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Commentary

Networking Between Cell Biology, Genetics and Personalized Management: Focusing on Circulating Tumor Cells and D1853N Polymorphism

Parvin Mehdiour*

Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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Abstract

Cells act as the bridges within the tissues' territory, capable for initiating the cascade of events.

Cancer is the platform of puzzles to be unmasked. There is available knowledge in cancer, but is required to be revised. However, restoration is a verbalizing item in cancer research.

This commentary is aimed to highlight: 1) The protagonist and influence of "Cell Biology" and "Genetics" in the personalized cancer management, and 2) to provide the key and basic information for the clinicians who are interested in' linking the insights' in brief.

In spite of the remarkable efforts by clinicians in cancer medicine, so far, the lack of comprehensive strategy towards cancer progression is noticeable. Bridging between Cell Biology and Genetics has an influential impact on cancer management including early detection and personalized approach in prognosis, prevention, and therapy. So, lets apply the multi-disciplinary movements in cancer managements by considering the bridging system between Cell Biology/Genetics/personalized clinical managements.

Conclusively, a triangle of Single Cell, Molecular, and Pedigree-based approaches would manage the personalized strategy in cancer managements. In this regard, the application of circulating tumor cells (CTCs) for an early detection and the key impact of D1853N polymorphism in ATM gene, as a predisposing factor, are provided at a glance.

Keywords: Cell Biology; Cancer Genetics; Early Detection; Personalized; CTCs; D1853N Polymorphism

Introduction

Cancer philosophy may be considered as a harmonizing vision to achieve the complementary understanding in this arena. Classification of cancer is, mostly, relied on the limited categories, including the traditional aspects of Pathology, and Genetics in the clinic. However, cancer requires a wide spectrum of values which could be considered as a "Medical Globe" including combination of managements.

Cancer with a multifactorial manner, is linked to the biological, Psycho-Somatic, Genetic, and environmental diseases [1].

The ataxia telangiectasia-mutated (ATM) is a member of the phosphatidylinositol 3-kinase -like family; which is located at chromosome 11q22-23; comprising 66 exons and is involved in cell-cycle checkpoints. This gene plays a key role in the repair of DNA double-strand breaks which was related to a variety of DNA-damaging agents including ionizing radiation [2,3]. It is reported that single nucleotide polymorphism D1853N of the ATM gene may increase the risk of breast cancer [4].

By considering the single cell strategy, the adequate enumeration of the circulating tumor cells (CTCs) is the most applicable diagnostic platform in cancer – early detection and prevention. The most challenging objects include the lack of basic data on the migrated cells into the blood stream and the classified data for the personalized application of CTCs at the pedigree level. Furthermore, controlling the metastatic process in cancer requires a CTCs-based guideline. Besides, the complementary Information on CTCs would be the directive channel for the therapeutic application of anti-VEGF, EGF and CCL2 in different cancers.

In this commentary, it was aimed to present the selected targets including the protein expression assay, detection of the CTCs, DNA mutation, and the roles of each paradigms in cancer development and progression.

It was also attempted, at a glance, to highpoint their impacts on basic science which could be linked to the cancer clinics. As a complementary scheme, the Priorities in Cancer Clinics is provided (Figure 1).

Results and Conclusions

Pedigree analysis

Regarding the key role of pedigree analysis, the impact of such strategy includes: 1) Unmasking any family history of malignant,

Figure 1: Establishing Priorities in Cancer Clinics.
A: Requirements
B: Achievements

non-malignant and any non-cancerous diseases through different generations that are related to the paternal- and maternal- side of the referral affected case with cancer; 2) to offer the essential tests either for the proband, or the relatives; 3) genetics and cell biological targets could be relevantly selected according to the type of cancer distribution in different generations and within different degree of affected relatives; and 4) cancer distribution within the pedigree could direct the researchers to select relevant genes for further screening test (s) as well (Figure 2). In the provided pedigree, only one family history of cancer in the far relative of our proband could be traced. Distribution of the involved exons including '39, 19' and introns '38 and 18' through different relatives of the proband is remarkable. Such data would facilitate to apply the preventive strategies for the proband's relatives who are at risk of being affected with cancer.

Figure 2: Pedigree of a patient with astrocytoma.
Distribution of the involved exons 39, 19 and introns 38 and 18 through different relatives of the proband is remarkable.
Left main box illustrates information on peripheral blood sample.
Right main box illustrates information on buccal smear sample for healthy relatives and tumor sample for proband.
Column right/top of each main box presents alteraions of the 3' splicing site of intron 18. Column right/bottom of each main box presents alteraions of exon19.
Column left/top of each main box presents alteraions of the 3' splicing site of intron 38.
Column left/bottom of each main box presents alteraions of exon 39.
Left –side numbers of each individual presents age of healthy relatives at the time of sampling and age of deceased for two affected persons in the pedigree.
Right-side numbers of each individual presents systematic reference number of individuals through each generation. (This figure is adopted from Ref. [10])

Circulating tumor cells 9CTCs

The CTCs have been considered in different cancers [5-9]. But, the classified cell-based diagnostic approach is not provided. Regarding the personalized management, it was aimed to explore the behavior of tumor cells and the CTCs in blood of 18 patients with brain tumors by exploring the protein expression (PE) at single cell level [9]. Through such strategy, heterogeneity and diversity would be unmasked which are the key events in the evolution and personalized insight [9]. Patients included 14 with meningioma and 4 with the metastatic brain tumors. The PE of the macrophage chemoattractant chemokine ligand 2 (CCL2), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) are illustrated (Figure 3). Besides, the complementary antibodies (images are not presented) including CD133, cyclin E, neurofilament marker, cytokeratin 19, and leukocyte common antigen (CD45) were also assayed by immunofluorescence [9]. The elevated PE in CTCs is reflective of: 1) The evolutionary event, and 2) paving the way towards metastasis. Besides, tumor progression could be related to the co-expression of CCL2/EGF and CCL2/VEGF. Furthermore, the assessment of Neurofilament marker/CD133/VEGF in the CTCs in meningioma and cytokeratin 19/CD45/cyclin E in the patients affected with the metastatic brain tumor would elucidate the complementary information on the brain tumor biology (details of the methods and results are provided in Ref. [9]).

Figure 3: Protein expression status of C-C chemokine ligand 2/vascular endothelial growth factor/epidermal growth factor of two cell population from tumor sample and circulating tumor cells in patient affected with meningioma.

C-C chemokine ligand 2 (CCL2), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) are conjugated with fluorescein isothiocyanate, R-phycoerythrin, and phycoerythrin–indodicarbocyanine, respectively. A: Vascular images accompanied by the partial tumor section [1: Merged of 4′,6-diamidino-2-phenylindole (DAPI)/CCL2; 2: Merged of DAPI/VEGF; 3: Merged of DAPI/ EGF; 4: Co-expression of CCL2/EGF/VEGF; 5: Co-expression of DAPI/CCL2/VEGF/EGF; 6: A cropped section of 5]; B: Image of a tumor section reflecting of the Co-expression of CCL2/VEGF/EGF; C: Illustrates the CTCs in the blood sample of the same patient. The arrows are indicative of expression status in tumor cells, in vasculature, and the microvesicles. (This figure is adopted from Ref. [9]).

Finally, it worth's to emphasize that screening of CTCs and D1853N- ATM polymorphism offer a reliable high impact on the personalized clinical management for the cancer patients and their relatives.

Conclusively the highlights reflect that

The CTCs is the reliable strategy in cancer- early detection and prevention; and the basic and key data of the migrated cells from the tumor- into the blood- territory could be considered as a personalized approach of CTCs.

Suggestions for further applicable CTCs-based early detection include: 1) The informative packages in cancer clinics or the related hospitals; and 2) Cancer Genetic counselling for tracing of metastatic sign by CTCs.

Molecular aspects

Three-hit hypothesis and D1853N polymorphism in Ataxia telangiectasia mutated gene (ATM)

The D1853N has not been reported in astrocytoma. The three-hit hypothesis is initially, reported in a 28 year-old female with astrocytoma in 2008 (10). The D1853N is deliberated as the 1st predisposing hit at germline level (Figure 4), followed by the 2nd hit (IVS 38- 63T→A) and 3rd hit (IVS38- 30 A→G), as a triangle alteration, reflecting the course of evolution in astrocytoma. Conclusively, the present evolutionary events reflect the fundamental role of an explicit intronic region of ATM gene and the significance

Figure 4: Partial sequencing results of the proband affected with astrocytoma; illustrating three-hit hypothesis through an evolutionary process (This figure is adopted from Ref. [10]).
a- Alterations of ATM gene in Blood tissue
b- Alterations of ATM gene in brain- tumor.
Arrows at N-positions, show the molecular alterations, as heterozygosity.

of pedigree analysis. Furthermore, the predisposing role of the D1853N polymorphism was also reported in breast cancer [11]. Interestingly, the Five-hit hypothesis was also, published in a 34 years old female affected with invasive ductal carcinoma of the breast without any family history of cancer. Furthermore, a patent has been also registered (Mehdipour, P., Application number: PCT/IB2014/065072) in which the D1853N polymorphism has been emphasized as a predisposing variant in different cancers including brain, breast, colorectal, esophagus, and leukemia. Accordingly, D1853N polymorphism is considered as the 4xP marker (Predisposing, Prognostic, Predictive and Preventive). Furthermore, based on the *in silico* analysis, protein expression assay, the dbSNP and COSMIC catalogue, D1853N is revealed to be a coding polymorphism (rs1801516) and confirmed as a predisposing sequence variant [12].

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