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Role of Cytogenetics and Molecular Genetics in Cancer Research

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Abstract: ***The current era is known as the genomic era thanks to the successful completion of Human Genome Project. It opened gates for a number of biomedical researches and threw light into a lot of unanswered questions related to biomedical research. Owing to this the last decade has witnessed an immense growth in knowledge, bringing genetics to a fore-front position in healthcare. This in turn has helped in the understanding of a number of diseases including cancer, their development and progression with better diagnostic and treatment options. Cytogenetics research earlier had successfully explained the chromosomal aberrations that are linked to cancer development and progression but with the advent of molecular techniques post genomic era more and more clarity regarding cancer development began. Thus the two major areas of genetics that now complements each other and has been widely explored in cancer research are Cytogenetics and Molecular genetics. Both the fields of study are crucial in understanding the genetic diseases, therapy, diagnosis and evolution. Molecular genetics is the study of chromosomes and DNA at the molecular level using DNA technology whereas Cytogenetics is the study of structure and number of chromosomes using microscopic analysis. Molecular genetics studies segments of DNA, genes at the molecular level whereas Cytogenetics is the study of how chromosomes relate to the behaviour of cells during the cell division process and it includes the microscopic examination of chromosomal abnormalities; for instance, a decrease or an increase in the chromosomal number or translocation of one to another chromosome. Advances now focus on molecular cytogenetics including standard Fluorescence In Situ Hybridization (FISH) preparations, Spectral Karyotyping and techniques for virtual karyotyping, such as comparative genomic hybridization arrays (CGH), and microarrays. These advanced techniques have been instrumental in providing deeper insights into the role of chromosomal aberrations in cancer development. Thus, it can be said that research in genetics post-genomic era is advancing at a very fast pace, and thus it is very important to keep pace with the most recent findings and conclusions derived from these investigations to have a better understanding of cancer and it can be very challenging. As these findings have given a re-conceptualization of genes and heredity and has filled the gap of knowledge in a major way. It seems that the combination of classic cytogenetics and molecular genetics is essential and can generate a vast amount of data, enhancing our knowledge of cancer biology and improving treatment of this disease. The current review describes some major work done by researchers throughout the world in the field of cancer research using cytogenetics and molecular genetics techniques since the early 90s till date.***

Keywords: Cancer research, Cytogenetics, comparative hybridization arrays, molecular genetics, microarrays

1. Introduction

The current review cites some important work done by researchers throughout the world that explores the cytogenetic and molecular genetics assays in the analysis of cancer from the early 1990s till date. It all started with the discovery of Philadelphia chromosomes that was linked with Chronic Myeloid Leukemia in the year 1959 by David Hungerford and Peter Nowell from Philadelphia city and hence the name. The name was given to a translocation of chromosomes 9 to **chromosome** 22 that was found in the bone marrow cells of chronic myelogenous leukemia patients. It is sometimes found in acute lymphocytic leukemia as well. This breakthrough discovery led to a number of cytogenetic researches throughout the world to look for other cytogenetic markers of cancer and till date thousands of other chromosomal aberrations have been linked with cancer (Mitelman, 2005). The Mitelman database has been recording all these cytogenetic changes from various research work done worldwide since the last 20 years. These chromosomal changes are indications of deregulation at the genetic level in cancer that leads to instability of the genome (Albertson *et al.*, 2003) and these chromosomal changes are highly variable in each type of cancers.

With the advancement of molecular genetics techniques post genomic era, greater emphasis was done on understanding the molecular pathways of cancer cells and DNA sequence analyses to understand the genetic mutations in cancer. Thus, cytogenetic approaches have given way to molecular analysis in cancer research.

In a review done by Heim S (1992), the difference between cytogenetic and molecular techniques was explored in terms of cancer research. While in cytogenetic investigations all chromosome aberrations are revealed, molecular genetics analyses are highly specific and only those aberrations are revealed that are tested for. Second, whereas the molecular approach determines the genotypic constitution of an idealized, average tumor cell, cytogenetic analysis is of real, individual cells. These may not necessarily be representative of the main population of the tumor, but at least whatever karyotypic differences exist between them is detected. Heterogeneity and clonal evolution within the tumor can thereby be assessed.

A review by Popescu *et al.*, in 1997 attempted to cover the trends in cancer molecular cytogenetics, and to highlight the importance of molecular chromosome analysis in the understanding of carcinogenesis and its clinical applications. The paper reviewed various molecular techniques like Polymerase Chain Reaction (PCR), Comparative Genome

Hybridization (CGH), Fluorescence In Situ Hybridization (FISH) for detection of genomic alterations in cancer along with battery of FISH and DNA probe based technologies that can resolve any type of chromosomal alterations regardless of their complexity. These techniques have huge potential in the identification of structural and numerical alterations on a global basis, mapping of tumor genome, complete derivation of complex rearrangements, and localization of the breakpoints of translocations and deletion

A review done by Speicher *et al.,* (2005) established the advent of new cytogenetics analysis that now extends beyond the study of chromosomal status to more detailed description of the genomic changes that are involved in tumorigenesis with the help of molecular biology techniques like FISH and microarrays. It has greatly helped in studying more fundamental questions of biology especially in regard to inherited conditions including cancer.

The role of cytogenetic markers in cancer was highlighted by Kee-Kim *et al.,* (2008), which is an important diagnostic as well as prognostic tool in cancer patients. The chromosomal translocations and rearrangements are key features of many neoplasias. The paper explores many of the best-known chromosomal aberrations and variant rearrangements in solid as well as hematologic cancer and also indicated the genes and underlying molecular mechanisms known to be involved in development and progression of disease. The paper also explored the advanced molecular cytogenetic techniques currently being used in cancer diagnostics.

A review done by Sayagues *et al.,* 2011, explores the various researches being done to look for biomarker of cancer using cytogenetic and molecular genetics techniques to gather information that could add value to the differential diagnosis, prognosis, and disease monitoring of cancer patients. This in turn will help to better comprehend and fight the deadly disease. In this review, various guidelines/suggestions for further research and standardization of established protocol and cataloguing were also described towards better understanding of the pathogenesis of cancer as well as therapeutic targets for treatment of cancer.

The role of cytogenetics and molecular diagnostics in the diagnosis of soft-tissue tumors was studied in detail by Bridge J. *et al.*, (2014) outlining the advances in cytogenetic and molecular science that have led to the discovery of genetic events in soft-tissue tumors that have enriched our understanding of these neoplasms and have also proven to be powerful diagnostic markers and indicators of molecular targeted therapy. Emphasis is now being placed by the pathologist on the role of molecular pathology in the management of soft-tissue tumors with increased familiarity of these genetic events.

Oliveira Junior *et al.,* (2014) proposed a hypothetical model to explain the influence of cytogenetic events in carcinogenesis. According to this review, two conflicting versions of tumorigenesis exists gene mutation and aneuploidy hypothesis. According to gene mutation hypothesis, gene-specific mutations occur and that they maintain the altered phenotype of tumor cells whereas according to aneuploidy hypothesis aneuploidy is the hallmark of cancer and plays important role in tumor development and progression. Because of this cytogenetic techniques are very important tools for not only basic research but also in determining the cause of carcinogenesis and in diagnosis, prognosis and selection of treatment. Thus, the combination of cytogenetics and molecular genetics techniques have the potential to generate huge data in enhancing our knowledge regarding cancer development and treatment of disease.

Roy *et al.,* (2014) explored the complexities of cytogenetics and molecular genetics and their undeniable role in a number of human diseases including cancer. They explained beautifully how the chromosomal aberrations and DNA damages can be correlated with various diseases including cancer.

Similarly Fonseka *et al.,* (2015) reviewed the use of molecular and cytogenetics in the diagnosis of Prostate cancer. SNP arrays have revealed very useful and uncovered novel information on genes associated with PCa. Thus the combined approach of cytogenetics as well as molecular genetic studies have greatly improved the PCa diagnosis scenario.

Chromosomal analysis is an increasingly important and useful diagnostic procedure in the clinical diagnosis of various diseases from areas as diverse as haematology, oncology, perinatology as well as obstetrics. It is an important tool for the identification of particular chromosomal abnormalities that are associated with particular diseases including cancer (Kalkan, 2017).

A recent review done by Dorfman *et al.,* (2018), looks at the role of cytogenetics and molecular biology in the diagnosis, treatment and monitoring of patients with chronic myeloid leukaemia. CML was the first cancer to be associated with the chromosomal aberration of a reciprocal translocation between the long arms of chromosomes 9 and 22 - Philadelphia chromosome. This review was an updated review on CML which talks about the role of cytogenetic analysis as well as new molecular approach for not only in the diagnosis of CML but also in a detailed monitoring that can assist in choosing the most effective therapeutic plan each patient, optimizing the treatment. The review establishes the fact that understanding the molecular mechanisms involved in the development of cancer will allow the development of more targeted drugs and a possible improvement in the overall survival of these patients.

According to Zhang Y (2018), diagnosis and prognosis of ALL can be done by cytogenetic and molecular analysis. The combined approach has been instrumental in determining the prognosis of ALL patients by measuring their WBC, doing immunophenotyping and Karyotyping.

A paper reviewed by Knuutila **(**2018**)** explored the diagnostic significance of novel cytogenetic and molecular genetics techniques in human malignancies. The paper emphasizes the point that rapidly novel cytogenetic and molecular markers of cancer are being discovered that are

not only diagnostic markers but also prognostic markers and therapeutic targets as well.

Sokolenko *et al.*, (2018), did a review on the various molecular tests used nowadays in cancer diagnostics including mutation assays, so-called liquid biopsy, and many other relevant DNA- and RNA-based markers. All these techniques have shown huge potential in the diagnosis of cancer and also in therapeutic interventions. Mutation analysis can help healthy carriers of cancer-predisposing mutations in the prevention of cancer by tight medical surveillance. Similarly personalized medicines based on the presence of specific mutations have become an integral part of cancer therapy.

A recent study by Ribeiro *et al.*, (2019) explored the power of cytogenetics and cytogenomics techniques in the identification and detection of tumor molecular signatures which has helped in better understanding of cancer initiation and progression. It threw light into the cellular heterogeneity in tumor development and progression and their specific resistance/sensitivity to cancer therapies. Advance techniques like single-cell sequencing have opened gates for a lot of applications with tremendous benefits to cancer patients in terms of diagnosis, prognosis as well as treatment.

It is essential to cite some case studies that will showcase the potential of cytogenetics and molecular genetics techniques in cancer diagnosis. Lee *et al.*, (2019) cited a case study of a 68-year old man suffering from AML. An acute myeloid leukemia (AML) that progressed from myelodysplastic syndrome (MDS) in association with acquisition of 1q JTs. The sequence of molecular and cytogenetic changes in our patient may provide a mechanistic model for the generation of JTs in leukaemia. The patient had MDS with pathogenic mutations of the *RUNX1*, *SRSF2*, *SXL1*, and *TET2* genes and developed 1q JTs at the time of progression from MDS to AML.

According to a recent study done by Lv *et al.*, (2020), abnormalities of chromosome 16 are found in about 5–8% of acute myeloid leukemia (AML). The AML with inv (16)(p13.1q22) or t (16;16)(p13.1;q22) is associated with a high rate of complete remission (CR) and favourable overall survival (OS). These kinds of findings have important outcome in terms of treatment plan and prognosis.

2. Conclusion

It can be concluded from the review that both the tools and techniques developed from both branches of genetics; i.e, cytogenetics and molecular genetics together have the potential to contribute towards the understanding of cancer in a big way and they have generated a lot of data that has helped to give insight into the pathogenesis of cancer and its development. To provide an analogy, while one branch cytogenetics, the study of chromosomes, is like a building; the other molecular genetics represent the rooms and whole infrastructure inside the building that together can give a whole picture of what the building holds. Similarly, the genetics behind cancer development can be fully understood by studying chromosomes and genes in full detail with the help of cytogenetic and molecular tools.

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