iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 10 **Issue:** V **Month of publication:** May 2022

DOI: https://doi.org/10.22214/ijraset.2022.43624

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 10 Issue V May 2022- Available at www.ijraset.com

"Genetic Profiling of Breast Cancer using cDNA Microarray."

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Abstract: ***In defining the grade, stage, and residual determination of Breast Cancer and its subtypes, the molecular basis of analysis has become increasingly important. Vast-scale research studies have discovered a large number of genetic changes that cause the development and progression of breast cancer subtypes. Microarray and biotechnological approaches of hybridization-based analysis and microtiter level evaluation have come a long way in determining the expression level of mutant or hereditary genes. For Genomic Research and Diagnostics, DNA Microarray analysis allows for the simultaneous investigation of thousands of DNA sequences. Breast cancer subtypes are distinguished by clusters of co-expressed genes discovered by the manipulation of mammary epithelial cells. The efficacy of a treatment is determined by the prognostic development of an individual patient. A comparison of gene expression levels in the Pre-treatment and Post-treatment stages has evolved into a concept that has the potential to change genetic dissection, drug development, disease diagnostics, and individualised therapeutic solutions. The goal of this review was to look into how to diagnose breast carcinomas using changes in gene expression patterns derived from cDNA microarrays and how to link tumour characteristics to clinical outcomes.***
Keywords: ***Breast Cancer, Genes, Mutations, Gene Expression, DNA Microarray, Microarray-Analysis***

I. INTRODUCTION

For decades, evidence of cancer's genetic origins has been accumulating. However, technological improvements in DNA sequencing and other approaches that allow the genome-wide study of cancer cells have only recently enabled a thorough accounting of the degree of these genetic abnormalities. Although the intricacy of these data is intimidating, and the messages concealed within them have yet to be fully decoded, some "genomic motifs" have arisen that are likely to be relevant to all cancers.

Carcinogenesis is driven by nonlethal genetic damage. The initial damage (or mutation) may be induced by environmental exposures, inherited in the germline, or spontaneous and random, and so fall into the category of "poor luck." Exogenous agents, such as viruses or environmental chemicals, or endogenous products of cellular metabolism that have the ability to damage DNA or modify gene expression through epigenetic mechanisms are referred to as environmental in this context.

Microarray technology is an excellent tool for biological research. For genomic research and diagnostic applications, microarrays allow the simultaneous study of thousands of DNA sequences. This technology represents the most recent and interesting advancement in the biological sciences in the use of hybridization-based methodologies for analysis. (1) Gene expression profiling of cancers represents the largest research category using microarrays and appears to be the most robust approach for molecular characterization of cancers (2). It is becoming recognized that microarray technology will be a fundamental tool for future genomic research. Soon after microarrays were introduced, many researchers realized that the technique could be used to find new subclasses in disease states (3,4) and identify biological markers (biomarkers) associated with disease (5) and that even the expression patterns of the genes could be used to distinguish subclasses of disease. (6–9)

II. WHAT IS BREAST CANCER?

Breast cancer is caused by a mix of an external (environmental) component and a genetically susceptible host, just like other malignancies. Normal cells divide for as long as they need to before stopping. They attach themselves to other cells and stay in tissues. Cells become cancerous when they lose their ability to stop dividing, adhere to other cells, stay put, and die at the appropriate time. Experiments have linked oestrogen exposure to breast cancer-causing mutations. (10) G-protein coupled oestrogen receptors have also been related to breast cancer and other female reproductive system cancers. (11)

Malignant cell proliferation can be aided by abnormal growth factor signalling in the interaction between stromal cells and epithelial cells. . (12,13) In breast adipose tissue, overexpression of leptin leads to increased cell proliferation and cancer. (14)

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Genetics is believed to be the primary cause of 5–10% of all cases. (15) Women whose mother was diagnosed before 50 have an increased risk of 1.7 and those whose mother was diagnosed at age 50 or after have an increased risk of 1.4. (16) In those with zero, one or two affected relatives, the risk of breast cancer before the age of 80 is 7.8%, 13.3%, and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively. (17) In those with a first degree relative with the disease, the risk of breast cancer between the age of 40 and 50 is double that of the general population. (18)

In less than 5% of cases, genetics plays a more significant role in causing a hereditary breast-ovarian cancer syndrome (19). This includes those who carry the *BRCA1* and *BRCA2* gene mutation(19). These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60–80% in those affected. (15) Other significant mutations include *p53* (Li–Fraumeni syndrome), *PTEN* (Cowden syndrome), *STK11* (Peutz–Jeghers syndrome), *CHEK2*, *ATM*, *BRIP1*, and *PALB2* (15) In 2012, researchers said that there are four genetically distinct types of the breast cancer and that in each type, hallmark genetic changes lead to many cancers. (20)

III. GENES INVOLVED IN BREAST CANCER

A. High Penetrance Genes

BRCA1, which is found on chromosome 17, was the first major gene linked to hereditary breast cancer. In 1990, linkage analysis in families with suggestive pedigrees led to the discovery of this gene. (21) BRCA2 was mapped to chromosome 13, in 1994. (22) Breast and other cancers are more likely if you have a BRCA1 or BRCA2 mutation. Large rearrangements and deletions in BRCA1 or BRCA2 can potentially affect BRCA function, resulting in a clinical condition similar to that seen in BRCA mutant carriers. The Hereditary Breast Ovarian Cancer (HBOC) syndrome is the clinical picture seen in BRCA mutation carriers, while there are people with this clinical picture who are determined to be negative for mutations in both BRCA1 and BRCA2. (23)

BRCA1 and BRCA2 mutations are autosomal dominant but act recessively on the cellular level as tumour suppressor genes involved in dsDNA break repair. (24) Female carriers of mutations in BRCA1 or BRCA2 have a lifetime risk of breast cancer of 50-85%. (25,26) Male carriers of BRCA1 have an increased risk of breast cancer, though to a lesser degree than carriers of BRCA2 who have an estimated 5-10% lifetime risk. (10)

B. Moderate Penetrance Gene

Additional replicable loci for highly penetrant genes leading to breast cancer have not been discovered by linkage studies. , (27) it should be highlighted, however, that these studies may not be sufficiently powerful to uncover extremely rare high penetrance genes. This has encouraged new research directions in the study of breast cancer's hereditary origins. Several studies have looked at genes that have been proposed to enhance the risk of breast cancer based on their known biological functions in families with breast cancer pedigrees. Several more DNA repair genes that interact with BRCA1, BRCA2, and/or the BRCA pathways and confer a twofold increase in breast cancer risk have been discovered in studies, including CHEK2(28), BRIP1 (BACH1)(29), ATM (30), and PALB2 (31). CHEK2*1100delC is the most common mutation, seen in up to 1-2% of the population; it is found in higher numbers in breast cancer patients, especially those with a family history or those who had negative BRCA1 and BRCA2 testing, where the prevalence may be as high as 5%. (28) CHEK2 is a protein kinase involved in cell cycle regulation at G2 that is rapidly phosphorylated in response to DNA damage. Activated CHEK2 interacts with BRCA1 and stabilises p53. The CHEK2*1100delC mutation increases female breast cancer by around twofold and male breast cancer by tenfold. Additional rare CHEK2 mutations have been discovered in the Ashkenazi Jewish population, suggesting a founder impact. (32) Co-carriers of the CHEK2 and BRCA1 or BRCA2 mutations have no increased risk, probably due to an overlapping effect on DNA repair. (28) Again, there is no documented biallelic phenotype for CHEK2, implying that it is embryonic lethal. (24)

C. Low Penetrance Genes

A modest number of polymorphisms in breast cancer-related genes have been linked to an elevated risk of the disease. In premenopausal women, a Pro919Ser polymorphism in BRIP1 has an odds ratio of 1.39 (p=0.002) but was not linked to an elevated risk of breast cancer in the general population. Low penetrance SNPs are frequently found in non-coding areas of the genome (e.g., 2q35, 8q24), making finding a related gene more difficult. Increased cancer risk could be caused by the activation of growth-promoting genes rather than the inactivation of DNA repair genes, which is the most typical mechanism for genes with moderate or high penetrance. On average, each allele raises risk just slightly and is additive rather than multiplicative, with odds ratios indicating a 1.26-fold rise in risk for heterozygotes and a 1.65-fold increase in risk for homozygotes. (24)

IV. DNA MICROARRAY – BACKGROUND

A. *Methodology*

Microarrays allow for massively parallel investigation of gene expression, DNA sequence variation, protein levels, tissues, cells, and other biological and chemical substances. Microarray manufacturing, hybridization, detection, and data analysis technologies are robust, allowing inexperienced users to quickly adapt to this intriguing technology while more experienced users push the limits of discovery. (33)

High-density microscopic array elements, planar glass substrates, low reaction volumes, multicolour fluorescent labelling, high binding specificity, high-speed apparatus for production and detection, and sophisticated software for data processing and modelling are all used in microarrays. The array of elements reacts with tagged mixtures in a precise way, generating signals that indicate the identification and concentration of each marked species in the solution. (33)

These characteristics enable the exploration of any organism on a genomic scale using tiny biological experiments. Similar to recombinant DNA, microarray analysis (34) and the polymerase chain reaction (PCR) (35), is a foundational technology with broad applications in areas including genetic screening, proteomics, safety assessment and diagnostics.

B. *Sample Collection transformation and Data Representation*

Gene-specific probes that represent thousands of individual genes are used in the microarray approach. The probes are arranged on an inert substrate, and gene expression levels in a target biologic sample are measured (Fig. 2). RNA is taken from target tissues, labelled with a detectable marker (usually a fluorescent dye), and allowed to hybridise into arrays. On the array, messenger RNA (mRNA) samples hybridise with complementary gene-specific probes.

The relative fluorescence intensity of each gene-specific probe is a measure of the degree of expression of the particular gene; images are created using confocal laser scanning. The stronger the signal, the greater the degree of hybridization, reflecting a higher relative level of expression.

Microarray data can be generated in one of two ways. Two samples of RNA, each labelled with a different dye, are hybridised into a two-colour array at the same time (Fig. 3). The query sample (for example, a sample of breast cancer) is labelled with one dye, while the reference sample (for example, normal breast tissue) is tagged with a different dye; the two samples are combined in an approximate 1:1 ratio based on the dye incorporation. The logarithm of the ratio of RNA in a query sample to that in a control sample is reported as an expression in this assay, which compares paired samples. Single-colour arrays, such as the GeneChip (Affymetrix), are ideal, each sample is labelled and individually incubated with an array **(**Fig. 3). The level of expression of each gene is presented as a single fluorescence intensity that represents an estimated level of gene expression after non-hybridized material in the sample is removed by washing. The data used in all future studies, regardless of the strategy or technique, are expression measures for each gene in each sample. (36)

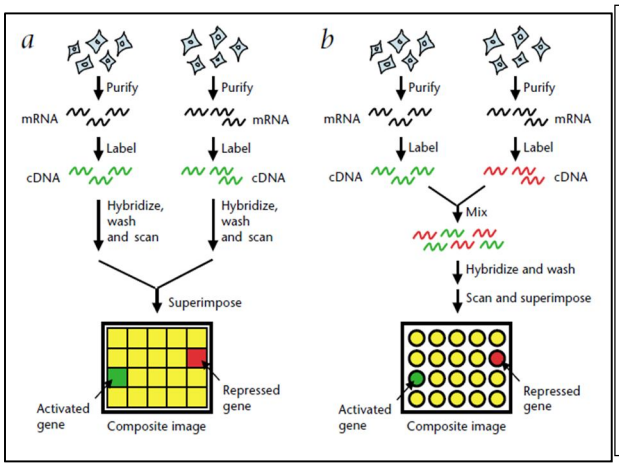


Figure 1: Expression analysis by microarray. ***a.*** *One-color expression analysis uses a single fluorescent label (green wavy lines) and two chips to generate expression profiles for two or more cell samples. Activated and repressed genes (green and red squares, respectively) are obtained by superimposing images obtained from different chips.* ***b.*** *Two-colour expression analysis uses two different fluorescent labels (green and red wavy lines) and a single chip to generate expression profiles for two different cell samples. Activated and repressed genes (green and red spots, respectively) are obtained by superimposing images generated in different channels on a single microarray. Genes expressed equally in the two samples appear as yellow squares or spots in the two analyses.* (33)

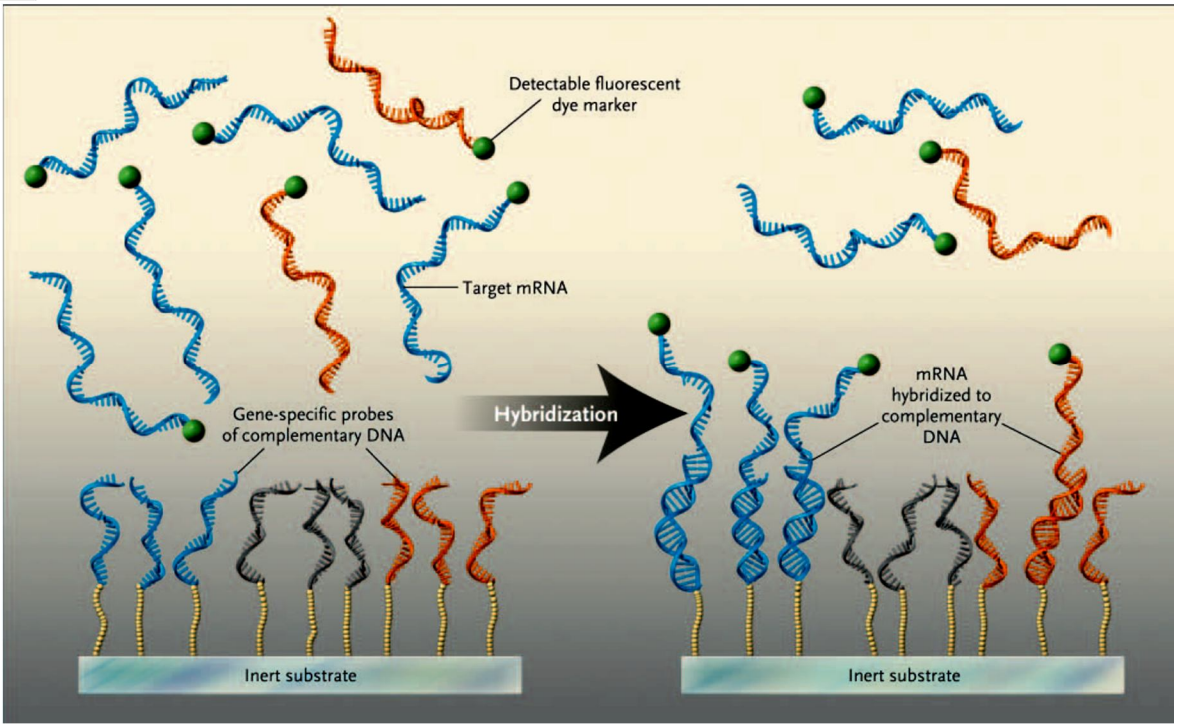


Figure 2: Hybridization with Gene Elements on a Microarray. (36)

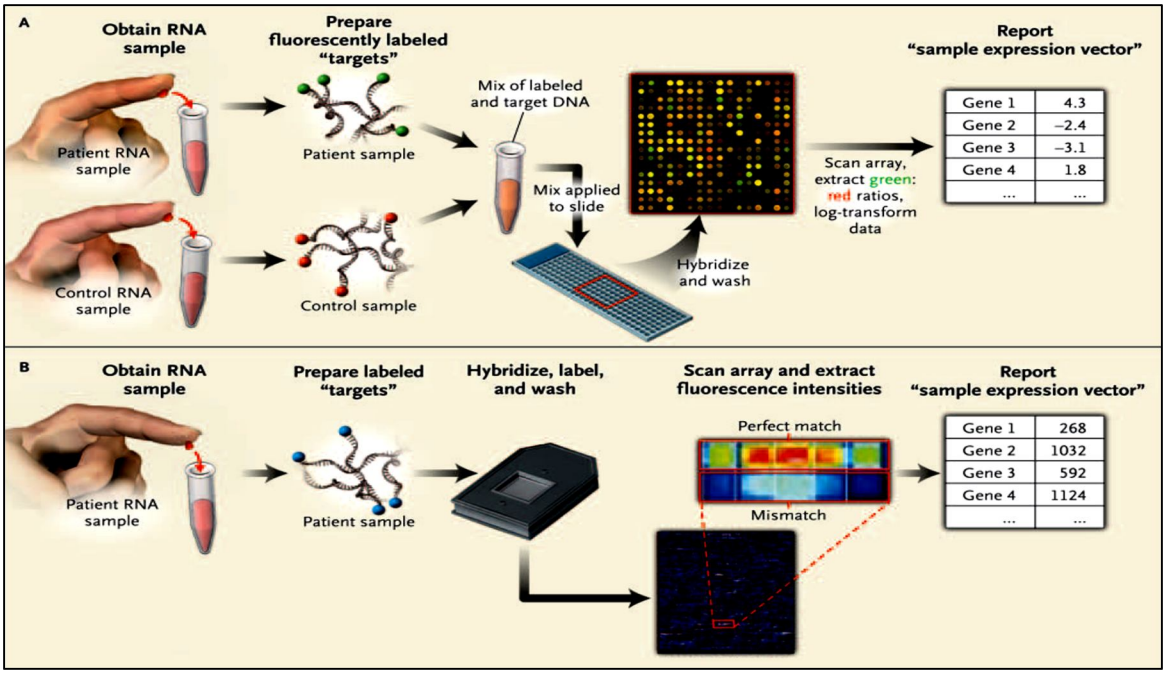


Figure 3: Overview of DNA Microarray Analysis. (36)

The data is frequently standardised after collection to make comparisons across different hybridization experiments easier. Differences in labelling, hybridization and detection procedures are compensated for using normalisation. There are numerous techniques for data normalisation; the most appropriate strategy will be determined by the type of array and assumptions about data biases. (36–40). Following that, the data is frequently filtered using objective criteria (e.g., eliminating genes with low variation in the samples) or statistical studies to pick genes with expression levels that correlate with specific groups of samples.

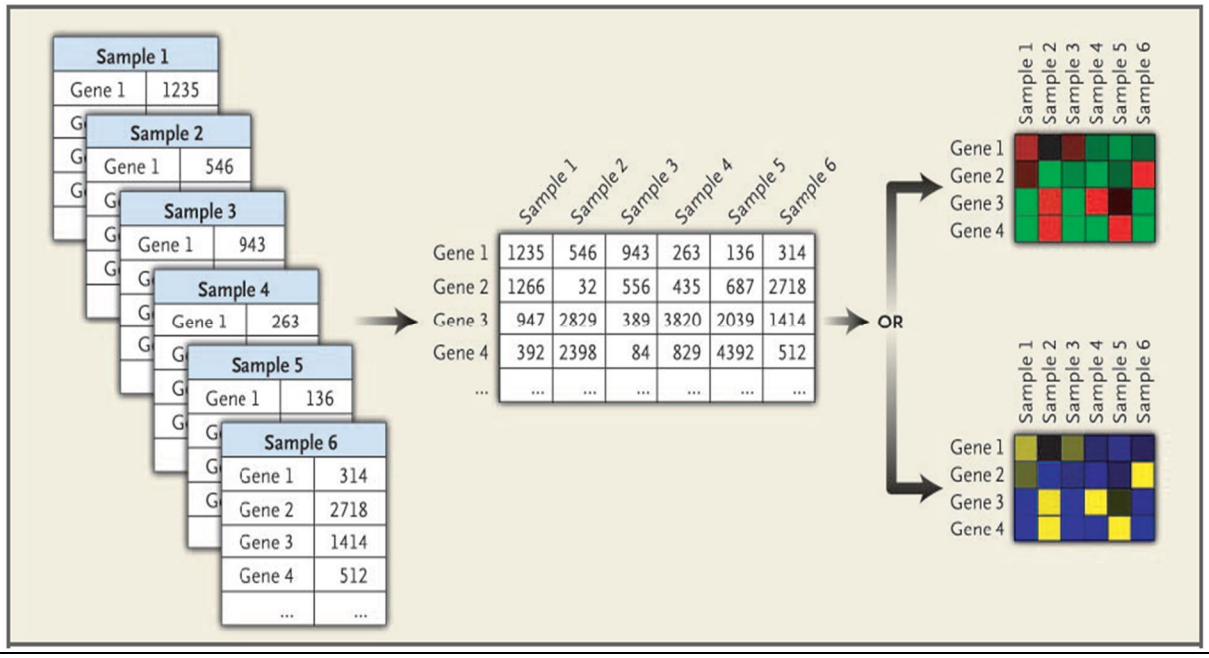


Figure 4: Development of an Expression Matrix. (36)

V. cDNA MICROARRAY IN BREAST CANCER DIAGNOSTICS

This multistep process may manifest as a series of pathologically defined phases in the development of breast cancer. Breast cancer is thought to start with the premalignant stage of atypical ductal hyperplasia (ADH), proceed to the preinvasive stage of ductal carcinoma in situ (DCIS), and finally to the potentially fatal stage of invasive ductal carcinoma (IDC) (41). The use of detection tools like mammography in the hopes of diagnosing and treating breast cancer at an earlier clinical stage has been justified by this linear model of breast cancer progression. (42). However, both within a tumour and among individual tumours, the stages of DCIS and IDC are variable in terms of mitotic activity and cellular differentiation. Several tumour-grading methods have been developed to better characterise DCIS and IDC in terms of heterogeneity. Clinically, such methods are used to divide DCIS and IDC stages into three tumour grades, with grade I, II, and III lesions corresponding to well, moderately, and poorly differentiated breast tumours, respectively. (43,44). Poorly differentiated, high-grade DCIS or IDC lesions are associated with much worse clinical outcomes, making tumour grade a highly helpful predictive indicator for breast cancer. (43–45)

VI. CONCLUSION

Breast carcinomas can be investigated using mRNA expression profiling. Similar arrays for analysing DNA and protein expression profiles are in the works. mRNA arrays have been utilised for predicting prognosis and responsiveness to therapy, assessing tumour changes following therapy, and defining hereditary carcinomas in addition to detecting tumour kinds, as in this case. Although transcriptome profiling may not be viable in every clinical case of breast cancer, this research will yield data that will lead to improved diagnostic, prognostic, and therapeutic testing for all patients. As malignancies originate from the accumulation of various genetic and epigenetic alterations, microarray technologies are becoming more essential in cancer research. Microarrays are increasingly being employed for cancer diagnostic categorization. In cancer research, comprehensive and high-throughput genomic analysis is an unavoidable research tool. However, there are certain disadvantages to using microarrays regularly. Microarray experiments are expensive, and experimental processes must be more reliable. Microarray and experimental protocol standardisation are also significant for comparing data amongst research organisations. Tools and procedures for data analysis must also be developed. Despite these drawbacks, it is apparent that microarray technology will become a standard tool in cancer research in the future. Gene expression profiling may be used to predict prognosis following chemo- or radiation, and oligonucleotide microarrays will be used to make an early cancer diagnosis. Gene expression analysis employing microarrays can assist researchers to find meaningful answers to cancer-related problems using conventional histopathology data.

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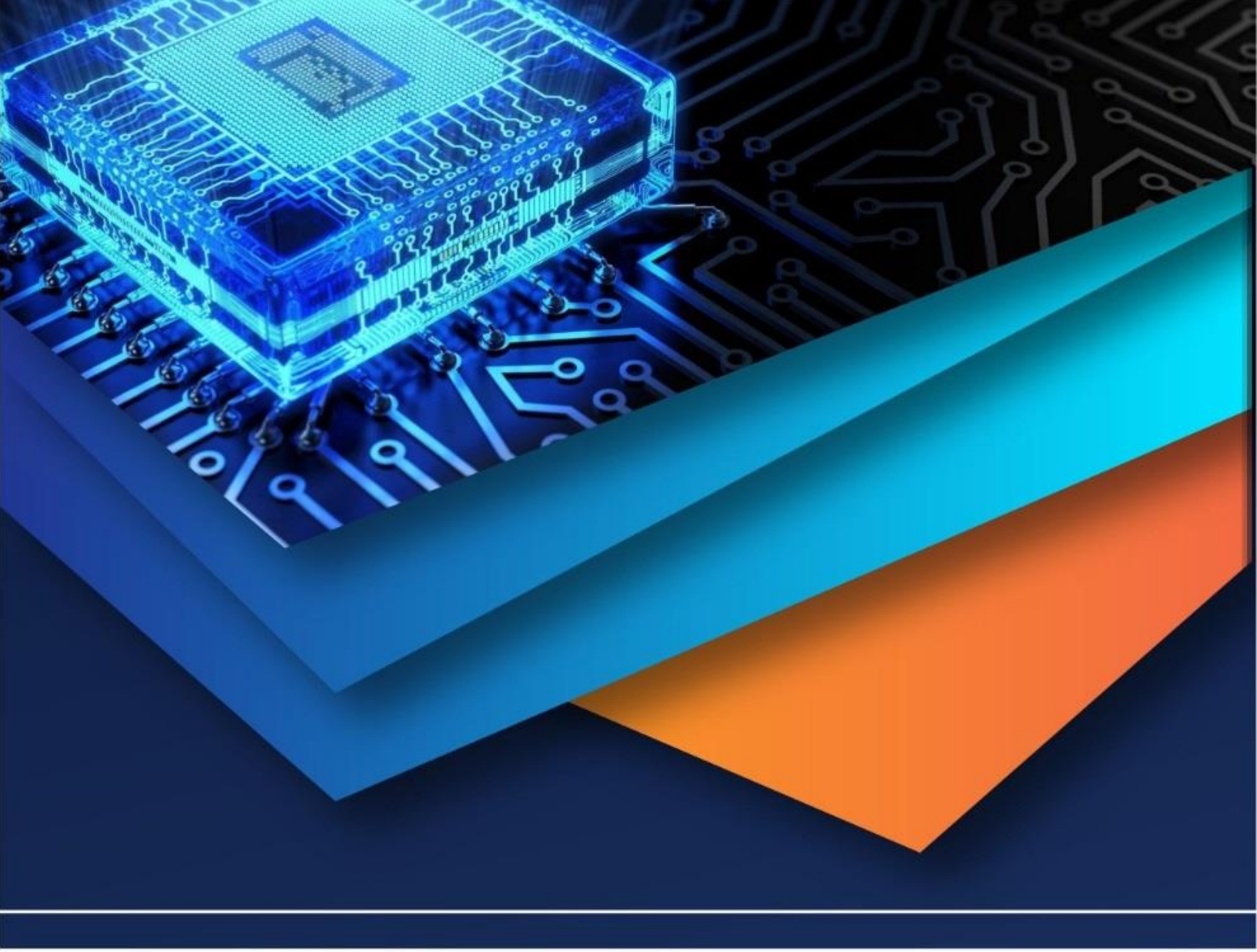
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