Spatial organisation of proto-oncogenes in human haematopoietic progenitor cells

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The eukaryotic cell nucleus is a highly organised organelle, with distinct specialised sub-compartments responsible for specific nuclear functions. Within the context of this functional framework, the genome is organised, allowing contact between specific genomic regions and sub-compartments. Previous work has shown that genes in both *cis* and *trans* can make specific contacts with each other. I hypothesise that such a preferred juxtaposition may impact the propensity for specific cancer-initiating chromosomal translocations to occur.

In this thesis, I describe how I have extended and developed a ligation based proximity assay known as enriched 4C. I have coupled this technique with high throughput sequencing to determine genomic regions that spatially co-associate with the proto-oncogenes *MLL*, *ABL1* and *BCR*. In addition to further developing the laboratory protocol, I have created bioinformatics tools used in the analysis of the sequencing data. I find that the association profiles of the three genes show strong correlation to the binding profile of RNA Polymerase II and other active marks, suggesting that transcribed genes have a propensity to associate with other transcribed regions of the genome. Each gene also exhibits a unique repertoire of preferred associations with specific regions of the genome. Significantly, I find that the most frequent *trans* association of *BCR* is telomeric chromosome 9, encompassing its recurrent translocation partner gene *ABL1*. Interestingly, *ABL1* is not at the maximum point of interaction. I use DNA-Fluorescence *in-situ* hybridisation to validate the e4C association.

My data supports a hypothesis that gene transcription has a direct role on genome organisation. I suggest that preferred co-associations of genes at transcription factories may promote the occurrence of specific chromosomal translocations.