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MEETING REPORT

Cancer and bone (IBMS/JSBMR joint meeting 2013)

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Meeting Report from the 2nd Joint Meeting of the International Bone and Mineral Society and the Japanese Society for Bone and Mineral Research, Kobe Island, Japan, 28 May–1 June 2013

The Second Joint Meeting of the International Bone and Mineral Society and the 31st Annual meeting of the Japanese Society for Bone and Mineral Research (2nd IBMS/JSBMR) was held in Kobe, which is located almost at the center of the Japanese archipelago on the Seto Inland Sea. As Kobe has a long history as a port town, creating a unique exotic atmosphere in which varieties of international and traditional Japanese cultures are harmonized, Kobe is a quite appropriate site for having the IBMS and JSBMR joint meeting. Kobe is also internationally well known for its tender, delicious, although a bit expensive, Kobe beef. I very much regret that I missed to taste it this time.

Having the joint meeting with IBMS was especially significant for JSBMR, because JSBMR just joined the member society of IBMS right before the meeting, starting to contribute to the expansion of the society and worldwide bone research community. The President of the 2nd IBMS/JSBMR was Professor Masaki Noda, Medical Research Institute, Tokyo Medical and Dental University and the President of the 31st Annual Meeting of the JSBMR was Professor Hideki Yoshikawa, Department of Orthopaedics, Osaka University Graduate School of Medicine. The 31st Annual Meeting of JSBMR was conducted on 30 May as Japan day, in which all papers were presented in Japanese, providing non-Japanese participants with a break for sightseeing. The number of attendees was more than 900 from more than 30 countries, and 380 ($>$40%) attendees were JSBMR members. It is noted that there are considerable numbers of participants from Eastern European countries including Slovakia, Czech Republic and Poland, demonstrating an increasing interest in bone research in these countries.

Professor Shinya Yamanaka of Kyoto University, who won the 2012 Nobel Prize in Physiology and Medicine, gave a keynote lecture entitled 'Mature cells can be reprogrammed to become pluripotent'. In his talk, Dr Yamanaka mentioned how he got the idea of iPS (induced pluripotent stem cells) and made that idea come true by referring to the landmark work conducted by Professor Gurdon of United Kingdom half a century ago, who also won the 2012 Nobel Prize in Physiology and Medicine together with Professor Yamanaka. It was unfortunate that Dr Yamanaka could not come to the meeting and that his talk was presented on a video.

There were seven symposiums in the meeting. I will briefly overview the topics presented in Symposium 4 entitled 'Cancer and Bone: basic, translational and clinical', and other sessions, which, I thought, were interesting.

In the first talk, Dr Yoneda of Indiana University School of Medicine and Dr Tanaka of Osaka University Graduate School of Dentistry[1] presented that breast cancer cells colonized in bone underwent epithelial–mesenchymal transition (EMT), a program through which cancer changes its phenotype from epithelial to mesenchymal and acquires increased aggressiveness and resistance to anti-cancer therapies. Zoledronic acid (ZA) inhibited the EMT in bone. ZA also inhibited breast cancer colonization in bone and metastasis to lungs and liver from bone. The authors proposed that inhibition of EMT in bone by bone-modifying agents (BMAs) such as ZA leads to the suppression of exacerbation of bone metastasis and secondary metastasis from bone through inhibition of EMT in breast cancer.

In the second talk, Dr Frenette of Albert Einstein College of Medicine presented that norepinephrine released from autonomic nerves of the sympathetic nervous system (SNS) regulated homing and egression of hematopoietic stem cells (HSCs) into and from bone marrow (BM) by downregulation of the expression of stem cell retention factor in the niche cells via adrenoreceptors.[2] He showed that Nestin$^+$ self-renewing perivascular mesenchymal stem cells (MSCs) were a target of the SNS and a likely candidate for niche cells. His data also demonstrated that CD169$^+$ macrophages promoted the retention of HSCs in the niche by upregulating the expression of stem cell retention factor in Nestin$^+$ niche cells, whereas the SNS inhibited it. He proposed that the SNS (inhibitory) and CD169$^+$ macrophages (stimulatory) have opposite effects on HSC retention in the niche.

In the third talk, Dr Coleman of Weston Park Hospital, Sheffield, UK, nicely overviewed the current status of breast cancer treatments by BMAs including zoledronic acid and denosumab.[3] He presented the results of several large randomized clinical studies that ZA combined with ovarian suppression therapy in adjuvant setting significantly improved disease-free and overall survival in early breast cancer patients

with low levels of reproductive hormones, including premenopausal women and those who have passed through menopause. He also presented that denosumab significantly improved bone metastasis-free survival in castrate-resistant prostate cancer. He proposed that BMAs are changing therapeutic modalities for bone-colonizing breast and prostate cancers.

Recent studies suggest that cancer cells, particularly breast cancer cells, first disseminate in the BM cavity (these cells are called disseminated tumor cells, DTCs) before the development of overt metastasis in distant organs. Patients with early breast cancer who have DTCs manifest increased relapse of primary tumor and metastasis not only in bone but also in lungs and liver and poor survival compared with the patients without DTCs. Hence, the presence of DTCs in BM is very critical to prognosis of breast cancer patients. Dr Frenette's presentation[2] raises the possibility that DTCs are nursed in the niche comprising Nestin$^+$ MSCs that are under the control of SNS and CD169$^+$ macrophages. Dr Yoneda's presentation[1] is consistent with the notion that a DTC in the niche acquires further aggressiveness by undergoing EMT. Dr Coleman's presentation[3] together with Dr Yoneda's data[1] that ZA inhibited EMT in bone suggests that BMAs are beneficial to patients with breast and prostate cancers, which exhibit strong predilection for spreading to bone, by disturbing the bone microenvironment that endows enhanced aggressive behaviors to DTCs. These three topics are mechanistically closely interrelated and provided the audience with basic, translational and clinical aspects of the behaviors of cancer cells in bone.

In the oral presentations, Dr Hata *et al.*[4] presented that the docking protein NEDD9, the expression of which in breast cancer was upregulated in bone, promoted the progression of the vicious cycle between breast cancer cells and bone, leading to the advancement of bone metastasis. Of interest, these authors showed that NEDD9 expression was associated with EMT. NEDD9 may be a novel molecule with a specific role in bone metastasis in collaboration with EMT in breast cancer.

Dr Yang *et al.*[5] presented that multiple myeloma (MM) cells isolated from patients with destructive bone lesions produced substantial amounts of heparanase (HPSE) on examination using an immunohistochemical technique. HPSE produced by MM cells inhibited osteoblastogenesis, whereas stimulated adipogenesis, by suppressing Wnt/β-catenin signaling. She proposed that HPSE would be thus a potential therapeutic target in the treatment of MM osteolytic bone disease. HPSE has been shown to be associated with increased tumorigenesis, invasion and metastasis in solid tumors. These results suggest that HPSE has a crucial role in the pathophysiology of hematologic malignancy as well as solid tumors.

Dr Hiraga *et al.*[6] presented that CD44, an adhesion molecule that primarily binds to hyaluronic acid, was expressed in breast cancer cells. They showed that CD44 promoted bone metastases by enhancing tumorigenicity, cell migration and invasion. As CD44 is a marker for cancer stem cells, these authors proposed that CD44$^+$ breast cancer stem cells may have a role in the development of bone metastases. Further characterization of CD44$^+$ stem cells present in breast cancer may add alternative points of view in our understanding of the pathophysiology of bone metastasis.

In the poster sessions, Dr Watanabe *et al.*[7] studied the effects of cathepsin K inhibition on MM bone lesions in an animal model they developed and found that it reduced MM tumor burden by inducing bone formation. It is unknown whether cathepsin K inhibitors directly promote bone formation or do that indirectly by decreasing bone resorption. This important issue could be addressed using this animal model.

In summary, the cancer and bone sessions in the 2nd IBMS/JSBMR were harmoniously and interactively organized. They were also educative providing with insightful overviews and new findings. It is appreciated that the program committee did an outstanding job. We should look forward to the coming 13th International Conference on Cancer-Induced Bone Disease in Miami, FL, USA, between 6 November and 9 November for further updated scientific information.

Conflict of Interest

The author declares no conflict of interest.

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