137
34 Thomas S, Jaganathan BG: Signaling network regulating osteogenesis in mesenchymal stem cells. J Cell Commun Signal 16(1): 47-61, 2022. DOI: 10.1007/s12079-021-00635-1
35 Liang W, Guan H, He X, Ke W, Xu L, Liu L, Xiao H, Li Y: Down-regulation of SOSTDC1 promotes thyroid cancer cell proliferation via regulating cyclin A2 and cyclin E2. Oncotarget 6(31): 31780-31791, 2015. DOI: 10.18632/oncotarget.5566
36 Roudier MP, True LD, Higano CS, Vesselle H, Ellis W, Lange P, Vessella RL: Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. Hum Pathol 34(7): 646-653, 2003. DOI: 10.1016/S0046-8177(03)00190-4
37 Ganesh K, Massagué J: Targeting metastatic cancer. Nat Med 27(1): 34-44, 2021. DOI: 10.1038/s41591-020-01195-4
38 Mavrogenis AF, Pala E, Romagnoli C, Romantini M, Calabro T, Ruggieri P: Survival analysis of patients with femoral metastases. J Surg Oncol 105(2): 135-141, 2012. DOI: 10.1002/jso.22061
39 Chandrasekar CR, Grimer RJ, Carter SR, Tillman RM, Abudu A, Buckley L: Modular endoprosthetic replacement for tumours of the proximal femur. J Bone Joint Surg Br 91-B(1): 108-112, 2009. DOI: 10.1302/0301-620X.91B1.20448
40 Jia Y, Li R, Li Y, Kachler K, Meng X, Gießl A, Qin Y, Zhang F, Liu N, Andreev D, Schett G, Bozec A: Melanoma bone metastasis-induced osteocyte ferroptosis via the HIF1α-HMOX1 axis. Bone Res 13(1): 9, 2025. DOI: 10.1038/s41413-024-00384-y
41 Li Y, Liu F, Cai Q, Deng L, Ouyang Q, Zhang XH, Zheng J: Invasion and metastasis in cancer: molecular insights and

therapeutic targets. Signal Transduct Target Ther 10(1): 57, 2025. DOI: 10.1038/s41392-025-02148-4

42 Roviello G, Molina-Cerrillo J, Massari F, Cerbone L, Fiala O, Fornarini G, Monteiro FSM, Cattrini C, Landmesser J, Messina C, Zgura A, Rebuzzi SE, Soares A, Carrozza F, Ansari J, Grillone F, Küronya Z, Incorvaia L, Bhuva D, Ortega C, Nasso C, Kanesvaran R, Zampiva I, Porta C, Buti S, Santoni M: First-line immune-based combinations or sunitinib in favorable-risk metastatic renal cell carcinoma: a real-world retrospective comparison from the ARON-1 study. Cancer Immunol Immunother 74(2): 65, 2025. DOI: 10.1007/s00262-024-03897-x