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Post-zygotic Mosaic Mutation in Normal Tissue from Breast Cancer Patient

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ABSTRACT

Even though numerous previous investigations had shed fresh light on somatic driver mutations in cancer tissues, the mutation-driven malignant transformation mechanism from normal to cancerous tissues remains still mysterious. during this study, we performed whole exome analysis of paired normal and cancer samples from 12 carcinoma patients so as to elucidate the post-zygotic mosaic mutation which may predispose to breast carcinogenesis. We found a post-zygotic mosaic mutation PIK3CA p.F1002C with 2% variant allele fraction (VAF) in normal tissue, whose respective VAF during a matched carcinoma tissue, had increased by 20.6%. Such an expansion of the variant allele fraction within the matched cancer tissue may implicate the mosaic mutation in association with the causation underlying the breast carcinogenesis.

The post-zygotic mosaic mutation is estimated to be deleterious by well-established variant annotation software programs, SIFT_pred, Polyphen2_HDIV_pred, Polyphen2_HVAR_pred,LRT_pred, utationTaster_pred, PROVEAN_pred,fathmm.MKL_coding_pred,MetaSVM _pred, and MetaLR_pred. additionally, we discovered 61 deleterious and pathogenic mutations, including 22 stop-gain, 12 splicing site, 13 frame shift and seven non synonymous mutations, in those patients. By performing mutational signature analysis, we identified three mutational signatures underlying breast carcinogenesis, including APOBEC cytidine deaminase and defective DNA mismatch repair.

Taken together, these results suggest that, additionally to the somatic driver mutations, post-zygotic mosaic mutation could also be a critical target that's worth deserving prior attention in ascertaining the causation underlying breast carcinogenesis within the upcoming future. Increasing theoretical and experimental evidence suggests that the genomes of both normal and cancer cells are subject to continuous changes as a results of copying errors during replication, defects in chromosome segregation during mitosis, and direct chemical attacks by reactive oxygen species. the method of cellular genetic diversification begins during embryonic development and continues throughout life, resulting in the phenomenon of somatic mosaicism. New information about the genetic diversity of cells composing the body makes us reconsider the prevailing concepts of cancer etiology and pathogenesis.

Here, I suggest that a progressively deteriorating microenvironment ("soil") generates the cancerous "seed" and favors its development. Cancer Res; 78(6); 1375–8. ©2018 AACR. Just like nothing has contributed to the flourishing of physics quite war, nothing has stimulated the event of biology quite cancer. The unprecedented intellectual and material efforts invested into combating the continued cancer pandemic have greatly enriched our understanding of fundamental processes of life and therefore the organization of a living cell. With reference to oncology, it's been established that "cancer may be a disease of genes," which genetic instability is that the drive of carcinogenesis and a key feature of tumor cells, which is predicated on the idea that the genome of a traditional cell is usually stable.

However, recent evidence contradicts this notion, because it appears that the physical body represents a mosaic composed of trillions of genetically distinct cells, to the extent that two identical cells can hardly be found. Such amazing genetic diversity are often explained by constant, life-long exposure of human cells to a mess of mutagens originating both inside the body and within the surrounding environment, which ends up in somatic mosaicism exemplified in its extreme form in tumors. In view of this, genetic instability cannot be considered a singular property of cancer cells but the one inherent to all or any somatic cells, to some extent, which makes it

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necessary to revise numerous generally accepted fundamental concepts in oncology.

Especially, the phenomenon of genetic mosaicism makes us view carcinogenesis as collective instead of individual "guilt" and put the blame on the entire cellular community instead of on one cell. In this Perspective, I discuss stochastic changes occurring only within the genome of somatic cells instead of programmed mosaicism of germ and immune cells.

***Keywords*:** Post-zygotic; Mosaic mutation; Breast cancer