UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Department of Pathology

2021 Seminar Programme presents

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Repeating the past: do cancers use early developmental repeat elements to drive malignancy?

The human placenta offers novel insights into the molecular mechanisms that drive cancer invasion and metastasis. During early pregnancy, the placenta invades into the uterus and mediates the maternal immune response, showing striking similarities to cancer. Moreover, some cancers reacquire an epigenetic landscape reminiscent of early human development, and many oncogenes have developmental origins. Interestingly, human developmental tissues (embryonic stem cells (ESCs) and the placenta) lack DNA methylation at some transposable elements (TEs). These viral-derived repeat sequences are silenced in healthy somatic tissues but are documented to become reactivated in cancer. We hypothesise that TEs contribute to oncogenesis by regulating early developmental pathways that, when activated inappropriately, can drive malignancy.

We have recently published a bioinformatic pipeline that quantifies and characterises TE expression within RNA-sequencing datasets. This pipeline was applied to identify TE-derived genes and regulatory elements that are specific to early human developmental tissues and melanoma. Importantly, these TE-derived genes are not expressed in somatic tissues but become reactivated in melanoma cell lines and patient datasets from multiple cancer types. Targeted-deep bisulfite-sequencing revealed low levels of DNA methylation within the promotor regions of TE-derived genes in early developmental tissues and in melanoma cell lines. High levels of promotor methylation were observed in healthy somatic tissues, supporting that DNA methylation may be a mechanism that regulates their expression. Furthermore, we have shown that antisense oligo-mediated knockdown of a previously uncharacterised TE-derived long non-coding RNA significantly reduces the invasiveness of melanoma cells, supporting that these genes may hold a functional role in melanoma progression.

Future work aims to functionally characterise additional TE-derived genes in melanoma and other cancer types. The restricted expression of these elements to early human development and cancer makes them promising diagnostic and therapeutic targets. Therefore, we ultimately hope to translate this work into a clinical setting.

Friday 5 November, 1 pm, D'Ath Lecture Theatre, Hercus Building