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Fork Stalling and Template Switching in the Context of a 'Rearrangement Factory': FoSTeS Can Mediate Higher Order Chromatin Rearrangements

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Editorial

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Editorial

The concept of 'Rearrangement factory' (R-factory) has recently been introduced by the current author, as an attempt to provide a mechanistic explanation for the recurrent complex rearrangements taking place in particular regions of the genome and inducing diseases [1]. In brief, an R-factory could be defined as a highly unstable chromatin state consisted of highly condensed region(s) of abnormal chromatin configurations, including folding, loops & twisted strands with highly dynamic inter- & intra-strand contacts & linkages that are compacted in a limited genomic region and predisposing them to breakages; all generated as a consequence of an interlink between two non-allelic regions with sequence homology, most notably the long control regions (LCRs).Based on robust scientific evidence from different studies, several deviations from the confirmed genetic pathways have been predicted to take place in an R-factory, most notable of them, enzymatic activities capable of affecting any chromatin-associated functions like DNA replication. Replication & repair pathways are two of the most intensively studied chromatin functions that are supposed to be perverted in the context of complex rearrangements. It has been predicted that complex rearrangements are specifically happening as a consequence of micro-homology mediated (MM) replication repair mechanisms, most notably the micro-homology-mediated break induced replication (MMBIR) and fork stalling & template switching (FoSTeS) [2,3].

Fostes in the Context of an R-Factory

According to its definition by Lee, et al. [2], FoSTeS takes place as a consequence of a replication fork stalling due to a single strand DNA damage, and the 3' end of the lagging strand could serially disentangles and switches templates to the nearby active replication forks advancing in either 3' to 5' or 5' to 3' directions. They also predicted that the new templates might be in physical proximity to the lagging strand but they could be largely distant linearly. To rephrase the idea in an R-factory context, it can be proposed that the fork stalling in a factory hot zone, which could take place for several reasons but most remarkably the repeated insults to replication machinery, would leave the 3' end of the lagging strand in a condition highly probable that it comes to occasional contacts with chromatin strands straying around in an area overcrowded with chromatin twists and loops that are dynamically moving (almost shaking). Some of these contacts may eventually make suitable disposition to the 3' end to switch the template and start replication using the new strand as template, while the processivity is inevitably very low due to several potential reasons including the same dynamically changing setting that started the process at the first place; or for the same reason the original replication fork stalled in an R-factory era; or simply due to the length of the lagging strand originating from an Okazaki fragment that is supposedly composed of just some dozens of nucleotide bases paired to the original template and if the processivity goes too high, it would be at least theoretically more likely that the Okazaki fragment, now rearranged by FoSTeS, to get disentangled from its origin (5' end) than to recruit back the rearranged sequences; or the original template breaks at the border to the FoSTeS-engaged Okazaki fragment (Figure), and this disposition would act as a driving force for a higher order rearrangement.

FoSTeS mediated non-allelic homologous recombination (NAHR)

As has been illustrated in Figure 1 in the original report [2], the preliminary FoSTeS product doesn't represent a normal DNA organization and therefore, in order to stabilize the DNA structure, there is a need for some reorganization, most ideally a single stranded breakage at the FoSTeS-involved Okazaki fragment to resolute the structure and institute the FoSTeS-mediated rearranged sequences. However, this is not the only rearrangement type possible to take place in order to resolute the preliminary structure and so, either with or without the interference of DNA repair mechanisms, the chromatin might break at other situations, most probably the FoSTeS-mediated rearrangement junction points (proximal or distal).

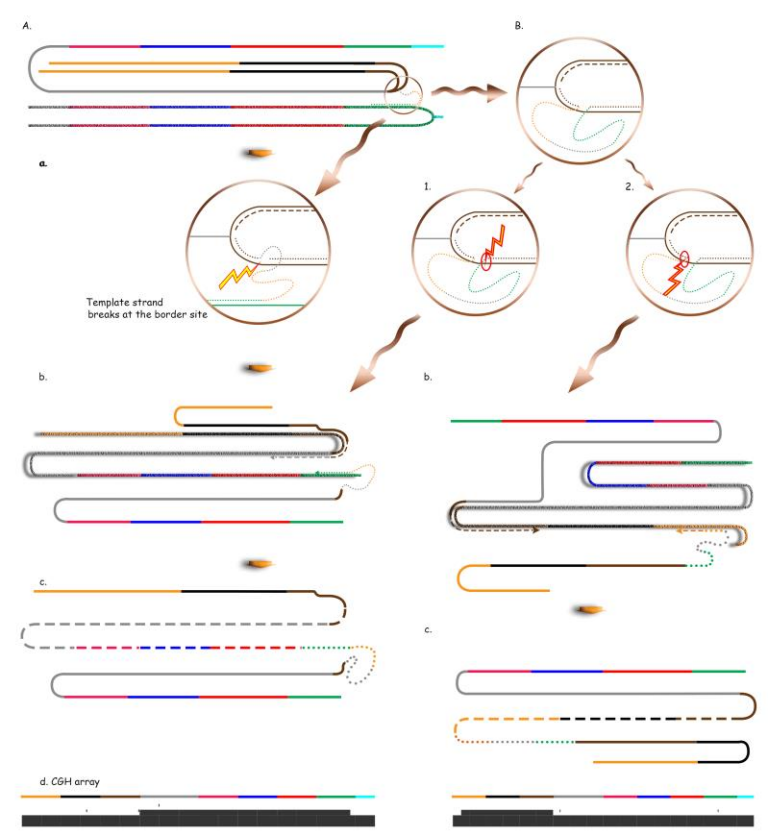

Figure 1: FoSTeS-mediated higher order rearrangement through non-allelic homologous recombination (NAHR). A; at its last template switch, FoSTeS product fails to get recruited back to the original chromatid due to the relatively high processivity or any other reasons, so instead a. due to a breakage at the original template, it gets fully engaged to the latest template (homologous chromatin here); b. the corresponding disentangled template side starts replication on the homologous chromatid in an break induced replication (BIR) model, which in this case is convergent to the separated FoSTeS product on the other DSB side; c. the two replication forks rejoin in a non-allelic homologous recombination (NAHR) model and make a tandem duplication in the downstream region relative to the original stalled replication fork; d. aCGH illustration of the rearranged region; B; after FoSTeS product gets successfully recruited to the original fork, resolution of the preliminary structure doesn't happen in a classical model, and instead, a DSB takes place in 1. Distal or 2. Proximal FoSTeS junction points; b & c. similar to the previous scenario, NAHR takes place between the FoSTeS replicated sequences and the original chromatid DSB site and a tandem duplication is made in the upstream region relative to the original stalled fork; d. aCGH illustration of the rearranged region. FoSTeS- mediated replications are shown as dotted lines; NAHR processes are shown in dashed lines. The template chromatids have been patterned and shadowed for distinction. The illustration of the FoSTeS-mediated rearranged segments are exaggerated in size (they might not even appear in real aCGH, even though they are illustrated as dots above the columns here).

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Figure 1 illustrates some of the most potential scenarios. In Figure 1A, the initial FoSTeS rearrangement product, due to any reason (notably the relative high processivity of FoSTeS mediated replication) could not be recruited back to the original chromosome and therefore, a breakage takes place on the template at its most susceptible point, the border to the FoSTeS-engaged Okazaki fragment where the template is not supported by the complementary strand. In case the FoSTeS-rearranged strand resides on the homologous template downstream to the affected replication fork (3' to the positive strand) and in a converging orientation, a simple non-allelic homologous recombination (NAHR) could take place, leaving a tandem duplication downstream to the breakage point (Figure 1A). Of course, more complex scenarios are also possible. Figure 1B, illustrates the two possible DSBs taking place at either borders of the FoSTeS-mediated rearranged region, after a successful recruitment of the replicated sequences to the original site. In case, the DSB takes place at the distal border (Figure 1B1), the supposed fate to the two sides of the DSB are indistinguishable from that of the above-mentioned. Nevertheless, in case the DSB happens at the proximal border (Figure 1B2), again if the last rearranged segment is in a converging orientation to the affected replication fork and at an upstream region (5' to the positive strand) to it, the same way to the above, a NAHR could be expected and duplication can take place, but at the upstream region to the DSB site.

Conclusion

Precise determination of junction points in the rearranged genomic regions has been a challenge to the scientists. Literature indicates that despite the simple copy number changes in genomic intervals, fine mapping confirms that the junction points usually contain templated or non-templated short sequence intervals from other chromatin regions [4]. According to the R-factory model, chromatin breakage sites are highly likely to come in contact with several neighboring chromatin regions due to the high chromatin strands concentration in the region, dynamically changing their conformations which could result in replication with short processivity in some of them. In the current study, a new concept has been presented in which FoSTeS can mediate higher order rearrangements like copy number variations (most notably tandem duplications), through NAHR. Already there is shortage of data about the fine mapping of the rearrangement junction points, and data from future studies providing more information on the subject is compelling to confirm or refute the herein recommended models.

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