Citation: IBMS BoneKEy **11**, Article number: 492 (2014) | doi:10.1038/bonekey.2013.226

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MEETING REPORT

Cancer and bone disease (ASBMR 2013)

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IBMS BoneKEy **11,** Article number: 492 (2014) | doi:10.1038/bonekey.2013.226; published online 22 January 2014

Meeting report from the 35th Annual Meeting of the American Society for Bone and Mineral Research, Baltimore, MD, USA, 4–7 October 2013

Introduction

This year's ASBMR annual meeting in Baltimore, MD had many exciting Cancer and Bone abstracts. It was organized quite differently when compared with the past years, with the cancer talks spread throughout the meeting and mixed in with the more general bone talks. This was an interesting approach that helped expose the cancer scientists to more general bone topics and helped give more exposure to some of the work by cancer biology laboratories. However, in doing this it made it more difficult to get to all of the Cancer and Bone talks. There were many excellent posters and presentations this year, and while I tried to cover many, I am sure that I missed some exciting work.

Part of the format this year was to do away with the stand-alone 'Malignancy and Bone Section' for oral presentation of abstracts, replacing it with the 'Greg Mundy Memorial Session: Malignancy and Bone'. This featured overviews of work from Drs Russ Taichman (University of Michigan), Roberta Faccio (Washington University) and Florent Elefteriou (Vanderbilt University). These were all great talks that covered long-standing projects in their laboratories as well as emerging topics in the cancer and bone field and introduced some of the major themes of the meeting. On the basis of these and other talks in the Cancer and Bone category, the major themes in the field this year were (1) Tumor Dormancy, (2) Tumor Microenvironment and (3) Emerging Treatments.

Tumor Dormancy

Dr Russell Taichman (University of Michigan) presented 'Cancer cells and their bone marrow niche', in which he discussed the importance of tumor dormancy in cancer and how the bone can be a 'home' for dormant tumor cells. Although a number of labs are now pursuing the mechanisms of tumor dormancy in bone, there have been many challenges developing models for these studies, which have severely limited translational advances in the tumor dormancy field. Dr Taichman's presentation focused on data from two papers from his lab.[1,2] The first suggests a competition between hematopoietic stem cells (HSCs) and prostate tumor (PCa), suggesting that they spread to the same niche (endosteal).[1] Furthermore, they speculate that once tumor cells metastasize to this niche, the interactions with HSCs can allow the tumor cells to lay dormant for years, but that eventually the tumor growth cannot be suppressed by the HSCs and clinical disease develops.[1] The second paper was driven by their observation that there are fewer tumors in the forelimb, but that there were no significant differences in HSCs in the forelimb. For these studies, they identify the expression of receptors for Growth Arrest Specific 6 (GAS6), a molecule known to induce quiescence of HSCs, on the PCa cells and suggest that the balance of these receptors may temporally regulate cell quiescence and proliferation.[2]

Another emerging topic in the field is the concept of bone as a site for dormant tumor cells to seed metastases to other organs. Although there was not much on this topic, Dr Toshi Yoneda (Indiana University) had an intriguing poster discussing 'Zoledronic acid inhibits epithelial-mesenchymal transition (EMT) of breast cancer cells in bone via ubiquitin/proteasome system'.[3] On injecting MCF-7 cells, which do not induce bone destruction, into the tibia or the mammary fat pad they observed that the cells were more likely to undergo epithelial to mesenchymal transition (EMT), determined by E-cadherin and Snail expression. Zoledronic acid (ZA) treatment reduced Snail expression, whereas proteasome inhibition increased Snail expression. Furthermore, they demonstrated that ZA treatment reduced metastases from the mammary fat pad to the lung and bone. This study suggests that the bone may be a site for seeding other metastatic sites through the stimulation of EMT, and that the use of certain drugs may inhibit or stimulate tertiary metastasis. This is an interesting concept and one that I look forward to seeing develop further.

Tumor Microenvironment

How the bone microenvironment regulates tumor metastasis to bone and establishment has been an emerging topic for the past several years, but this year the area received more time on the podium. Two talks in the opening session revolved around this topic, with one focusing on immune cells (Faccio) and the other on the effect of stress on bone metastases (Elefteriou). The major areas of focus within the tumor microenvironment were immune cells, bone cells and other regulators.

Immune cells. The main talks in the immune regulation were from Roberta Faccio with 'Immune regulation of tumor/bone vicious cycle' and her postdoctoral fellow Aude-Helene Capietto with 'Downregulation of PLCγ2/β-catenin pathway promotes activation of and expansion of Myeloid-Derived Suppressor cells in cancer'.[4] These talks together painted an interesting picture of how MDSCs through their ability to inhibit T cells stimulate tumor growth and metastasis to bone. They went on to show that inhibiting T-cell function through alternative methods caused similar effects, and further characterized the role of the MDSC. Dr Capietto demonstrated that using MDSCs isolated from PLCγ2$^{-/-}$ showed aberrant expansion of MDSCs that suppressed CD8^{+} T cells more efficiently. This was shown to be through a reduction in β-catenin-dependent mechanism, and the increase in tumor burden could be reversed when β-catenin was constitutively expressed. These data have been published since the meeting in the *Journal of Experimental Medicine*.[5] These data further confirm studies from other groups regarding the role of MDSCs in tumor bone disease that have been presented at ASBMR in previous years. Several of these papers that investigated the role of MDSCs in tumor-induced bone disease have been published over the past year.[6–9] Two of these studies were performed in mice lacking T cells, yet they show similar results as the studies in immune-competent mice, therefore indicating a T-cell-independent role for MDSCs in the regulation of bone metastases.[6,7]

Bone cells. There were two talks involving the effect of osteoblasts on tumors that nicely blended the genetic mouse models used in bone development laboratories with bone metastasis models. The idea of bone cells regulating tumor behavior and bone destruction is an important one that has not been explored in-depth previously, in part due to the lower abundance of these cells in the bone marrow compared with immune cells and fibroblasts. This year two groups presented how osteoblasts regulate tumor burden. The first was by Kode *et al.*, 'Leukemogenic transformation of hematopoietic stem cells by constitutive activation of canonical Wnt signaling in osteoblasts'.[10] These studies used βcat(ex3)$_{osb}$ mice in which there is a disruption in the differentiation of stem cells that leads to acute myeloid leukemia (AML), and suggested that genetic alterations in osteoblast precursors may induce AML. Data beyond the abstract were also presented that further suggested interplay between the osteoblasts and AML cells, and it appeared that reducing osteoblasts could increase AML tumor burden. Devignes *et al.* presented 'Control of breast cancer growth and dissemination by the skeleton'.[11] with an OSX-cre model in which Hif1A was reduced, resulting in a decreased number of osteoblasts and reduced bone mass. By using this model they found a reduction in breast cancer metastasis not only to bone but also to other organs, and suggested that osteoblasts may affect metastasis to distant organs. However, it remains unclear whether there are other effects on hematopoietic cells in the bone and whether the observed effects are directly caused by the osteoblasts or due to indirect effects. Both groups are investigating the hematopoietic cells to determine whether these are affected, and it will be interesting to follow this area of research as they explore their results in more detail.

Although osteocytes have been very important over the past years for bone biologists, they have not been a major focus of cancer work. One poster abstract 'Osteocytes promote prostate cancer bone growth' by Sottnik *et al.* began to explore the importance of osteocytes in bone metastases.[12] Conditioned media from osteocyte cultures were shown to increase prostate cancer proliferation, migration and invasion. Garimella *et al.* investigated how osteosarcomas affect the microenvironment through the secretion of extracellular membrane vesicles with a poster entitled 'Osteosarcoma cells modulate bone microenvironment via extracellular membrane vesicle (EMV) biogenesis and calcium signaling pathways'.[13] This was an interesting poster that traced EMVs from osteosarcoma cells and showed that they regulated calcium-dependent pathways and that this effected osteoclasts.

Other cell types that had surprisingly little coverage this year were the macrophages and cancer stem cells. Bleau *et al.* describe a lung cancer stem-like cell in their poster 'Lung cancer stem-like cells (CSC) display a retarded osseous prometastatic activity'.[14] In this poster they describe stem-like cells that show a delay in establishment in bone, suggesting a potential model for recurrence and tumor dormancy for lung cancer studies. Cho *et al.* describe the association of bone marrow-derived tumor-associated macrophages with tumor cells, which are a hot topic in the cancer metastasis field, in 'Macrophages support proliferation, invasion, and angiogenesis in thyroid cancer'.[15]

Other regulators. Non-traditional regulators of tumor-induced bone disease were also highlighted this year and included SNS regulation in bone with a presentation by Florent Elefteriou, 'Stress, depression and skeletal metastasis'. Dr Elefteriou presented his work in which they stressed mice pharmacologically or by using restraint stress, and demonstrated that this resulted in an increased skeletal metastases through a β-adrenergic receptor-dependent response of the host bone marrow stroma. They further showed that this is dependent on RANKL and blocking sympathetic activation with a β-blocker, or blocking RANKL signaling in cancer cells, inhibited the increase in bone metastases. This work was published before the meeting in *PLoS Biology*.[16]

Another presentation by Page *et al*. (presented by Ushashi Dadwal) 'Integrin-beta 3 is required for breast tumor cell response to bone rigidity', highlighted the effect of the physical rigidity of the bone and how this can modulate gene expression.[17] This presentation went on to demonstrate that this rigidity-mediated response is mediated through mechanical signaling that is dependent on Integrin β3 and TGF-βRII colocalization that stimulates downstream expression of Gli2 and PTHrP. In contrast, a poster by Fong *et al.*, 'Development of a 3D *in vitro* co-culture system to model bone metastatic prostate cancer', demonstrated that soft materials replicating the rigidity of bone marrow could support prostate cancer survival in a subcutaneous site.[18] This study did not investigate the ability of these tumor cells to induce bone disease, but was able to culture cells isolated from clinical samples for up to 10 days. Although not directly related, this brings up the question of what rigidity tumor cells actually see when they metastasize to skeletal sites, and is one that we often get asked when presenting our breast cancer cell rigidity data. We propose that cells that metastasize to trabecular-rich regions will 'sense' the rigid bone fairly quickly, but what is definite is that cells that metastasize to the bone marrow are mobile and in a dynamic situation in which they are likely to be in contact with both the soft marrow and the rigid bone. It is important when generating

in vitro and *in vivo* models to keep this complexity in mind. In line with this dynamic situation, a poster by Pagnotti *et al.* described the 'Immunomodulatory role of mechanical signals in regulating the expansion of hematopoietic precursors in a murine model of multiple myeloma'.[19] This group used low-intensity vibration to stimulate mechanical signaling in a myeloma model, and demonstrated that there was a detectable reduction in the number of KLS, $CD3^+$ and NK cells in the LIV-treated mice. Although very preliminary, this suggests that we should be aware of the effects of mechanical signaling on other cell types that could influence tumor growth within the bone marrow microenvironment.

New Treatment Strategies

Novel treatment strategies are always a major focus of the cancer and bone sessions, and this year was no exception. While many of the previously discussed talks discussed novel pathways and potentially new treatments, others focused primarily on treatment strategies.

The major new development was the PTHrP antibodies from McGill University. Although this approach was published in the mid-90s by Theresa Guise to inhibit tumor-induced bone diseases in animal models[20] and an antibody from Chugai in Japan went to clinical trials, they ultimately were not pursued. This group has pushed the development of a PTHrP antibody again; their data look very promising and have resulted in two oral presentations. The first oral poster presentation by Kremer *et al.*, 'Anti-PTHrP monoclonal antibodies are potent proliferation inhibitors in triple negative human breast cancer cells and potentiate the effects of taxol and doxorubicin', demonstrated that PTHrP inhibition was very effective in inhibiting tumor proliferation of triple-negative breast cancer cell lines in combination with standard chemotherapeutic agents.[21] The second presentation by Luco *et al.* 'Parathyroid hormone-related peptide (PTHrP) blockade inhibits the development of bone metastasis and potentiates the effect of zoledronic acid *in vitro* and *C* in a mouse model of breast tumor progression' showed that PTHrP blockade has a direct effect on tumor growth of breast cancer cells *in vitro*[22] and, similar to the data generated by Therese Guise in the 1990s,[20] can potentiate the effect of ZA inhibition of tumor growth within bone. Suva *et al.* also described the potential of using the 12–48 form of PTHrP as a biomarker in 'Biological characterization of PTHrP (12–48): novel biomarker of breast cancer bone metastases or new active peptide'.[23] It was great to see PTHrP become a popular molecule for studying cancer-induced bone disease again.

TGF-β inhibition was also discussed at the poster presentations. Nyman *et al.* presented a plenary poster 'Combined TGF-β and proteasome inhibition improves bone architecture and reduces tumor burden in myeloma bone disease'.[24] This poster described how the TGF-β inhibitor, 1D11 (Genzyme), improved bone quality in myeloma-bearing mice yet had little effect alone on tumor burden. However, when 1D11 was combined with the proteasome inhibitor Velcade, a significant reduction (above that of Velcade alone) was observed and bone architecture was improved, suggesting a potential use of 1D11 to improve bone architecture when combined with an anti-tumor therapy. Interestingly, when Juarez *et al.* blocked TGF-β signaling in the 'Beneficial effects of combined therapy of halofuginone and zoledronic acid on breast cancer bone metastases and normal bone remodeling',[25] they saw very different results. When Halofuginone (Hfg), which inhibits both TGF-β and BMP signaling, was given to mice they saw not only a reduction in tumor burden but also a reduction in BMD and trabecular bone volume, likely due to the effects on BMP signaling. However, combination with ZA improved BMD, suggesting a benefit with combined therapy. Both of these studies describe that inhibitors of TGF-β will need to be used carefully in order to maintain a good balance between inhibiting the tumors while improving bone quality.

Several other emerging targets for the cancer and bone field were described throughout the meeting. Croset *et al.* described the role of Twist-1 in cancer metastasis to bone in 'Ectopic expression of twist-1 in breast cancer cells promotes bone metastasis formation'.[26] This work, which was presented by Dr Philippe Clezardin, demonstrated that overexpressing Twist-1 in metastatic breast cancer cells accelerated increased bone destruction and accelerated tumor take in the bone, and thus is a potential target for inhibiting bone metastases. Another potential pathway for inhibiting tumors in bone was described by Zhang *et al.* in an oral poster presentation, 'Role of stathmin gene in development of prostate cancer bone metastasis'.[27] This group showed that knocking out stathmin, a microtubule-targeting protein, reduced prostate cancer growth and bone disease, suggesting that inhibitors of this pathway may be potential therapeutic targets. Finally, Harhash *et al.* presented 'Estrogen depletion by ovariectomy or aromatase inhibitors increase breast cancer bone metastases in female nude mice', which demonstrates that Aromatase Inhibitors (AI), which are frequently used to treat women with ER^+ tumors, can increase bone turnover and increase bone metastases.[28]

Other

A few other highlights that did not fit neatly into the major themes included Dr Janine Danks' poster 'Are BMP4 and Runx2 more prevalent in malignant canine mammary tumors?'[29] Their data nicely showed a correlation between BMP4 and Runx2 in canine mammary tumor as prognostic markers, and they have organized an impressive network of canine mammary tumors that may be a very valuable source for many laboratories studying cancer metastasis. Finally, I was very impressed by the State-of-the-Art Lecture on Sunday afternoon 'Bringing back muscle and bone'. These talks by Drs Rowe, Badylak and Laurencin were all spectacular and nicely demonstrated the approaches for regenerating muscle and bone primarily in cases of traumatic injury. Although in the cancer and bone field we rarely think of this, some of these techniques may be valuable in patients who require surgical intervention to remove large tumors in bone. This may be particularly relevant in osteosarcoma patients who often require invasive surgeries and are younger patients.

Conclusion

As always, the annual ASBMR conference was an exciting meeting with many new areas of research beginning to develop. Much of the work investigating tumors and the microenvironment have become much more sophisticated and I am sure this work will continue to grow. I look forward to seeing the progress of this work next year and also the new and exciting

findings that laboratories will discover over the next year. I look forward to seeing all of you in Houston next year!

Conflict of Interest

The author declares no conflict of interest.

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