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Mini Review

Prominence of the Evolutionary and Personalized Strategy in the Breast Cancer Management: A Junction Between Cancer Cell Genetics and Clinical Oncology

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Abstract

ATM has the key role in different cancers including breast. The molecular alteration of D1853N polymorphism, accompanied by the IVS 38- 63T>A and IVS38-30A>G alterations in the exon 37 and its 5'-splicing region, played the instructive role in the development of astrocytoma, as three-hit hypothesis. The D1853N polymorphism, is considered as a predisposing factor in a proband affected with primary BC.

The eight-hit event in a breast cancer patient, presented the sequential molecular alterations including the inherited D1853N predisposing factor as the first hit. The cascade of additional molecular alterations include IVS 36-8 T>C as the 2nd hit, V1833M as the 3rd hit and L1888L as the 4th- hit and the complementary somatic variants (IVS 36-46 C>T, L1842L, H1864H, and S1872R). Protein expression of ATM revealed, as a confirmative role is found to be low.

The hits with influential impact on the function of ATM was, also, confirmed by *in silico* analysis.

The strategic and programmed events of the breast cells are shaped through the multi-developmental processes including the programmed proliferation accompanied by different cascade of events to secure the occurrence of breast carcinoma (BC).

The major focal points of this commentary includes the evolutionary events including Five-hit and Eight-hit hypothetic personalized events in the breast cancer patients.

Key considerations: Major Concerns and the essential step in Cancer Prevention includes: 1) an early detection; 2) Considering the right of the proband's relatives through the pedigree-based strategy; 3) considering the personalized insight; 4) application of combination of technologies including molecular and single cell-based functional assays.

Keywords: *Evolution; Personalized; Hit Hypothesis; Breast Cancer; ATM Polymorphism; Predisposing Gene*

Five-hit hypothesis

As a major public health problem, breast cancer (BC) is considered as the most frequent malignancy in women. Despite the rapid advancements in the diagnostic strategy in cancer, intensification in incidence and death is reported to be approximately 18 percent from 2008 cases rendering to GLOBOCAN statistics [1]. The frequency of the sporadic BC cases and the inherited form are observed between 90-95 percent and 5 - 10 percent respectively [2]. Regarding the molecular aspect, BCRA1, BCRA2, and P53, as the high penetrance targets; followed by group of ATM, CHECK2, BRIP1, and PALB2 as the intermediate penetrance indicators; some SNPs as low penetrance, and PTEN, STK11/LKB1, CDH1 as an undefined penetrance factors [2,3].

Ataxia telangiectasia mutated (ATM) gene is located at chromosome (11q22.3) and encodes an instruction for producing a 370-kDa-protein which is a key checkpoint kinase in cell cycle, responses to the DNA damage and genomic stability [4-6]. ATM plays an important role in different cancers including breast, ovarian, stomach, bladder, pancreas, and lung [7,8]. The molecular alteration of D1853N is, frequently, traced in BC patients compared to the control groups [9-11]. D1853N polymorphism alongside with IVS 38- 63T>A and IVS38-30A>G alterations in the exon 37 and its 5'-splicing region, played the directive role in the development of astrocytoma, as three-hit hypothesis [12]. Based on our three-hit-hypotheses in ATM, we introduced the D1853N polymorphism, as a predisposing factor, and possibly the additional evolutionary alterations at genomic and somatic level in a proband affected with primary BC.

Eight-hit hypothesis in breast cancer

BC is reported as the most common malignancy within women in almost all of the geographical regions [13]. ATM enrolled to the sites of double strand breaks (DSBs) and assists the cells to distinguish the broken DNA through activation of cell cycle checkpoint. Henceforth, it is the preliminary recognizing factor of DNA damage [14]. Interestingly, the functional loss of ATM straightly leads to Ataxia telangiectasia (AT) disease, besides; the individuals who carry the *ATM* mutations face a remarkable risk of developing BC. In this regard, we have reported that the substitutional missense of aspartic acid with asparagine in codon 1853 (D1853N) is remarkably more frequent in the patients affected with than the control individuals [15].

By considering the evolutionary process, initial hit in the key genes such as oncogenes, tumor suppressors, and repair genes could increase the chance of different mutation acquiring in cells by conferring a growth advantage or by inducing genomic instability [16]. The two-hit hypothesis was also reported by Knudson in the development of retinoblastoma [17].

The pedigree of a proband affected with IDC-BC is presented to highlight the importance of the family history and the preventive strategy for the proband's relatives (Figure 1).

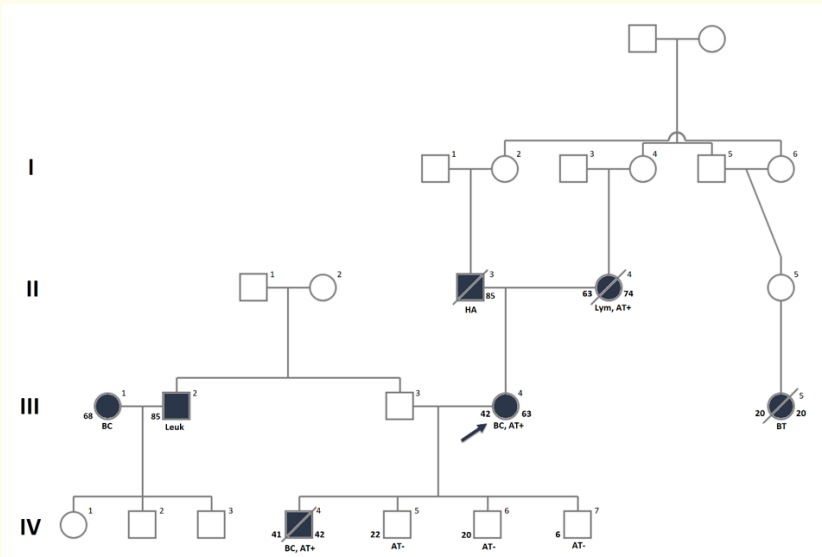

Figure 1: *The pedigree of a proband affected with IDC-BC. Right-side numbers of each individual presents systematic reference number of individuals through each generation. Left/bottom-side numbers of each individual current age of onset (years) and right/bottom-side number presents deceased age (years) in the pedigree. Right/bottom-side number of proband presents her current age. AT+ represent "positive D1853N" and AT- represent "negative D1853N". The carcinoma-type of each person is indicated in the bottom of subjects: BC = Breast Carcinoma; Lym = Lymphoma; BT = Brain Tumor; Leuk = Leukemia; HA = Heart Attack. Adapted from Mehdipour P, Azarnezhad A (2021) [18].*

The multi-hits could occur through- per-differentiation, embryonic/fetal periods, post-birth and through the individual's life (Figure 2). However, a predisposing element, such as D1853N polymorphism in our case is hypothesized to be essential for initiation and promotion of HIT- process [12].

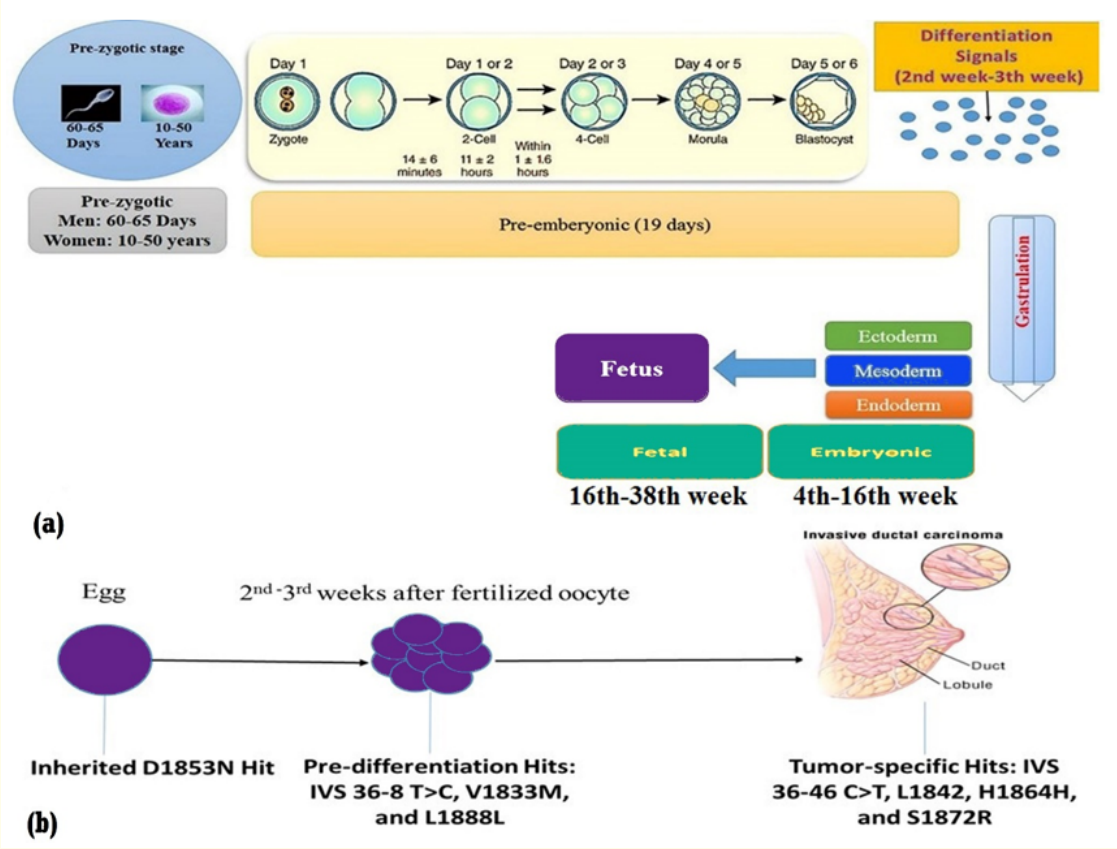

Figure 2: *Development of human embryo from zygote to birth. The alterations including IVS 36-8 T>C, V1833M and L1888L that were observed both in blood and tumor tissues are as the result of events occurred in pre-differentiation stage between 2nd and 3rd weeks of gestation. further evolution has occurred at tumor level which are found as tumor-specific hits including IVS 36-46 C>T, L1842, H1864H, and S1872R, characterized as the 5th, 6th, 7th and 8th hits, respectively. Adapted from Mehdipour P, Azarnezhad A (2021) [18].*

In eight-hit event, the sequential alterations at the molecular level included: the inherited D1853N predisposing factor as the first hit; the pre-differentiation stage hits including IVS 36-8 T>C as the 2nd hit, V1833M as the 3rd hit and L1888L as the 4th- hit, and the somatic variants shaped the 5th to 8th hits including IVS 36-46 C>T, L1842L, H1864H, and S1872R. Low protein expression of ATM in the majority of cells was indicative/ confirmative of the protein miss-function [18]. Interestingly, the protein expression of cyclin E, CDC25A, P53, and Ki-67 was more diverse (Figure 3).

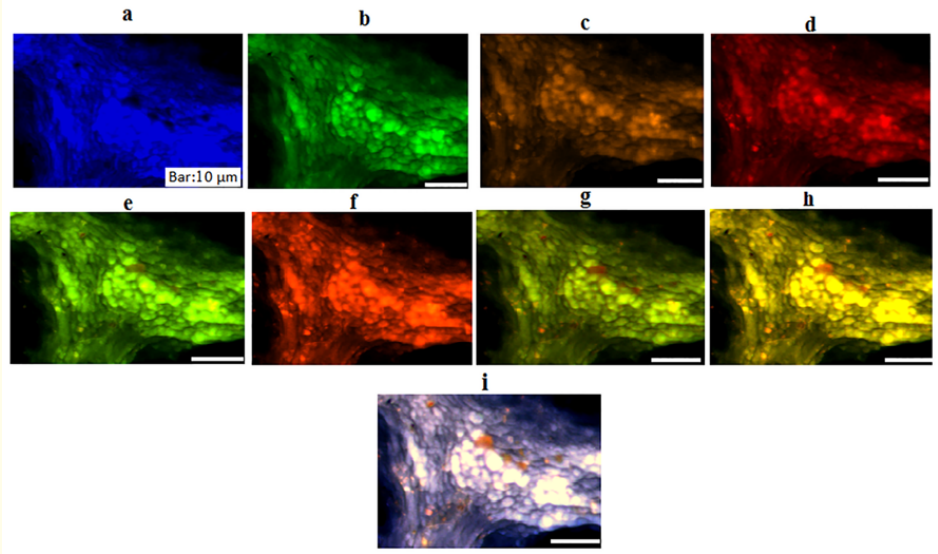

Figure 1: *"Protein expression of Cyclin E, ATM and CDC25A in tumor of a patient with breast carcinoma". a) Breast tumor cells with dapi; b) The same cells conjugated with FITC, reflecting the expression of Cyclin E; c) The same cells conjugated with Rpe, reflecting the expression of ATM; d) The same cells presenting the expression of CDC25A and conjugated with Pe-cy5; e) The co-expression of Cyclin E/ATM; f) the co-expression of cyclin ATM/ CDC25A; g) The co-expression of Cyclin E/CDC25A; h) the co-expression of Cyclin E/ATM/CDC25A; i) The co-expression of dapi/Cyclin E/ATM/CDC25A. Diverse expression and remarkable co-expression is observable. Adapted from Mehdipour P, Azarnezhad A (2021) [18].*

Remarks included the sequential molecular and functional events through the entire patient's life from the pre-differentiation embryonic stage and all through the post-birth periods. The hits influenced on the function of ATM which confirmed by the application of the expression and *in silico* analysis.

By considering the hypothetic insight and the course of evolution, linking the Science to the clinics will be clarified. Evolution is very complicated, diverse and enthralling in different aspects of cell biology and requires the multi- disciplinary experiments including the molecular and functional aspects.

Tracing the D1853N polymorphism of ATM gene at pedigree-based level leads to plan for an early detection of the predisposing factor either in the affected proband with breast or other cancers or the relatives who may be at risk of being affected with cancer (Figure 1). Although the hit-event is rather rare, but offers an early detection by application of the 4xp package including predisposing, predicting, prognostic and preventive protocols. Besides, the severity of cancer will be facilitated by the complications of hit process, according to the frequency of hit-events. Besides, the harmful nutritional habits could be also considered and corrected according to the nutrigenomics protocols.

Conclusion

The key characteristics of the 4xP strategy includes the translatable role of D1853N polymorphism, unmasking any course of evolution in the cancer patients, and formulating the five- and 8-hit hypothesis. Overall, the present data are reflective of the sequential molecular

and functional events through the entire patient's life from the pre-differentiation in embryonic stage and all through the post-birth periods. The hits are effective on the function of ATM, which confirmed by the expression and *in silico* analysis.

Competing Interests

The author disclose any financial or non-financial interests that are directly or indirectly related to the present work commentary.

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