Forward and reverse mutations in stages of cancer development

Mutations in somatic genomes are known to be the basis of cancers, understanding of which is essential for cancer prevention, diagnosis and therapy. In our study, mutations changing the genomic DNA sequences of a cell from its original form to any altered form are regarded as forward mutations. Mutations converting any altered form back to the original, pre-altered form are regarded as reverse mutations. It is generally believed that reverse mutations are produced by error-correcting mechanisms and therefore rare compared to forward mutations.

This general view is changed by our recent discovery of massive occurrences of interstitial loss-of-heterozygosity (LOH) type of single nucleotide variations (SNVs) in cancers. On average across different cancers and different patients, this newly discovered LOH type of SNVs is no less frequent than the commonly investigated gain-of-heterozygosity (GOH) type of SNVs. Hitherto, these LOH mutations have been completely left out of basic and clinical studies, which focused instead only on the GOH mutations changing nucleotides from their “wild-type” forms to “mutant” forms to result in either heterozygous or homozygous mutant genotypes.

The massive LOH type of SNVs are likely generated not by any error-correcting mechanisms, but by DNA double-strand break repair based on inter-sister chromosome recombination, which is a mechanism discovered from molecular genetics studies on brewer yeast and often referred to as gene conversion. Massive appearance of interstitial LOHs are indicative that overwhelming double-strand breaks and jeopardized DNA break repairs have occurred, thereby invoking inter-sister chromosome recombination as a backup repair mechanism. Because recombination is a much more powerful repair mechanism than other known error-correcting mechanisms, the reverse mutations revealed by our study were much more abundant than expected.

Driven by the powerful DNA repair mechanism of recombination, heterozygous sites in genome regions with high incidences of double-strand breaks could be effectively repaired and converted into homozygosity in either the maternal or paternal allele, effectively eliminating heterozygous sites either inherited from germline or produced by somatic mutations, to give rise to interstitial LOHs in the former case and reverse mutations in the latter case. Moreover, recombination or gene conversion may also increase forward mutations, often in the form of GOH type of SNVs, near the crossing over sites. Therefore, through enhancement of both the forward and the reverse mutations, DNA double-strand break repair by gene conversion would accelerate forward-reverse mutational cycles.

In the stage-specific mutation profiles observed in our study, the mutations early on in tumorigenesis in the apparently normal tissues of tumor-bearing organs were mostly GOH type of SNVs, particularly enriched in CpG-to-TpG alterations that likely arose from deamination of methylated CpG. The next stage of tumorigenesis occurred in the para-tumor tissue characterized

by abundant interstitial LOHs, suggesting that gene conversion became the dominant mechanism of DNA repair due to overwhelming double-strand breaks coupled with compromised repair machineries. Once this happened, tumorigenesis would become irreversible. Since gene conversion as a form of localized recombination, is a powerful generator of segmental duplications and deletions, or collectively copy number variations (CNVs), the burst of interstitial LOHs in para-tumor tissue was followed by increased occurrence of CNVs. Finally, mutations whether in the form of GOHs, LOHs or CNVs were all relatively subdued in the final tumor stage compared to the two previous stages of tumor development. A plausible explanation could be that methylated CpG islands as a major source of mutations had been exhausted by the preceding rounds of forward-reverse mutations. Altogether, our study has thus led to the proposal of a Stage Specific Population model of tumorigenesis.

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