Creation of bone in the lab to design treatments for metastatic disease

By Kalli Spencer

As mentioned in previous research blogs, advanced prostate cancer is treated with androgen deprivation therapy to suppress the levels of testosterone and slow down tumour growth. With time the cancer develops mechanisms to outsmart this therapy (castrate resistant prostate cancer [CRPC]). One of the results is the spread of cancer to bone (found in up to 90% of patients with metastatic CRPC[mCRPC]). These deposits result in pain and pathological fractures. Very few treatments have shown survival benefit. Recent data suggest that targeting the tumour cells and the bone microenvironment improves survival. The role of the tumour microenvironment as a key modulator of tumour cell response to therapy is still unclear. Since bone metastasis is mostly always present in the castration-resistant phase it is important to determine the effects of standard androgen deprivation therapy (ADT) in the bone tumour microenvironment. Cancer cells induce stem cell osteogenic differentiation and osteoblast activation (the processes that are responsible for laying down bone). While some mechanisms have been proposed, the factors involved in the cross-talk between cancer cells and the bone microenvironment still need to be identified. Understanding the molecular actors involved in the adaptation of the bone tumor microenvironment to ADT is crucial for the identification of molecular drug targets for mCRPC. The main challenge has been adequately modelling the disease process in the lab. Previously bone modelling has been on animal tissue which has its limitations.

Dr Nathalie Bock and her team from the Queensland University of Technology have developed and validated a highly reproducible microtissue-engineered human construct in the lab that comprises osteocytic and osteoblastic cells (the cells responsible for the breakdown and formation of bone), with relevant protein expression and mineral content. The mature mineralized engineered tissue are cultured for up to 12 weeks. They then add metastatic prostate cancer cells to the mineralized microtissue. This model reproduces some of the cellular alterations seen in the human body under androgen deprivation therapy, followed by three-dimensional morphometric and functional characterization at the cellular level. They are also able to demonstrate the interactions between the tumor and the bone microenvironment. They looked at the outcomes in two different drug classes: bicalutamide and enzalutamide combining 4D live microscopy, cell morphometry, and gene and protein analysis.

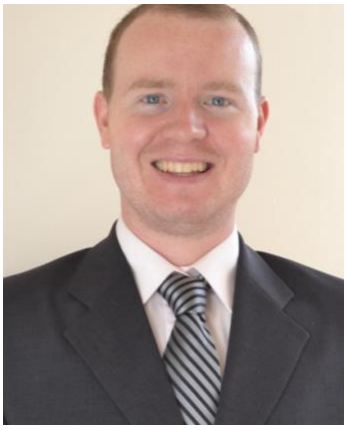
The researchers found a strong correlation between the architecture and function of their model compared to bone in a person with metastatic prostate cancer. One of the mechanisms for the cancer to outsmart drug therapy is by altering the testosterone receptors in cells where the drugs take their effect. In the bone model this adaptive response by the tumour cells was confirmed. The cancer is able to resemble a resident bone cell (osteomimicry) and take over its normal functioning. They are also able to evade the effects of the ADT and continue to grow and invade the bone further. Bock and her team were also able to demonstrate that in some cancers, resistance to treatment might already exist before treatment even begins, suggesting that alternative modes of treatment (i.e that don't target testosterone receptors) may need to be offered upfront. Another interesting finding was that the routine PSA blood test did not always reflect what was happening at the cellular level in the bone. If PSA could

be sampled from bone with cancer metastases it could prove to yield a higher value. In terms of the two drug classes it was shown that there may be worse outcomes with bicalutamide yet stronger genomic dysregulation using enzalutamide in this microenvironment.

This breakthrough work by Dr Bock and her team will be paramount in offering preclinical diagnostic testing at the initial visit to the urologist before surgery or radiation occur. Often the journey for someone with mCRPC is long and complex, trialling and failing multiple treatment options along the way. With the rise in personalised and tailored treatment approaches, models like these may aid in diagnosing who may developed mCRPC, why they develop it and the design of specific treatment. In this way we can outsmart the cancer and beat it at its own game.

Reference article

N. Bock, T. Kryza, A. Shokoohmand, J. Röhl, A. Ravichandran, M.-L. Wille, C. C. Nelson, D. W. Hutmacher, J. A. Clements, In vitro engineering of a bone metastases model allows for study of the effects of antiandrogen therapies in advanced prostate cancer. Sci. Adv. 7, eabg2564 (2021).



About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through publichealth advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.