Preface

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Genome (genomic) instability, a predominant hallmark of cancer, is gaining increasing attention in the field of cancer research. It is evident that genome instability is intimately involved in all major transitions essential to cancer evolution, including immortalization, transformation, tumor formation, metastasis, and drug resistance. Many well-established molecular pathways have been linked to genome instability, but despite its importance and popularity, the general mechanism of genome instability and its implications remain unclear and have been widely debated.

Current research efforts focus primarily on the identification of specific molecular mechanisms that either lead to genome instability or result from it. This strategy has been successful, as a plethora of individual molecular mechanisms have been discovered. Paradoxically, the accumulating data reveal a highly diverse and complex relationship between individual gene/epigene/pathways and genome instability. These findings also raise the following questions: How many more molecular mechanisms will be linked to genome instability? Are any of them clinically more significant, especially considering that each mechanism only explains a small portion of cases? Finally, are we chasing a large number of moving targets? Given the fact that there are a large number of identified, functionally diverse molecular mechanisms of genome instability, it may be time to ask, “What is the general mechanism of genome instability in cancer?”

Recently, some exciting developments have provided new avenues to understand the general mechanism of genome and specifically chromosome instability (CIN). First, the current cancer genome sequencing project has revealed large-scale cancer heterogeneity at different genetic and epigenetic levels. In particular, genome level heterogeneity has been commonly

observed but has been generally ignored. For example, the structural and numerical alterations of chromosomes are commonly detected in the vast majority of cancer genomes, with many displaying drastically altered karyotypes with massive intra- and inter-chromosomal translocations. The overwhelming presence of chromosome change in tumors demonstrates the need to prioritize CIN studies and its relationship with other types of genome instability. Furthermore, different patients display minimal overlap of these genetic/epigenetic aberrations, and a great number of mutations discovered can be characterized to establish a link between specific gene mutations or pathways to CIN. Second, systems biology has melded transcriptome dynamics and CIN-mediated genetic heterogeneity. Global gene expression profiles have been analyzed in cells containing karyotype aberrations including aneuploidy and structural variations using various model systems. These analyses have identified both the aneuploidy-associated stress pathway and stochastic transcriptome dynamics during punctuated karyotypic cancer evolution. Third, new efforts are combining nongenetic and genetic changes in the context of evolutionary adaptation models. Rather than focus on individual genes, these studies focus on the status/behavior of the system, shedding new light on the understanding of the cancer landscape and its relationship among different genetic/nongenetic levels. Similarly, the advantages of karyotype variation to the cell and organism have been identified as an adaptive evolutionary strategy in response to various stressful conditions, and in normal somatic cells, the contribution of somatic cell mosaicism has received increasing attention. Finally, the concept that cancer represents a typical somatic cell evolutionary process has reenergized the field. Punctuated cancer evolution has been confirmed by single cell sequencing and advanced karyotypic analyses, and genome chaos has been demonstrated directly in tumors. Now is the time to unify diverse molecular mechanisms of cancer using the evolutionary mechanism of cancer, where CIN-mediated genome replacement is the key driver of cancer evolution.

To illustrate these new developments and their impact on genome instability research, this thematic issue “Genome

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Instability and Cancer” strives to highlight these new frontiers.

Heng *et al.* outline the current state of CIN research in cancer by discussing multiple aspects of CIN including its definition, methods used to measure, and challenges of study. This comprehensive analysis leads to the proposal that a general evolutionary mechanism of CIN should unify the diverse molecular causes.

Pikor *et al.* discuss the different levels of genomic instability commonly detected in cancer and compare various methods to study them. Using these approaches, they have analyzed the current public tumor data and have provided a survey of genome instability across numerous tumor types.

Fox *et al.* focus their discussion on the mutator phenotype, an excellent example with links to genomic instability and cancer. With recent evidence from cancer genome sequencing projects that support the mutator phenotype hypothesis, they briefly discuss major arguments against this concept and the clinical consequences of the mutator phenotype. They propose targeting cellular pathways that alter the rate of mutation rather than target mutant driver genes or driver pathways to better treat cancer.

Thompson *et al.* review the misregulation of three specific types of histone posttranslational modifications: histone H3 phosphorylation at serines 10 and 28, H4 monomethylation at lysine 20, and H2B ubiquitination at lysine 120, as epigenetics and specific histone posttranslational modifications have essential roles in maintaining genome stability under normal conditions.

Potapova *et al.* update the relationship between aneuploidy and CIN. Based on the studies that combine gene expression and chromosomal copy number changes, and the analyses of aneuploidy in biology in general, they propose that the relationship between aneuploidy and chromosomal

instability can be envisioned as a “vicious cycle,” where aneuploidy potentiates chromosomal instability leading to further karyotype diversity in the affected population.

Stevens *et al.* discuss how stochastic chromosome change results in transcriptome dynamics. The vast majority of diverse molecular mechanisms that “cause” cancer are linked to karyotypic heterogeneity through the evolutionary mechanism of cancer. Karyotypic change and the resultant transcriptome change alter network function within cells increasing the evolutionary potential of the tumor.

Tarabichi *et al.*, using the idea of entropy-driven evolution, propose that cancer progression involves a constant dynamic reprogramming of the invasive and metastatic characteristics, with the emergence of a sort of collective intelligence.

Finally, Huang provides a timely synthesis of genetic and nongenetic (including epigenetic) instability in cancer using the theory of fitness landscapes. By explaining the basis for the “epigenetic landscape” and its relationship to “fitness landscapes,” he discusses the complicated interaction between genetic and nongenetic instability within the evolutionary context of cancer.

While the discussion provided in this issue covers only a fraction of the ongoing genome instability research and many subjects deserve to be discussed, these reviews provide up-to-date comprehensive information regarding important aspects of genome instability both from conceptual and methodological points of view. In particular, they share the common trend of focusing on multiple levels of genetic and nongenetic instability, and apply the evolutionary principle into the studies of how genome instability contributes to cancer. Together, these timely discussions will certainly promote an understanding of the evolutionary meaning of genome instability in cancer.