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A Literature Curated Profile of miRNA IN Modulating Multi-Drug Resistance for Cancer Therapy

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Abstract: ***At present, cancer is one of the major causes of death, affecting millions of people each year. Multi Drug Resistance (MDR) remains the major clinical obstacle in cancer treatment. Till date various mechanisms of MDR has been elucidated which includes- over expression of drug transporter, defect in cell cycle and apoptotic machinery, induction of autophagy, alteration in drug metabolism and drug target. microRNAs (miRNAs) are an extensive class of 22 nucleotide long non coding RNAs which are involved in gene regulation. Recent work has underlined the involvement of miRNA in cancer development with several studies regarding their involvement in drug resistance, thereby holding much promise for developing novel and more effective therapy for cancer treatment. This review presents the mechanisms of MDR and focuses on the profile of miRNA in regulating MDR in cancer treatment.***
Keywords: miRNA, Cancer, Multi-drug resistance, Drug target, Drug transporter, Apoptotic machinery.

I. INTRODUCTION

Cancer is a disease caused by uncontrolled division of abnormal cells in specific part of the body. However cancer is one of the major cause of death worldwide. One of the major cancer treatment method is chemotherapy. However the major clinical obstacle in successful cancer treatment is the multi drug resistance of the cancer cells to chemotherapy. Multi drug resistance is defined as the resistance of cancer cells to diverse panel of structurally and functionally unassociated drugs. MDR development is a multifactorial process. In last few decades, diverse mechanism has been implicated in the development of intrinsic and acquired multidrug resistance against anti cancer drug. Some of them include-

A. Over expression of MDR transporters
B. Defect in cell cycle and apoptotic machinery
C. Induction of autophagy
D. Alteration of drug metabolism
E. Alteration in drug target and DNA repair.

miRNA are 19-22 nucleotide long non-coding RNAs which regulates gene expression post transcriptinally. They are mostly reported in invertebrates and vertebrates. In human, approximately 60% gene predicted to be regulated by miRNA. They generally binds to 3' UTR of their target mRNAs and repress protein production by destabilizing the mRNA and also promote translational silencing.

The exact mechanism of miRNA is not yet determined but from recent data it has been shown that the stages of translation, which is inhibited by miRNA is dependent upon a promoter used for transcribing the target miRNA. miRNA are transcribed from genes but cannot be translated further into protein.

Recent studies have demonstrated the role of miRNA as key regulatory factor in MDR through modulating many of the biological and biochemical processes. Therefore miRNA could be the potential biomarker and target for circumventing MDR in cancer therapy.

This review focuses on the mechanism of MDR in cancer therapy and the profiling of miRNA in regulating MDR in cancer treatment.

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II. MECHANISMS OF MULTI DRUG RESISTANCE IN CANCER CELLS

A. Over Expression of MDR Transporter

One of the most important cause of chemotherapeutic resistance of anti cancer drug is the over expression of MDR transporter like ABC transporter family. The ABC transporter protein has similar trans membrane domain that can pump out or efflux anti cancer drugs from the cancer cell against concentration gradient in an ATP dependent manner and thus protects the cancer cell from toxicity. The most extensively characterised ABC transporter protein includes p-glycoprotein/ ABCB1, ABCC1/MRP1, ABCG2, ABCC2, ABCC3. According to An et al, 2016 the over expression of ABCB1 is shown to be associated with wide variety of chemotherapeutic resistance to anti cancer drug which include anthracyclin, epipodophyllatoxins, vinea alkaloids and taxens. Overexpression of ABCC1 transporter is shown to confer resistance to a wide variety of chemotherapeutic drugs such as anthracycline, vinea alkaloid, epipodophyllatoxins, camptothecin, methotrexate and mitoxantrane. Overexpression of ABCG2 is frequently observed in breast cancer cells treated with chemotherapeutic drugs like anthracycline, camptothecin derived topoisomerase I inhibitor, methotrexate and flavopiridols.

B. Defect in Cell Cycle and Apoptotic Machinery

The DNA damage induced by anti cancer drug can direct the cancer cells to react in two ways- either by cell cycle arrest or by apoptosis**.** However tumour suppressor protein P^{53} plays an important and effective role in drug resistance. Mutant P^{53} often causes loss of function resulting in multidrug resistance, as reported in many cancer cells.

One of the major type of cell death is triggered by chemotherapeutic drug is apoptosis. There are two established pathway of apoptosis - the intrinsic pathway or mitochondrial pathway and the extrinsic pathway or death receptor pathway. The intrinsic pathway is mainly under the control of both pro-apoptotic protein (BAX, BAK, BID, BIM, BAD) and anti- apoptotic protein (Bcl2, Bcl-XL, MCL1). The extrinsic pathway is mainly regulated by the death receptor or transmembrane receptor of the TNF family.

Various anti cancer drug has been reported to induce apoptosis. Defect in this apoptotic machinery results in anti cancer drug resistance. However cancer cells can escape apoptosis by either over expression of anti apoptotic protein or under expression of pro-apoptotic protein. Several other factors like activation of protein kinase B, nuclear factor kappa B, PTEN plays an important role in developing drug resistance in various cancer types through inferring apoptotic machinery.

C. Induction of Autophagy

In many recent studies, autophagy has been reported as a new mechanism in anti cancer drug resistance. Autophagy is characterised by self digestion and removal of dysfunctional organalles and protein via endolysosome which result in formation of autophagosome. Autophagy occurs as a physiological process in normal cell to eliminate damaged organelle and thus maintain cellular homoeostasis and protect against cancer. In tumour cells autophagy helps the cell evade apoptosis and contribute to chemoresistance to drugs like cisplastin. Cancer cells that respond to drugs by autophagy are more resistant to drugs.

D. Alteration of anti cancer drug metabolism

Another mechanism by which cancer cells can acquire resistance is by altering the metabolism of drug. The enzyme responsible for this alteration is cytochrome P450 which is mostly expressed in human liver, intestine and kidney. Recent studies have reported the involvement of cytochrome P450 in metabolism of wide variety of chemotherapeutic drug which includes taxens, vinblastine, vincristine, doxorubicin, etoposide, irionotecan, cyclophosphamide, ifosphamide. However the enzyme activity of cytochrome P450 gets reduced due to genetic polymorphism resulting in low production of active metabolites.

E. Alteration of drug target and DNA repair

Resistance to chemotherapeutic agent can also take place by either qualitative or quantitative alteration of drug target. In An et al, 2016, it was reported that DNA topoisimerase II, an essential enzyme for DNA replication induces resistance to drugs such as doxorubicin, idarubicin, mitoxantrone etc.

However DNA repair machinery also plays a role in the MDR development in cancer cells. There are three fundamental pathway for DNA repair mechanism – nuclear excision repair, base excision repair and DNA mismatch repair pathway. Dysregulation of these repair system may be involved in chemotherapeutic resistance.

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III. MiRNA AND ITS BIOGENESIS

miRNA are small single stranded RNA molecule of 19-22 nucleotide, encoded in the genome of plants, animals and viruses. They are highly conserved and appears to regulate gene expression post transcriptionally by binding to 3' UTR of specific miRNA resulting in translational repression.

Victor Ambros and colleagues identified the first miRNA , lin-4 from nematode Caenorhabditis elegans in 1993. The lin-4 gene was unusual in that it did not encode a protein but rather a small RNA that imperfectly base paired to complementary sequence on target mRNA in order to block gene expression. The lin-4 control the expression of lin-14 gene. The lin-4 transcripts are complementary to the sequence present in the 3'UTR of lin-14 mRNA. In 2000 a second miRNA, let-7 was discovered by Gray Ruvkun's group in C. elegans that works in a similar manner to lin-4. These small miRNAs have been shown to play critical role in development timing, hematopoietic cell differentiation, cell death, cell proliferation and oncogenesis.

miRNA are synthesised in the nucleus as long(1000 nucleotide) RNA Polymerase II transcripts, called pri-miRNA, that are characterised by imperfect hairpin structures. RNA Polymerase III also transcript some pri-miRNAs.

An RNase III enzyme Drosha acts as dsRNA specific endonuclease, in conjugation with a dsRNA binding protein called pasha (in Drosophila) and DGCRB (in mammals), processes the

pri-miRNA into hairpin RNAs 70-100 nucleotide in length called pre-miRNAs. Complex of DGCRB or pasha with the enzyme Drosha is called microprocessor complex. Pre-miRNAs also derive from introns and known as mitrons. However mirtrons not involve processing by microprocessor complex. Pre-miRNAs are transported to the cytoplasm. It is mediated by exportin-5. In the cytoplasm, dicer processes the pre-miRNA into miRNA duplex and load it into the RISC. Members of the Argonaute(Ago) protein family are central to RISC function. Argonaute are needed for miRNA induced silencing and contain two conserved RNA binding domains; a PAZ domain that can bind the single stranded 3' end of the mature miRNA and a PIWI domain that structurally resembles ribonuclease-H.

Gene silencing may occur either via mRNA degradation or prevent mRNA from being translated. miRNA functions by base pairing with complementary sequences within target mRNA molecules. If there is complete complementation between the miRNA and target miRNA sequence, Ago can cleave the mRNA and lead to direct mRNA degradation. If there is no complete complementation, then silencing is achieved by preventing translation.

Each miRNA can regulate numerous target genes and vice versa. miRNA may be involved in broad range of human disease like cancer. Dysregulation of miRNA in up or down regulation could affect the function of multiple target miRNAs and thus alter the expression of multiple protein involved in cancer development and drug resistance. However miRNA can be used as a prognostic marker in cancer treatment and this review focuses on the role of miRNA in anti-cancer drug resistance.

IV. RESULT AND OBSERVATIONS

A. *Abberant role of miRNA in Multidrug Resistance*

In numerous studies, it has been documented that the miRNA expression profile between cancerous cell and paired normal tissue from the same organ is different. This dysregulation of miRNA expression in cancer cells can lead to anti cancer drug resistance by modulating the expression of genes involved in multi drug resistance mechanisms which include- ABC transporter gene, genes that regulate apoptosis, autophagy, drug metabolism genes. Therefore modulation of miRNA expression can alter this resistant cell into sensitive one towards anti cancer drug. However this could be achieved by inhibiting or changing the expression of miRNA responsible for MDR.

1) *miRNA regulated MDR Transporter:* miRNA can modulate chemotherapeutic drug resistance by regulating the expression of ABC membrane transporter. According to An et al.,2017, the over expression of miRNA 27a regulates the ABCB1 target gene by up regulating the P-gp gene in ovarian cancer cell. The over expression of miR541 regulated the ABCB1 target gene by down regulating the P-gp in lung cancer cell thus leading to resistance of various anti cancer drugs (Zhu et al.,2008). A number of miRNA has been found to modulate MDR by regulating ABCB1, ABCC gene expression. In Zhao et al.,it was reported that the up regulation of miR138 leads to down regulation of p-gp and it causes anti cancer drug adriamycin to become resistance on MDR cell line in leukemia. Other miRNAs like miR298 down regulates to decrease p-gp expression and reverses doxorubicin resistance in breast cancer cells. miR381, miR9, miR122 is found to negatively regulate ABCB1 gene thus promoting anti cancer drug resistance. Yang et al reported that miR223 could down regulate ABCB1 at both mRNA and protein translational level and thus increase the HCC cell sensitivity to anti cancer drug. miR328 could also down regulate ABCG2 gene and increase the sensitivity to mitoxantrone in breast cancer cell. Other miRNAs like miR519, miR212 and miR281a also

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negatively regulate ABCG2 expression. Liang et al reported that down regulation of miR326 could down regulate ABCC1 gene expression and sensitize breast cancer cells to VP-16 and doxorubicin. However it was found that the under expression of miR106a reverse MDR in human glioma cells by decreasing the expression of P-gp, MDR1 as well as expression of other apoptosis, survival and inflammatory related protein.

The expression of various miRNA that regulates the drug resistance in cancer is tabulated below

Table 1

Sl. No	miRNA	Dysregulation	Target	Cancer
1	miR27a miR451	Up Regulated	ABCC1	lung
2	miR326	Down regulated	ABCC1	breast
3	miR508	Up regulated	ABCB1	gastric
4	miR186	Down regulated	ABCB1	ovary
5	miR129	Down regulated	ABCC1	gastric
6	miR326 miR200c	Down regulated	ABCA2	leukemia
7	miR27a	Up regulated	ABCB1	Ovary
8	miR451	Up regulated	ABCB1	ovary
9	miR122	Down regulated	ABCBI	Liver
10	miR296	Up regulated	ABCB1	Esophagus
11	miR298	Down regulated	ABCB1	Breast
12	miR253	Down regulated	ABCB1	Breast
13	miR1291	Down regulated	ABCC1	Breast
14	Let 7g	Down regulated	ABCB1	Ovary
15	miR297	Down regulated	ABCC2	Colorectal
16	miR9	Down regulated	ABCC3	Glioma
17	miR212	Down regulated	ABCG2	Leukemia
18	miR328	Down regulated	ABCG2	Breast
19	miR519c	Down regulated	ABCG2	Breast
20	miR520	Down regulated	ABCG2	Pancreas
21	miR181a	Down regulated	ABCG2	Colon
22	miR487a	Down regulated	ABCG2	Breast
23	miR508-5p	Down regulated	ABCB1	Gastric
24	miR27b	Down regulated	ABCB1	Gastric
25	miR138	Up regulated	ABCB1	Leukemia
26	miR381 miR495	Up regulated	ABCB1	Breast

2) *miRNA Regulate cell Cycle and Apoptotic Machinery:* Several miRNAs are found to regulate P^{53}. P^{53} is one of the critical mediator of cell cycle and apoptotic machinery in response to different chemotherapeutic drugs like doxorubicin, vincristine, etoposide and many more. It was reported in Iida et al that over expression of miR125b could suppress P^{53} dependent apoptosis and thus induce chemoresistance. However miR140 and miR122 could increase P^{53} protein stability and hence contribute to chemosensitivity. Other miRNAs like miR34a targets cdk6 gene (which induces apoptosis) and thus inhibits cell death. Bcl2 is the most important anti apoptotic protein which prevent apoptosis to ocuur. However several miRNA has been reported which modulates MDR by targeting Bcl2. Xia et al found that down regulation of miR15 and miR16 could up regulate Bcl2 protein level and thus sensitize the cell to various anti cancer drug. miR21 was found to up regulate Bcl2 thus promoting resistance of the cancerous cell to gemcitabine. Other miRNAs, which target Bcl2 includes- miR34a, miR200bc, miR195, miR205, miR214, miR497, miR1915. Other miRNAs, miR101 targets Mcl-1 and thus sensitize hepatocellular carcinoma cells to doxorubicin induced apoptosis. miR494was reported to down regulate the BIM gene. However up regulation of miR365 directly down regulates apoptosis promoting protein BAX and thus induces gemcitabine resistance. Other important tumour suppressor gene is PTEN and several miRNAs were found to modulate this gene which includes- miR21, miR22, miR221, miR214, miR19a/b, miR175p, miR222.

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The regulation of miRNA on their target genes are tabulated below.

Table 2

Sl. No	miRNA	Dysregulation	Target	Cancer
1	miR21	Up regulation	PTEN	Breast
2	miR130b	Up regulation	PTEN	Breast
3	miR15b, miR16	Down regulation	Bcl2	Gastric
4	miR181a	Down regulation	Bcl2	Breast
5	miR663	Up regulation	HSPG2	Breast
6	miR19	Up regulation	PTEN	Breast
7	miR19a/b	Up regulation	PTEN	Gastric
8	miR125	Down regulation	Bcl2	Nasopharyngeal
9	miR200	Down regulation	Bcl2	Breast
10	miR497	Down regulation	Bcl2	Gastric
11	miR295	Up regulation	Bcl2	Esophagus
12	miR1915	Down regulation	Bcl2	Colorectal
13	miR34a	Down regulation	Bcl2	Prostrate
14	miR200c	Down regulation	SIRT1	Melanoma
15	miR125	Up regulation	P^{53}	Neuroectodermal
16	miR140	Up regulation	P^{53}	Pancreas
17	miR21	Up regulation	Bcl2	Pancreas
18	miR494	Up regulation	BIM	Liver
19	miR365	Up regulation	BAX	Lung

3) *miRNA Regulated Autophagy:* Induction of autophagy in another mechanism of chemotherapeutic resistance, modulated by miRNA. According to An et al, various miRNA has been reported whose dysregulation could regulate autophagy and promote sensitization of cancerous cell to particular anti cancer drugs. The combined expression of miR16 and miR17 inhibit autophagy and promotes apoptosis. The miRNAs that regulate autophagy include- miR30a, miR30d, miR155, miR15a, miR16, miR200b and miR181a.

The regulation of these miRNAs on their target gene is tabulated below.

Table 3

Sl No	miRNA	Target	Cancer	Role of miRNA
1	miR30a	Beclin 1	Leukaemia	Activates Beclin1 related autophagy
2	miR30d	Beclin	Leukaemia	Inhibits Beclin1 mediated autophagy
3	miR155	Unknown	Osteocarcoma	Induces autophagy and Enhances chemo sensitivity
4	miR200b	ATG12	Adenocarcoma	Suppresses autophagy
5	miR181a	ATG5	Gastric	Suppresses autophagy

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4) *miRNA Controls anti cancer Drug Metabolism:* According to Kong et al, it was documented that miRNA modulate MDR by regulating CYP enzyme. CYP enzyme is essential for drug metabolism. Various miRNA are reported which includes- miR27b, miR892a, miR148a and Let 7b.

The regulation of miRNAs are tabulated below.

Table 4

Sl No	miRNA	Target	Role of miRNA
1	miR27b	CYP1B1	Negatively regulates CYP1B1 expression
2	miR892a	CYP1A1	Sensitizes cancer cell to anti cancer drug
3	miR148a	CYP3A4	Down regulated expression of CYP3A4

5) *miRNA Modulated Drug Target and DNA Repair:* In An et al, it was reported that miRNA could modulate MDR by modulating drug targets. miRNAs involved in modulating drug target include- miR192, miR215, miR27a, miR27b, miR134, miR582, miR211, miR21, miR155, miR182 and miR9. miR192 modulates TS enzyme in colorectal cancer cells and influence 5 FU sensitivity. Sun et al reported that miR9 could down down regulate BRAC1 and prevent DNA repair in cancer cells thus increase sensitivity of cancer cell to PARP inhibitor.

The regulations of miRNAs on drug targets are tabulated below.

Table 5

Sl no	miRNA	Target	Role of miRNA
1	miR192	TS enzyme	Influence 5 FU sensitivity
2	miR27a	DPD enzyme	Modulate sensitivity of 5Fu Based chemotherapy
3	miR211	RRM2	Sensitizes PDAC cells to Gemcitabine
4	miR21	MMR	Down regulates hMSH2, hMSH6
5	miR155	MMR	Down regulates hMSH2, hMSH6
6	miR182	BRACI	Down regulates BRACI expression & Increases sensitivity of cancer cells to Cisplastin & PARP inhibitor
7	miR9	BRACI	Down regulates BRACI expression & Increases sensitivity of cancer cells to Cisplastin & PARP inhibitor

V. MIRNA AS PROGNOSTIC MARKER FOR CHEMOTHERAPEUTIC RESPONSE

The profiling of miRNA expression in cancer cells and normal cells reveal that miRNA can be employed clinically as biomarkers for cancer classification, diagnosis and prognosis. However, at present, miRNA are rapidly gaining popularity for predicting response to chemotherapy. Blower et al, documented that miRNA plays a prominent role in mediating chemo resistance. However when combined with gene expression, miRNA expression profile may help elucidate the complex mechanism involved in chemo sensitivity and chemo resistance. Recent studies suggest that miRNA expression could be used in chemotherapeutic response to mediate cancer. Few miRNAs are reported till date where regulation of miRNA expression in response to anti cancer drug led to change in response of cancerous cell from resistant to sensitive one. It was reported that down regulation of let-7i in ovary and breast cancer cells lead to resistant to cisplastin drug. However contradictorily it can be said that by inhibiting let-7i miRNA could enhance the sensitivity of cancerous cell towards its anti cancer drug agent. Similarly, till date other miRNA are also represented as predictive marker for treatment outcome in cancer which include- miR26a, miR181b, miR215, miR146b-3b, miR486-5p, let 7, miR200b, miR143, miR21 and miR26.

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In many studies it has been concluded that the circulating miRNA can be used as non invasive biomarker for predicting chemotherapy response circulating miRNA are however bound to protein which include Argonaut 2, lipoprotein which render them highly resistant to RNase enzyme activity. They can be reliably measured by the relatively inexpensive method of quantitative PCR. Few circulating miRNA has been reported as useful predictive biomarker for chemotherapy response which include miR125b, miR210, miR17-3p, miR29a, miR27b, miR148a, miR326, miR2, miR21, miR192.

VI. DISCUSSION

A. miRNA as druggable Target for Circumvention of anti cancer drug Resistance

Since the dysregulation of miRNA expression is observed in cancer cells, therefore it can be concluded that miRNA could potentially produce anti cancer effect. However the advanced technology can be used to modulate the expression of miRNA in several ways. Tumour suppressor miRNA can be up regulated by using synthetic miRNA mimics for anti cancer effect. Oncogenic miRNA can be down regulated by using various antisense oligonucleotides for anti cancer treatment. Some miRNA can be silenced in vivo in order prevent MDR in cancer therapy. Some recent studies showed the use of artificial synthetic miRNA to target few oncogene and produce anti cancer effect.

In Kw et al, a list of miRNA as target for cancer therapy is tabulated below-

Cancer type	miRNA and its role in cancer	Delivery system to modulate miRNA in vivo
Breast	miR34a- Tumour suppressor	Cationic liposomes
Glioblatoma	miR145- Tumour suppressor	Adenoviruses
Glioblatoma	miR221-222- Oncogene	Adenoviruses
Glioblatoma	miR9- promote expression of p-gp protein	To deliver anti-miR-9 to temozolomide-resistant GBM to reduce P-gp expression for resistance reversal. Mesenchymal stem cell-derived exosomes
Hepatocellular	miR26- Tumour suppressor	Adenoviruses
Lung	Let7- Tumour suppressor	Adenoviruses
Lung	miR34a- Tumour suppressor	Cationic liposomes
Lymphoma	miR155- Oncogene	Polymer-based nanoparticles
Medulloblatoma	miR17	8-mer seed-targeting locked nucleic acid (LNA)-modified anti-miR oligonucleotides(nude mice)
Pancreas	miR21- Oncogene	Lentiviruses

Although the miRNA expression in cancer therapy has not yet been widely used in clinical trials, few miRNA modulatory approach to circumvent anticancer drug resistance reported till date is tabulated below-

Cancer type	miRNA targeted for inhibition	Type of resistance circumvented	Delivery system for modulation of miRNAs
B-cell lymphoma	R-21oncomiR addiction	-	Antisense strategy
Cholangio -carcinomas	miR-21 & miR-200b	Gecitabine resistance mediated by PTEN-dependent activation of PI3K signaling	Transfection with miRNA-specific antisense oligonucleotides
Glioblastoma ultiforme (GBM)	miR-9 – indirectly promoting expression of the MDR transporter P-gp	P-gp-mediated resistance to temozolomide	Mesenchymal stem cell-derived exosomes

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GBM	miR-21	Enhance apoptosis	Transfection with anit-miR-21 oligonucleotide
GBM	miR-9 – indirectly promoting expression of the MDR transporter P-gp	Temozolomide	To deliver anti-miR-9 to temozolomideresistant GBM to reduce P-gp expression for resistance reversal
Lung cancer	miR-92b	Cisplatin resistance mediated by downregulation of the tumor suppressor gene PTEN	Transfection with anti-miR-92b

In An et al, 2011, it has been shown that several miRNA expression can be differentially altered by xenobiotic drugs in human cell lines. These drugs are basically not the anti cancer drugs but can be safely administered with other anti cancer drug in an attempt to reverse the miRNA expression which mediate drug resistance. The therapeutic outcome of miRNA targeted resistance reversal depends on a number of miRNA targets and the affinities of each targets are expressed in given tumour microenvironment. In order to prevent unwanted side effect, an appropriate method to deliver the miRNA antagomirs to the right cell type must also be considered. These difficulties should be overcome before an effective miRNA targeted strategy can be released for circumvention of anti cancer drug resistance to cancer patient.

VII. CONCLUSION

Multidrug resistance in cancer treatment is highly complex process and mediates resistance to anti cancer drug in many different mechanisms. However the emerging role of miRNA in regulating the gene expression and dysregulation in human cancer has provided an opportunity for their therapeutic application as cancer detection, prognostic biomarker and diagnosis. By modulating the regulation of selective miRNA, it was found to enhance chemosensitivity of cancer cell to anti cancer drugs. Similarly several miRNA have future application in modulating chemotherapeutic response in selected cancer cell types. Better understanding of these miRNA is required for future use in cancer diagnosis, chemotherapy and in circumvention of MDR.

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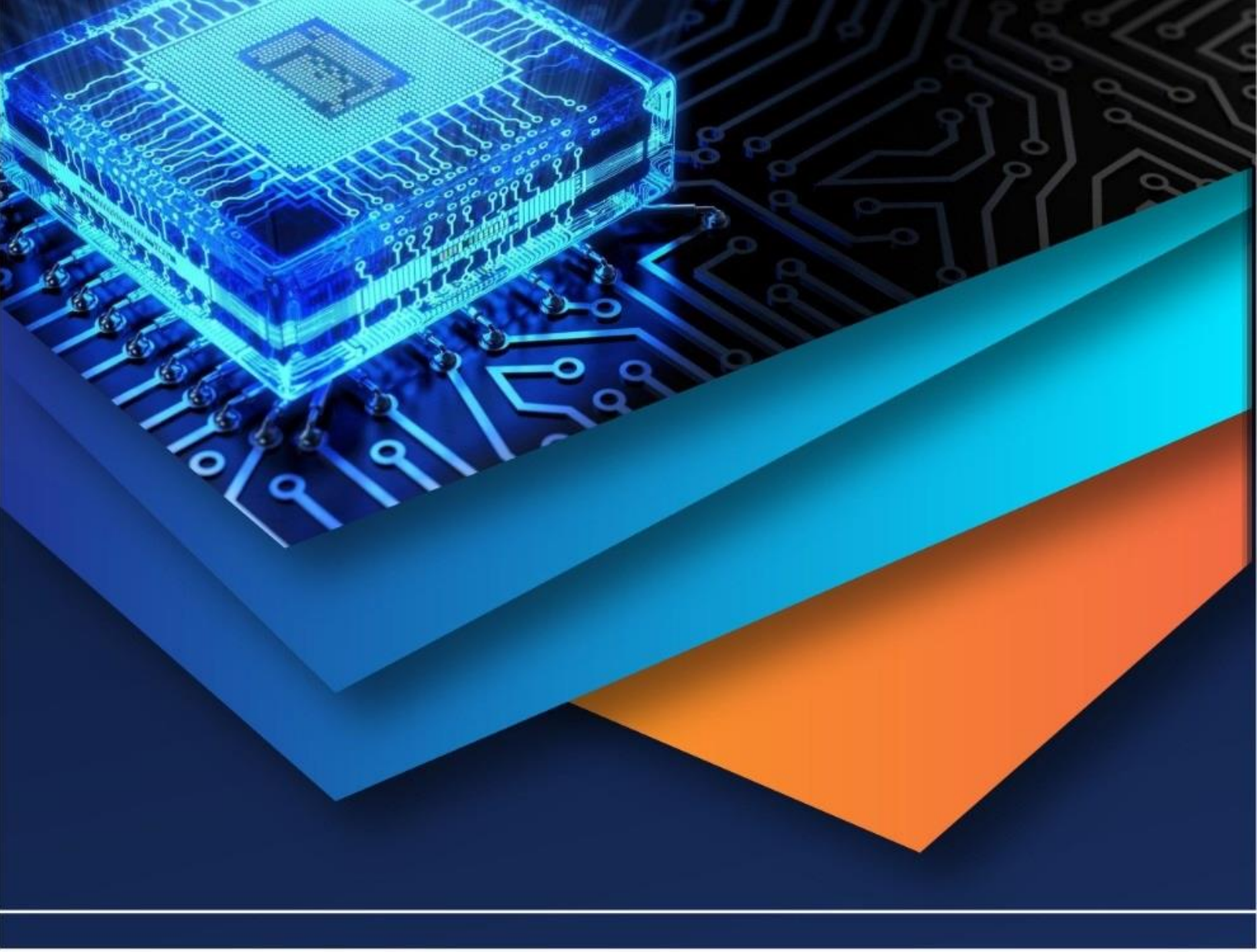
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