

Radium 223-mediates zonal cytotoxicity of prostate cancer in bone

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Background. Bone-targeting radiotherapy with Radium-223 (Rad-223), a radioisotope emitting genotoxic alpha-radiation with limited tissue penetrance (<100 μm), prolongs the survival of patients with metastatic prostate cancer (PCa). Rad-223 efficacy in patients correlates with a sustained decline of osteoblast-derived alkaline phosphatase (ALP) in serum, denoting reduced bone turnover, whereas levels of tumor-cell derived prostate specific antigen (PSA) are variable, without predicting outcome. It has been speculated that these clinical results may be attributable to a primary effect of Rad-223 on the tumor-associated microenvironment in bone, and such stromal reprogramming might reduce the microenvironmental support for PCa growth, consequently delaying disease progression. Direct toxicity of Rad-223 on cancer cells has been detected after high-dose application *in vitro*, but the relevance of this effect *in vivo*, given the low tissue penetration of alpha particles and divergent clinical PSA responses, was uncertain.

Methods. By integrating intravital multiphoton microscopy (iMPM) and a tissue-engineered bone window system with mathematical modeling of therapy response, advanced 3D *in vitro* and *in vivo* validation, we addressed Rad-223 direct cytotoxic effects on tumor cells.

Results. We recently developed and characterized a miniaturized tissue-engineered bone construct (mTEBC) suitable for iMPM, which is generated upon subcutaneous implantation of bone morphogenetic protein 7. The mTEBC fully matures in ~ 30 days and displays a continuous cortical bone that surrounds a well-defined cavity interspersed with trabecular bone and bone cells (including hematopoietic bone marrow, adipocytes, osteoclasts, osteoblasts, and osteocytes). After direct implantation of cancer cells in the mTEBC, an adjacent window system is positioned to perform non-destructive intravital microscopy of tumor growth. As a result, this model displays the temporal and spatial resolution required to monitor the kinetics of tumor progression (Dondossola, 2018). By applying this system we identified that Rad-223 induces profound but zonally confined cancer cell lethality along the bone interface (up to hundreds of μm), while the more distant tumor core remains unperturbed (Dondossola, 2019). Similar results were identified using a novel 3D *in vitro* bone-mimetic system (Paindelli, 2019). *In silico* simulations predicted greater efficacy of Rad-223 on single-cell lesions and minimal effects on larger tumors, further confirmed *in vivo*.

Conclusions. As consequence, large lesions persist and grow, whereas micro-tumors in the bone niche are effectively controlled by Rad-223. The relative inefficacy in controlling large tumors points to application of Rad-223 in secondary prevention of early bone-metastatic disease and in co-targeting regimens.

Conflict of interest: none

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