**Onco-exaptation of Endogenous Retroviral LTRs in Cancer Evolution**

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It is well established that exaptation of transposable elements (TEs) into functional and, in some cases, necessary genes or regulatory units can occur over evolutionary time. We postulate that an analogous process, termed “onco-exaptation”, occurs in cancer in which TEs and especially endogenous retroviral long terminal repeats (LTRs) can be exploited in the evolution of the cancer transcriptome. Such a process could be facilitated by genome-wide epigenomic dysregulation in cancer, allowing for the de-repression of normally dormant TE/LTR sequences, which in turn drives ectopic transcriptional initiation across the genome. We further postulate that TE-initiated transcripts advantageous for cancer development will be selected for during oncogenic evolution. To investigate the magnitude of this phenomenon, we developed a software suite *LIONS* for analyzing whole transcriptome data to detect and quantify novel transcripts, including chimeric transcripts with known genes, which initiate within TEs. Using this method we found that TE-initiated transcripts are present in both normal B-cells and in B-cell derived Hodgkin Lymphoma (HL) cell lines but there is a notable increase in LTR derived transcripts in HL. Most interestingly, certain TE derived transcripts are recurrent and specific to HL, including the previously reported THE1B LTR driven *CSF1R* isoform, shown by others to be oncogenic and correlated with poor patient outcome. Our analysis also revealed that increased levels of the transcription factor interferon regulatory factor 5 (IRF5), recently shown to be upregulated in HL and a key regulator of the aberrant HL transcriptome, is largely driven by a normally silent LOR1a LTR alternative promoter. These validated oncogenic innovations are but two examples among hundreds of HL specific and recurrent TE-derived transcripts identified, leading us to postulate that this set of transcripts may be enriched for RNAs conferring neomorphic- or malignancy-associated functions. This repurposing of otherwise dormant TE regulatory sequences (particularly LTRs) may represent a distinct mechanism of oncogene activation and a model through which the evolutionary process of exaptation may be studied.