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Breast Cancer: Forecasting an Evolving Ecosystem

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Abstract

Advances in gene-expression profiling and parallel sequencing technology in the past two decades resulted in unravelling the pathophysiological molecular signatures in the progression of cancer in general and breast cancer in particular. In the current state of the art it has been well established that cancer cells within a single tumor are not alike at genetic, morphological and behavioral levels. Nevertheless, there occurs heterogeneity of cancer cells at inter-and intra-tumor levels. Intra-tumor heterogeneity comprises of coexistence of clones of cancer cells that differ in their genetic, phenotypic or behavioral characteristics in primary tumor and its metastasis.Genome-based stratification of breast cancer is one of the evolving research area in the mainstream of breast cancer research. Recently series of research investigations have prepared landscapes ofsomatic driver and passenger mutations conferring clonal advantages to the growing tumors. It has been clearly demonstrated that the genomic landscape of breast cancer is complex, and the evolving inter- and intra-tumor heterogeneity is emerging as a major threat and challenge in the treatment and diagnosis of breast cancer. The present review offers an understanding about the emerging pathophysiological complexities in concert with tumor heterogeneity in breast cancer and strategic plan to curb the heterogeneity driven molecular mechanisms in cancer progression.

Keywords: Breast cancer; Gene-expression; Cancer cells

Introduction

Breast cancer is the most common life threatening diseasein women. It is leading cause of cancer associated death amongst the women and second most common cancer worldwide [1]. The incidence of breast cancer continues to rise and around 1.7 million new cases are diagnosed per year and it additionally remains major source of death [2]. According to World Health Organization, breast cancer accounts approximately 520,000 deaths yearly [3].

Breast cancer is defined as cancers emerging from the breast tissue, mainly from the inner lining of milk ducts or from the lobules which supply the ducts by milk. The rest of the breast is composed of fatty and connective tissue [4]. Breast cancer is usually identified either during screening examination or after a woman detects a lump. Majority of masses are observed on a mammogram and most breast lumps are categorized as benign (non-cancerous) and malignant (cancerous) [5]. There are numerous established risk factors that are associated with breast cancer. Gender is major risk factor as breast cancer is diagnosed 100 times more frequently in women as compared to men.Another crucial risk factor is women's age, because women with the age of 45-50 are mostly diagnosed with breast cancer.About 5% to 10% of breast cancer cases are considered to be hereditary. The most frequent cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes [6].

There are certain types of breast cancer and it can be invasive or noninvasive. Noninvasive breast cancer is referred as the "in situ" as it has not invaded other tissue. There are two major type of noninvasive breast cancer such as, Ductal carcinoma in situ (DCIS) and Lobular carcinoma in situ (LCIS). DCIS is the most common type of in situ breast cancer where, normal epithelial cells of the breast ducts are replaced by the abnormal cells. Likewise LCIS refers to the cells that resemble cancer cells growing in the lobules of breast and it is recognized as marker for the increased risk factor for causing invasive cancer [7].

In case of breast cancer, molecular classification has effectively been used for the development of specific therapies. Based on gene expression profiling, breast tumors are categorized into minimum three subtypes as luminal, human epidermal growth factor receptor 2+ (HER2+), and basal like. Luminal tumors are estrogen and progesterone receptors positive and give response to the

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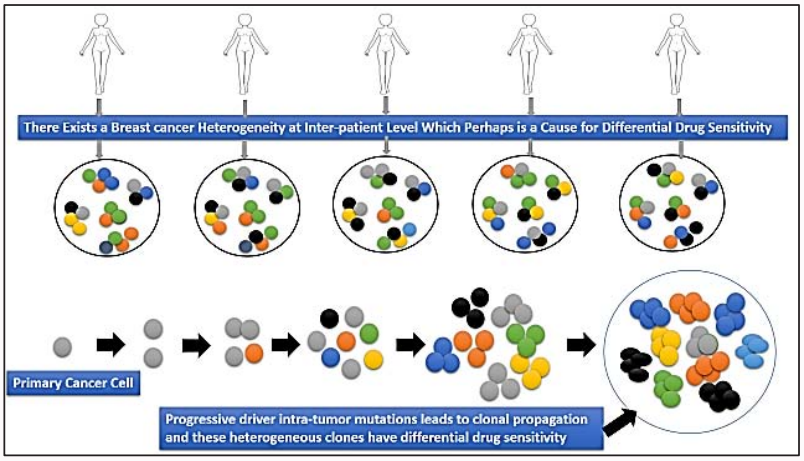

Figure 1: There exist breast cancer heterogeneity at patient level as well as within the single tumor body which perhaps is the most complex imbroglio limiting the efficacy of current anti-breast cancer chemotherapy drugs.

hormonal therapies. While HER2+ tumors have overexpression of the ERBB2oncogene and can be efficiently prohibited with a various range of anti-HER2 therapies. Basal-like tumors usually devoid hormone receptors and HER2; therefore, these tumors are called as triple-negative breast cancer (TNBC). This type of breast cancer accounts for 15–20 % of all breast cancer cases and at present there is no any molecular based targeted therapy against TNBC. Therefore development of potential treatments against TNBC is greatly attracted area in breast cancer research [8,9].

Adjuvant therapy can possibly eliminate the breast tumor cells which have effectively spread to other nearby tissue. Currently almost 80% of the patients with metastatic breast cancer receive adjuvant therapy.In case of the women having breast cancer who are under the age of 50 years, chemotherapy can raises their 15-year survival rate by 10% [10]. Nevertheless, chemotherapy has a various long-term side effects. Another obstacle with the current chemotherapy treatment is 'Drug resistance'. Patients receiving chemotherapy can establish resistance to previously efficient drugs to the point that the drugs are no longer effective. This is the leading factor in the failure of many forms of chemotherapy. Apart from the chemotherapy surgery and radiotherapy is practiced for treatment [11].

Heterogeneity in Breast Cancer: a Cause for Emerging Drug Resistance

Tumor heterogeneity represents diversity amongst the tumors of the same type in different patients, and in between the cancer cells within the tumor. Both cases can results into the distinct responses to chemotherapy. Breast cancer is a heterogeneous disease, at both interand intra-tumor level; it is characterized by diverse pathological aspects, distinct responses to therapy, and significant divergence in long term patient survival [12]. The heterogeneity detected between breast cancers represents the well acknowledged perception that this is not only just single disease with some various subtypes but breast cancer rather represents a set of distinct neoplastic disease of the breast cells. The diverse nature and attribute of this disease can be demonstrated through conventional pathological examination. The definite extent of divergence amongst breast cancer can be resolved only through molecular analysis [13].

The mechanism representing for breast cancer heterogeneity has leftover ambiguous. Nevertheless, previously established two theories as cancer stem cells and clonal evolution have implemented few feasible descriptions.The clonal evolution theory was demonstrated by 'Nowell' in 1976 [14]. Both theories contribute numerous resemblances such as; both conclude that cancers are introduced from cancer stem cells. Both conclude that, precise genetic abnormalities are required for carcinogenesis and both conclude that, the tumor microenvironment significantly influence the action of tumor progression. However, these both theories differ principally in the major conception. According to the cancer stem cell theory, various tumors are developed from dissimilar stem cells, and that all cells within a tumor could advance to a greater extent of malignancy. In contradiction, the clonal evolution theory states that, various tumors are derived from evolution of an individual stem cell and that only the more aggressive clone develops further [15].

In brief, the clonal evolution model demonstrates that, cancer cells over time attain diverse combinations of mutations within a tumor and that genetic drift and gradually natural selection for the fittest one. Greater aggressive cells accomplish tumor progression. In accordance with the consideration of this concept, tumor initiation happen once multiple mutations takes place in a random single cell, contributing it with a selective growth influence over nearby normal cells [16]. As the tumor develops over time, genetic instability and uncontrolled proliferation permit the generation of cells with further mutations and thus new characteristics. By chance these cells may leave a huge number of offspring or the new mutation may be responsible for growth influence over another tumor cells such as resistance to apoptosis. In either condition, principally the recent new subpopulations may contract which results into tumor heterogeneity. By this mechanism which happens throughout life spam of tumor, every cancer cell can probably develop into invasive and act resistant to therapies and results into recurrence [14] (Figure 1).

Diminished successes of chemotherapy treatment and tumor resistance to anticancer therapy have all been associated to intra-tumor diversity amongst sub-population of cancer cells, and to the existence of cancer stem cells with the capacity for self-renewal. Heterogenic tumors may demonstrate dissimilar sensitivities to cytotoxic drugs amongst distinct clonal populations. This is ascribed to clonal interactions that may hinder therapeutic efficiency; posing a challenge for advantageous therapies in heterogenic tumors [17]. Drug administration in heterogenic tumors will infrequently kill

every tumor cells. The primary heterogenic tumor population may interrupt, such that only some drug resistant cells will remain alive. This permits resistant tumor populations to replicate and produce a fresh tumor cells. The emerging repopulated tumor is heterogenic and resistant to the preliminary drug therapy administered. The repopulated tumor may perhaps as well return in a further aggressive behavior [18].

Evolutionary Aspects of Breast Cancer

Carcinogenesis is thought to be evolutionary process that demonstrates hallmarks of cancer through natural selection of cell clones that have attained beneficial heritable characteristics. Evolutionary adaptation has moreover been recommended as a mechanism that advances drug resistance throughout cancer therapy [19].

According to the Charles Darwin theory, natural selection is the mechanism that results into evolutionary change of species over time. As described above, Nowell firstly demonstrated the cancer as an evolutionary process; he proposed that, natural selection occurs in tumors through clonal selection resulting into consistence evolutionary change and probably to drug resistance [20].

Clonal heterogeneity is requirement for Darwinian evolution which offers the substrate for selection to proceed on. The entire profiling of somatic mutations in tumors has facilitated the depiction of the properties, incidence and consequences of genomic instability and it'sprospective as a resource of heterogeneity. Indeed, genomic instability is considered as an enabling characteristicwhich allows achieving mutations. Cells that deliberate a mutator phenotype are additionally potent at attaining mutations than those devoid of a mutatorphenotype [21,22]. While the cancer is diagnosed, tumors may be at diverse phases of genomic evolution or have dissimilar levels of genetic instability, consequently demonstrating a broad range of somatic mutations. As like in the subset of TNBC, basal like breast cancers are more genetically unstable and demonstrate more extent of clonal heterogeneity than nonbasal-like tumors. In case of breast cancer, BRCA1 and BRCA2 genes are usually mutated. The inactivation of these two genes develops in the precise pattern of point mutations [23].

Strategic Plans to Curb Heterogeneity Driven Complexities: Need of Developing Multi-Targeted Drug Candidates

The investigations on molecular aspects of tumor heterogeneity has begun in recent time and the detailed molecular signatures driving tumor heterogeneity are yet to be evolved.Series of strategies for targeting intratumor heterogeneity are currently under preclinical and clinical investigation, however, a deeper understanding of the molecular mechanisms that govern tumor heterogeneity are needed. While tailoring the novel approaches for circumventing the heterogeneity driven drug resistance, it is imperative to investigate new molecular targets that play key roles in the generation of intratumor heterogeneity. One important culprit of tumor heterogeneity are driver mutations that results into production of abnormal proteins, which per say are effectively buffered by molecular chaperones like heat-shock proteins (HSPs). It is known that cancer cells have upregulated expression of HSP70 and HSP90, which assure cell survival besides increased levels of aberrant proteins [24]. Perhaps, the increased tolerance of random mutationsfuels the genetic and phenotypic diversity in cancer cells and is strongly associated with upregulation of HSP expression [25,26]. Interestingly, HSPs also plays a key role in sensing the environmental stress and accordingly offering adaptations to the stress experiencing cells via regulation of phenotypic diversity. Therefore, targeting of HSPs might serve as a check point for evolving tumor heterogeneity and might offer a strategy for circumventing drug resistance [27].

To deal with the heterogeneity aspect, there is an increasing need for developing multi targeted drug candidates which can alter the aggressive sub population within the tumor which hampers the current chemotherapy resulting into the aggressive recurrence. Therefore, there is an urgent need of more advanced multi targeted treatment strategies that integrate knowledge of heterogeneity to acquire greater efficiency.Owing to the complex and daunting nature intratumor heterogeneity, at present it seems impossible to tailor effective breast cancer therapies targeting heterogeneity. However better understanding of how tumors evolve might offer us to design and develop more rational treatment modalities. For example, in general, chemotherapy targets the more proliferative cell populations in a tumor, developing drug leads that target slower-growing cells that resist treatment might prove instrumental curbing heterogeneity. Moreover, employing metronomic therapy approach, which involves the administration of lower doses chemotherapeutic agents and increasing the frequency of doses, in principle might slow down the clonal selection process and may improve therapeutic efficacy of chemotherapy agents [28]. Heterogeneous tumors comprise of multiple subclones, invariably some of which may possess intrinsic resistance towards chemotherapy agents. In general physiological notion, in the absence of therapy, the resistant cells typically have more fitness disadvantage as compared to the chemosensitive cells owing to their higher demands of substrate and energy. Therefore, principally, chemosensitive cells possess a fitness advantage and perhaps dominate the tumor population. But during treatment these cells will be eliminated and thereby providingan survival opportunity to resistant cells. A concept of adaptive therapy, introduced by Gatenby and colleagues [29] is specifically tailored for encouraging the steady population of fitter chemosensitive cells, which thereby will keep vigilance on resistant cells and will allow them to grow at a minimal fraction. This concept has been effectively demonstrated in animal model studies, however its clinical utility is yet to be established. Translating such therapeutic approaches at clinical level, requires in-depth insight of molecular intra-tumor clonal dynamics. One thing is very clear that the molecular understanding of interactions between different clonal populations within a tumor might open new avenues for developing novel therapeutic approaches circumventing the heterogeneity driven poor performance of chemotherapy agents.

Conclusion

The Drug resistance has left over a major obstacle to the delivery of remedial therapies in case of cancer. There has been growing interest towards the identification of specific mutations within tumors that could serve as therapeutic targets. As a result of that, up till now there is a clinical experience with several novel classes of targeted and non-targeted therapies. The targeted therapies include anti-angiogenic drugs, inhibitors of different growth factors and respective signaling pathways, anti-stromal drugs and epigenetic modifiers [17]. Current advances in clinical practice have acknowledged that the single-target drugs may not always induce the preferred effect to the entire tumor even if they effectively inhibit a specific target. For example, the intratumor epigenetic heterogeneity is more complex than that

of genetic heterogeneity, wherein cancer cells constantly change the DNA methylation and chromatin states. Owing to the important role of histone deacetylase in intra-tumor epigenetic heterogeneity, the combination of histone deacetylase inhibitors with targeted therapy might offer more effective strategy over a one drug-one target approach [30].

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