Circular RMST cooperates with lineage-driving transcription factors to govern neuroendocrine transdifferentiation

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Summary
Circular RNA (circRNA) is a large class of noncoding RNA with regulatory potency and exhibits dynamic transcriptional changes during developmental processes, such as neurogenesis. In prostate and lung cancer, adenocarcinoma cells can hijack neuronal developmental programs and transition to neuroendocrine prostate cancer (NEPC) and small cell lung cancer (SCLC) as an adaptive mechanism to evade targeted therapies. It remains unclear how circRNAs are functionally involved during neuroendocrine transdifferentiation. Here, using total RNA-sequencing, we profiled and curated circRNA expression in more than 500 prostate tissue and tumor samples, and performed functional screening against 10,000 of the circRNAs identified.

We identified an exceptionally abundant circRNA, circRMST, that is predominantly expressed in NEPC and SCLC compared to their adenocarcinoma counterparts. About 90% of the *RMST* transcripts exist in circular form in both patient tumours and cell line models. Functionally, circRMST is essential for tumour growth and maintaining NE lineage identity. Depletion of circRMST results in the loss of ASCL1, a master regulator of NE fate. *RMST* is highly conserved in mice for both sequence and circularization patterns. We utilized NEPC genetic engineered mouse models and further deleted *Rmst* with CRISPR-Cas9. No NEPC tumours were observed in *Rmst*-null mice and tumours were sustained in adenocarcinoma state. Mechanistically, circRMST physically interacts with and stabilizes NKX2-1 protein, as well as with SOX2 and regulates its chromatin interaction, which collectively drives *ASCL1* transcription and downstream NE transcriptional programs. Altogether, this study constitutes the first functional exploration of circRNA in NE tumours, highlighting circRMST as an evolutionary-conserved essential component of a regulatory circuit that governs NE transdifferentiation.

Funding: This work was supported by the Princess Margaret Cancer Foundation (886012001223 to H.H.H.), CIHR project grants (142246, 152863, 152864 and 159567 to H.H.H.), Terry Fox New Frontiers Program Project Grant (1090 and 1124 to H.H.H.). H.H.H. holds the Tier 1 Canada Research Chair in RNA Medicine. M.T. is supported by the Canadian Institutes of Health Research (CIHR) Doctoral Fellowship for graduate students.

Conflicts of Interest

The authors declare no conflict of interest related to this work.