Citation: IBMS BoneKEy **9,** Article number: 145 (2012) | doi:10.1038/bonekey.2012.145

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MEETING REPORT

Cancer and bone: ECTS 2012

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IBMS BoneKEy **9**, Article number: 145 (2012) | doi:10.1038/bonekey.2012.145; published online 8 August 2012

Meeting Report from the European Calcified Tissue Society 39th Annual Congress, Stockholm, Sweden, 19–23 May 2012.

The ECTS meeting usually dedicates a session (oral and poster) to bone cancers. In Stockholm, this session included 3 oral presentations, 2 orally presented posters and 15 posters. Presented data concerned both bone primitive tumors and tumor metastasis to bone.

Regarding primary bone tumors, osteosarcoma was the main subject of research with three significant reports. The first by Taipaleenmaki *et al.*[1] was the demonstration that RUNX2 overexpression in osteosarcoma cells was consecutive to a deregulation of a RUNX2-P53-miRNA-regulatory network. More specifically, authors evidenced that the P53-dependent miR-34c was the most significantly downregulated RUNX2 targeting miRNA in osteosarcoma with consequences on tumor cell proliferation and migration. Thus, miR-34c and in a larger extend miRNAs appeared as promising new targets for osteosarcoma therapy. The second report by Georges *et al.*[2] evidenced that the metalloproteinase ADAM12, which expression was only observed in osteolytic models of osteosarcoma, significantly increased the proliferation of tumor cells without modifying their cell migration ability. Moreover, authors showed that TGFβ induction of ADAM12 expression was part of TGFβ pro-tumoral effect. Thus, downregulating ADAM12 in osteosarcoma cells might be a way to block TGFβ pro-tumoral effect and so constitutes a new therapeutic approach for osteosarcoma. The third report was relative to the direct effect of aminobisphosphonates (ibandronate) on osteosarcoma cell proliferation. Thaler *et al.*[3] elegantly evidenced that ibandronate induced apoptosis of tumor cells via epigenetic demethylation of the tumor suppressor gene *Fas* by interrupting the RAS/MAPK/DNMT1 pathway. Such results outlined, if necessary, the importance of DNA methylation in tumorigenesis and constituted a breakthrough in the understanding of bisphosphonate mechanism of action on osteosarcoma cells. In addition to these reports on osteosarcoma, Talbot *et al.*[4] gave interesting data on the implication of connexin 43 in Ewing's sarcoma as a direct target of the aberrant fusion protein EWS-FLI1. Authors evidenced that rescuing connexin 43 expression in Ewing's sarcoma cells lines lead to an important reduction of the tumor growth, to a significant decrease of the peri-tumoral bone resorption and finally to an increase of the animal life span. This study suggested that connexin 43 could be considered as a new promising therapeutic target in the treatment of Ewing's sarcoma.

Regarding tumor metastasis to bone, data on breast and prostate cancers metastasis have been reported. Interestingly, researches on breast cancer were focused on two complementary subjects, the direct bisphosphonate action on tumor cells and the bone resorption induced by tumor cells. Concerning bisphosphonates actions on breast tumor cells, a first report by Ebert *et al.*[5] evidenced variable efficacy of different bisphosphonates on breast cancer cell apoptosis and proliferation inhibition. Interestingly, although the efficacy on tumor cell proliferation is common to all bisphosphonates and might depend on the mevalonate pathway, the induction of apoptosis was different according to the bisphosphonate considered (zoledronic acid (ZA) being the most efficient) and observed only on estrogen receptor (ER) -negative tumor cells. Similar results were obtained with prostate cancer cells, suggesting that blockade by estrogen signaling of the bisphosphonate induction of tumor cell apoptosis can be a conserved mechanism among tumors. These results open new therapeutic perspectives as for instance the use of antiestrogen in combination with bisphosphonates for ER-expressing tumors. A second report by Rachner *et al.*[6] went deeper in the mechanism of action of bisphosphonates (ZA) on breast tumor cell proliferation. The authors evidenced that ZA was able to strongly suppress the expression of the endogenous inhibitor of the Wnt pathway Dickkopf-1 (DKK-1), which was highly expressed by breast tumor cells, via inhibition of the mevalonate pathway, more precisely inhibition of the geranylation process. These two reports support the use of bisphosphonates as adjuvant in the treatment of tumor metastases to bone.

Concerning the bone resorption induced by breast tumor cells, two interesting reports on the interest of TRAF and VEGF inhibitors to breast cancer metastases treatment were presented. The first by Peramuhendige *et al.*[7] evidenced that the TRAF inhibitor ABD56 was able to inhibit the M-CSF and RANKL osteoclastogenesis enhanced by breast tumor cells. Interestingly, this inhibitor was shown to act both on osteoclast precursor blocking the membrane localization and ubiquitination of TRAF6 and subsequent phosphorylation of various factors induced by RANKL as IkB, and on breast tumor cells inhibiting the adhesion, spreading and migration with no impact on the cell viability. Such dual effect of TRAF inhibitor, not observed for RANKL inhibitor[5] and different from the previously described

for bisphosphonates, suggests great therapeutic potential for such inhibitors. The second report by Bagi *et al.*[8] evidenced that the VEGF inhibitor sunitinib was able in an intermittent dosing protocol to help normalized vascularization of highly osteolytic bone metastatic tumor and to improve efficacy of the associated cytotoxic therapy. Such an inhibitor might be of great interest in preventing the occurrence of breast cancer bone metastases and the associated bone deteriorations. Regarding prostate cancer, an interesting report by Van Driel *et al.*[9] evidenced that on the one hand growth of prostate metastases was stimulated by early osteoblasts and inhibited by late osteoblasts, and on the other hand that the osteoblast differentiation was affected by metastatic cells. These findings form an important basis for identifying osteoblastic factors important for bone metastases.

To conclude, despite a limited number of presentations relative to bone cancer (less than 20), very interesting data have been presented at the ECTS meeting in Stockholm. New targets for therapy have been characterized as connexin 43, miR-34c and ADAM12. New information concerning bisphosphonate action has been presented as the implication of DKK-1 and DNMT1. Finally, interests of TRAF and VEGF inhibitors for bone metastases treatment have been demonstrated.

Conflict of interest

The author declares no conflict of interest.

References

1. Taipaleenmaki H, Van der Deen M, Zhang Y, Lian JB, Stein JL, Stein G *et al.* Inverse biological coupling between the bone-specific transcription factor RUNX2 and the tumor suppressor P53 levels in osteosarcoma. *Bone* 2012;**50**:OPB08.
2. Georges S, Verrecchia F, Hervouet S, Chesneau J, Heymann D, Fortun Y *et al.* Role of ADAM12 in osteosarcoma development and in TGFβ/SMAD pathway activity. *Bone* 2012;**50**:393.
3. Thaler R, Spitzer S, Karlic H, Klaushofer K, Varga F. Ibandronate arrests tumor cell proliferation by epigenetic mechanisms. *Bone* 2012;**50**:392.
4. Talbot J, Picarda G, Amiaud J, Chesneau J, Brion R, Tirode F *et al.* Transcriptional inhibition of connexin 43 by EWS-FLI1: implication in tumor development of Ewing's sarcoma. *Bone* 2012;**50**:OC66.
5. Ebert R, Zeck S, Meissner-Weigl J, Jakob F. Differential effects of antiresorptive drugs on the proliferation and apoptosis rates of breast and prostate cancer cells. *Bone* 2012;**50**:390.
6. Rachner TD, Tsourdi E, Hadji P, Hofbauer LC. The WNT inhibitor Dickkopf-1: a novel target of the mevalonate pathway in bone cancer dialogue. *Bone* 2012;**50**:394.
7. Peramuhendige P, Marino S, Unciti-Broceta A, Ralston SH, Idris AI. A novel small molecule inhibitor of TRAF-dependent signaling inhibits breast cancer-induced osteoclastogenesis and prevents osteolysis. *Bone* 2012;**50**:OPB10.
8. Bagi CM, Berryman E, Andresen CJ. Intermittent dosing with sunitinib (PF-02783926) and docetaxel provides effective therapy against lytic bone metastasis of human breast cancer. *Bone* 2012;**50**:384.
9. Van Driel M, Koster R, Boers-Sijmons B, Chiba H, Van Leeuwen JP. Osteoblast differentiation stage determines the bidirectional cross-talk with bone metastatic prostate cancer cells. *Bone* 2012;**50**:389.