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PROSTATE CANCER

Feel it in your bones: MAOA mediates metastasis

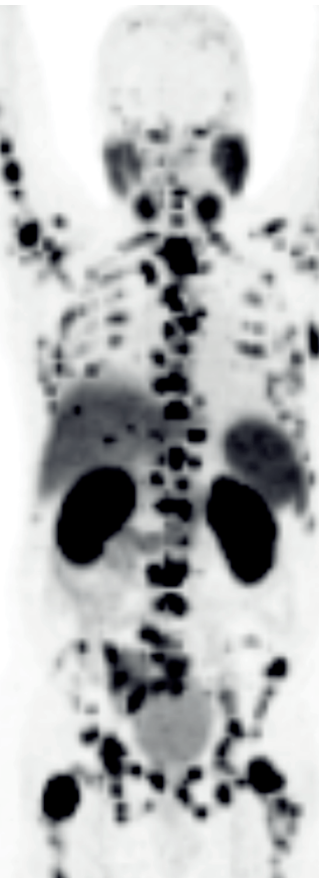

Image from Maurer, T. *et al. Nat. Rev. Urol.* **13**, 226–235 (2016), Macmillan Publishers Limited

Monoamine oxidase type A (MAOA) mediates prostate cancer metastasis to bone by activation the Shh–IL6–RANKL signalling pathway. Treatment with the MAOA inhibitor and antidepressant clorgiline reduced bone metastases and improved survival in mouse models of prostate cancer and this therapy could be translated to the clinic for treating men with advanced prostate cancer.

Wu and colleagues observed increasing MAOA expression from normal prostate tissue to metastatic prostate cancer samples from bone. Analysis of metastases-derived sublines of prostate cancer cell lines also showed elevated *MAOA* expression compared with their parental counterparts.

Overexpression of MAOA in PC-3 cells injected intracardially into mice increased the development of bone metastases and overall tumour burden; these mice also had increased levels of circulating tumour cells in peripheral blood. Mice harbouring MAOA-overexpressing cells had more severe osteolytic bone lesions and more TRAP-positive osteoclasts than control mice and significant decreases in relative bone volume and trabecular thickness. Stable knock down of MAOA delayed the development of metastases, decreased tumour burden, and improved survival. The severity of osteolytic bone lesions was reduced as was the number of TRAP-positive osteoclasts in these mice. Moreover, the reduction in relative bone volume and trabecular thickness was not as pronounced as in mice bearing MAOA-overexpressing cells. MAOA-knockout tumour-associated bone cells also had reduced expression of osteoclastin and a panel of osteoblastic metastases markers.

Wu and co-workers showed that *SHH* expression is positively associated with MAOA expression *in vitro* and ablation of *SHH* reduced MAOA-induced cell invasion and migration. The investigators identified TWIST1 as a regulator of *SHH* regulation and knock down of *TWIST1* reduced MAOA-induced *SHH* expression. Coculture of osteoblasts with MAOA-silenced prostate cancer cells reduced the expression of SHH target genes in osteoblasts, *GLI* reporter activity and osteoblast-derived RANKL expression. This effect was abbrogated by treatment with cyclopamine. Knock out of MAOA in coculture reduced tumour cell proliferation to a greater extent than in monoculture. Moreover, coculture of osteoblasts with prostate cancer cells induced *IL6* expression, which was further increased when MAOA-overexpressing cells were used; however, *SHH* siliencing reduced *IL6* expression. Inhibition of IL-6 reduced cell proliferation in coculture, whereas treatment with recombinant IL-6 increased proliferation. Additionally, treatment with a RANKL-neutralizing antibody decreased MAOA osteoclastogenesis in preosteoclast cells treated with coculture-conditioned media.

In vivo, treatment of mice with clorgiline delayed the onset of metastasis, reduced tumour burden and improved survival. These mice had less reduction in relative bone volume and trabecular thickness than controls and fewer TRAP-positive osteoclasts. Clorgiline treatment also reduced *Shh* signalling and *Rankl* and *Il6* expression.

These results provide evidence for MAOA mediation of bone metastasis in prostate cancer; furthermore, they indicate that treatment with clorgiline improves outcomes in a mouse model of this disease. Future translation of these findings to the clinic could provide a new therapeutic option for men with advanced prostate cancer.

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ORIGINAL ARTICLE Wu, J. B. *et al.* MAOA-dependent activation of Shh-IL6-RANKL signaling network promotes prostate cancer metastasis by engaging tumor-stromal cell interactions. *Cancer Cell* **31**, 368–382 (2017)