

# Towards the elucidation of the mechanisms underlying breast cancer mutations

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The genome of cancer cells is characterized by the presence of somatic mutations acquired during the processes of neoplastic transformation and clonal expansion. A small fraction of these mutations, called *drivers*, causally affect oncogenesis by conferring growth advantage. The remaining mutations, also called *passengers*, do not contribute to the advantage of tumor growth (1,2). Somatic mutations are the result of a balance between the DNA damage and repair events occurring during tumorigenesis. With the analysis of both driver and passenger mutations in the cancer genome it is possible to follow the processes active during the lifetime of cancers. Yet, the mechanisms by which these events specifically affect somatic mutations are poorly understood. Furthermore, most of the published studies have focused only on limited number of cancer genes.

In the last decade, the development of high-throughput sequencing technologies has permitted the completion of whole cancer genome sequences (3-9) and the generation of comprehensive catalogs of somatic mutations (10,11). The investigation of the full repertoire of cancer-specific mutations can importantly contribute to our understanding of the processes modeling the genomic landscape of tumors. Recent studies have demonstrated the potential of this approach in revealing mutational signatures in melanoma and lung cancer (10,11). Very importantly, these studies have also elucidated the molecular mechanisms underlying the mutations detected in these tumors. Yet, it is unknown how the mutational processes alter the genome of breast tumors. The study published by Nik-Zainal *et al.* in *Cell* (12) aimed to identify the mutational mechanisms remodeling

the genome of human breast cancers.

Nik-Zainal *et al.* sequenced the complete genome of 21 breast cancers typed for the expression of Estrogen Receptor (ER), Progesterone Receptor (PR) and Epidermal Growth Factor Receptor 2 (HER-2/ERBB2) and for the presence of BRCA1 and BRCA2 germ line mutations. The authors aimed at the identification of all the cancer-specific mutations by comparing tumor DNA and normal DNA obtained from the same patient. By performing this analysis, a comprehensive catalog of somatic mutations from the 21 breast cancer genomes was defined. In agreement with previous studies (13-15), substitutions were identified in cancer genes such as GATA3 and PIK3CA. Furthermore, the amplification of genes implicated in breast cancer development was also reported (e.g., *ERBB2*, *CCND1*, *MYC* and *ZNF703*).

The authors also focused to investigate the active mutational processes, by considering each base substitution and the bases immediately 5' and 3' to it. The analysis of base substitution evidenced that various mutational signatures and processes were present in the majority of the tumors. To define the signatures featuring the mutational processes and to evaluate the contribution of these events in each breast tumor sample, Nik-Zainal *et al.* applied a nonnegative matrix factorization (NMF) model. The evaluation of NMF decompositions revealed five mutational signatures (A, B, C, D and E) characterized by different profiles of trinucleotide mutations. In particular, signature B is mainly represented by C>T and C>G mutations at TpCpX trinucleotides. Moreover, various combinations of

each signature defined the mutational spectra in each breast cancer genome, demonstrating that multiple mutational processes may have been arranged either at the same time or in different phases of tumor growth.

In order to evaluate the possibility of regional clustering of substitutions, the authors analyzed the distance between somatic mutations. Very importantly, they showed a remarkable phenomenon of localized hypermutation, termed *kataegis*. Various extents of *kataegis* were observed in the diverse cases, with examples of hypermutation spanning both large and short regions. Moreover, these clusters showed a typical mutational pattern, similar to the one defined in signature B. Interestingly, the regions showing *kataegis* were also associated with somatic genomic rearrangements. All these findings suggested that mutational processes inducing specific localized hypermutation patterns might promote chromosomal rearrangements, which are, indeed, very relevant features of cancer genomes. In addition, the authors hypothesize that the AID/APOBEC deaminase protein family members might be involved both in *kataegis* as in the molecular mechanisms underlying signature B. Indeed, these proteins are involved in somatic hypermutation and class-switch recombination at immunoglobulin loci. This suggests that AID/APOBEC proteins might also play a critical role in tumors carrying signature B.

Previous studies in other cancer types have shown that transcription-coupled DNA repair processes are able to influence the mutational genomic spectrum (10,11). The work by Nik-Zainal *et al.* has revealed a mutation transcription strand bias for G>T and T>G transitions, suggesting a possible role for the transcription-coupled repair mechanisms in the removal of guanine or thymine bulky adducts. Moreover, an inverse correlation between mutation prevalence and gene expression levels was reported, confirming a similar observation in melanoma cancer (11). Interestingly, in Nik-Zainal *et al.* study, the prevalence of mutations was superior at increased distance from the transcription start site. Altogether, these data suggested that transcription processes might act as suppressors of mutagenic forces.

The study conducted by Nik-Zainal *et al.* is the first example of analysis of the complete mutational spectra of breast cancer samples. Furthermore, this work emphasizes the importance of the whole-genome sequencing studies and the generation of comprehensive catalogs of somatic mutations accumulated in tumors. Human cells are subjected to factors that induce DNA damage, which might

be repaired or transmitted to the daughter cell. Importantly, these processes may leave imprint on the genome depending on their strength and duration. The analysis of whole-genome catalogs of somatic mutations can provide a great help in our understanding of the mutational events to which every cell is subjected during the whole lifetime. It can become an important approach to shed light not only on the mechanism of neoplastic transformation and progression, but also of cell aging, and can therefore give hints on the origins of genetic instability in cancer. The extraction of mutational patterns can improve our understanding of the molecular mechanisms underlying DNA damage and repair. Moreover, they can provide information about the history of tumors and how somatic mutations are occurred, as it has been previously reported (16).

Finally, this study opens important perspectives on clinical applications. The extraction of signatures linked to specific breast cancer subtypes may improve the commonly applied histological typing. Further research may highlight signatures linked with breast cancer prognosis and efficacy of specific therapies.

The study considers mutations derived from only 21 genomes but mutational pattern analyses will be performed in thousands of cancers (17). Future studies should compare mutational signatures identified in different cancer types and correlate these with both genetic and environmental factor exposure. These studies would allow getting insight in the tumor growth mechanisms and it would give some hints about the mutational pathways to target in diverse tumor types.

All in all, signature analysis may not only be a great tool to discover DNA damage and repair mechanisms operative in cancer lifetime, but also provide remarkable insight in diagnosis and in therapy personalization.

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## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2013.04.14>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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