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Are genomic translocations predictable? (Retrospective on DOI 10.1002/bies.201100122)

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It is sometimes useful for biologists to be reminded that the rules governing the physical universe apply to biological systems. Thermodynamic principles stipulate that rates for chemical reactions are proportional to the concentration(s) of reactants, a basic rule that applies equally to inorganic chemical reactions as well as to complex genomic rearrangements such as translocation and recombination.

Jerome Dejardin recently predicted that genomic translocation and recombination in pathologic circumstances are facilitated by alterations in chromatin that permit aberrant transcription factor binding [1]. Transcription factor binding is posited to result in co-localization of non-adjacent loci in three dimensional space within the nucleus. This transcription-factor driven colocalization increases local concentration of the reacting species for translocation or recombination, thus accelerating genomic rearrangement. This prediction, while simple in concept, is powerful in terms of predicting sites of aberrant genomic transactions: they are predicted to be concentrated in the vicinity of binding sites of transcription factors found in the cell type(s) of interest and to occur at loci with locally accessible chromatin features.

Issues relevant to Dejardin's predictions have recently been addressed experimentally by a pair of elegant studies. Roukos et al. [2] examined translocation in an engineered system utilizing ultrahigh-throughput imaging that permits real-time monitoring of DNA ends (the reactants) within nuclei. Double-strand breaks were induced at two distinct (and uniquely marked) genetic loci by a restriction enzyme. The resulting DNA ends sampled nuclear space, occasionally finding and pairing with a translocation partner. Importantly, the distance between the two induced double strand breaks prior to end joining was critical for the frequency of translocation: ends closer to each other prior to pairing were more likely to translocate. This study suggests that an important component of the prediction by Dejardin is likely to be true, i.e. increasing the proximity of DNA double-strand breaks to each other (increasing the local concentration of reactants) leads to a higher likelihood of translocation.

While this study supports the 'concentration' component of Dejardin's prediction, it does not speak to the nature of the chromatin surrounding such an event. Evidence speaking for the role of chromatin in the generation of translocations was recently published by Hakim and colleagues [3]. This study defined the nuclear interaction partners of enhancers of

immunoglobulin heavy chain (the well characterized Igh enhancers E μ and E α) in activated B lymphocytes using chromosome conformation capture (4C) experiments. The interactome of these transcription factor binding sites was enriched in active chromatin marked by high levels of histone acetylation, RNA polymerase occupancy, and active transcription. Introduction of DSBs at Igh (using a restriction enzyme) resulted in productive translocation to regions with similar chromatin features. This study indicates that translocation events occur with higher frequency at regions that are in close proximity in three dimensional space *and* that bear local chromatin features consistent with increased accessibility – precisely as predicted.

The predictions of Dejardin – that translocation and recombination may be driven by transcription factor binding, colocalization of non-adjacent loci, and alterations in chromatin features – appear to be in strong agreement with newly emerging experimental data. It remains to be determined whether all features of the prediction agree with experimental data. The field awaits the emergence of additional studies directed at understanding these genomic rearrangements that may shed new light on the ability of this model to predict their location.

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