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. Actively transcribing genes in both *cis* and *trans* co-associate at shared transcriptional sub-compartments called transcription factories. Remarkably, genes exhibit a preference to co-associate with certain other genes at the factories. I hypothesise that such preferred juxtaposition at transcription factories may impact the propensity for specific cancer-initiating chromosomal translocations to occur.

I have employed a ligation based proximity assay known as enriched 4C, coupled with high throughput sequencing to identify the genomic regions that spatially co-associate with the proto-oncogenes *MLL*, *ABL1* and *BCR* in human $CD34^+$ haematopoietic progenitor cells and lymphoblastoid cell line GM12878. I find that the association profiles of these three genes show strong correlation to the binding profile of RNA Polymerase II and other active marks. This suggests that transcribed genes have a propensity to associate with other transcribed regions of the genome, consistent with previous studies showing that genes can co-associate at transcription factories. 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*. I use DNA-Fluorescence *in-situ* hybridisation to show that the maximal point of association lies near the highly expressed *SURF* cluster of genes, suggesting a mechanism for mediating the interaction.

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.