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Chapter

Recent Advancements in Apoptosis-Based Therapeutic Approaches for Cancer Targeting

Mehmet Evren Okur, Panoraia I. Siafaka, Merve Tutar and Yusuf Tutar

Abstract

Apoptosis, known as programmed cell death, has been considered a potent target for the pharmacy industry. The scientific community has actively participated to research which evaluate active molecules for possible inhibition or induction of apoptosis. Nanocarriers especially for cancer targeting are widely found through literature; they mainly based on inorganic, lipid or polymer nanoparticles which incorporate anticancer drugs. Another important and innovative category of anticancer agents is that of microRNAs. In this chapter, a discussion about the most recent applications of apoptosis-based agents mainly focusing on cancer target is done.

Keywords: apoptotic agents, anticancer agents, microRNAs

1. Introduction

In the last decades, a huge advancement in the development of novel drug targets and drug delivery systems for inhibiting or inducing apoptosis has been done. Apoptosis, the programmed cell death plays a major role in cellular homeostasis, normal development, and clearance of cells. Non-programmed cell death can take place by various external factors, such as infection, toxins, and physical injury [1]. The dysregulation of apoptosis has been related with the pathogenesis of numerous diseases such as degenerative, autoimmune, and cardiovascular as well as have been associated with tumorigenesis. It has been reported that apoptosis is reduced on pathological disorders such as malignant neoplasm and autoimmune diseases while it is raised in inflammatory and neurodegenerative disorders as well as ischemic diseases, *i.e.* myocardial infarction, liver ischemia, stroke [2]. Apoptosis can induce cancer formation while cancer cells may elude apoptosis via the downregulation or blockage of apoptosis signaling pathways [3]. Similarly, cell death modalities (apoptosis, necrosis, and autophagy) have been linked with cardiovascular, autoimmune, and neurodegenerative diseases. In example, it has been reported that the apoptosis is impaired by various factors (*i.e.* caspases, amyloid β, tumor necrosis factor-α, amyloid precursor protein intracellular C-terminal domain, etc.) leading to Alzheimer's disease and other neurodegenerative diseases (such as Huntington's disease) [4–6]. Moreover, cardiovascular disorders such as myocardial infarction, diabetic cardiomyopathy, ischemic cardiomyocyte, and congestive heart failure have been associated with cell death modes in cardiac myocytes [7].

Identification of key players in cellular apoptosis regulation as B-cell lymphoma 2 (BCL-2) proteins, caspases, etc. has proofed that targeting apoptosis can lead to outstanding management of various diseases, especially cancer [8, 9].

2. Nanocarriers inducing apoptosis

In general, pharmacological approaches related to apoptosis can be categorized as inhibiting and inducing apoptosis molecules. Inhibitors of apoptosis (IAPs) are proteins important for maintaining apoptosis; IAPs have been identified in tumors and thus therapies targeting them have raised the research interest. It is well known that cancer cells are more resistant to apoptotic cell death, and high dosages of drugs are needed to eliminate them [10]. Consequently, the usage of apoptotic pathways via IAP antagonism can act as a promising alternative therapeutic choice for cancer management, limiting the apoptotic effect on cancerous cells [11]. In case of cardiovascular disorders, inhibiting myocardial apoptosis has been recognized as a therapeutic target. In the past, caspase inhibitors [12] and control of apoptosis of cardiovascular fibroblasts/vascular smooth muscle cells by p65 nuclear factors NF-κB and B-cell lymphoma-extra-large (Bcl-xL) antisense oligonucleotides or p53 overexpression [13] have been reported as potent drug targets. A recent study [14] revealed that the upregulation of miR-29b-3p (miRNAs), can protect cardiomyocytes against hypoxia-induced injury through downregulation of TNF receptor-associated factor 5 which can be an important therapeutic alternative for acute myocardial infarction. BH3 interacting-domain death agonist [BID (belongs to BCL-2 family)] inhibitors have been recognized as key factors in the apoptotic pathway mediating cytochrome C and Smac/DIABLO from mitochondria, resulting in caspase activation and cell apoptosis. The inhibition of BID by pharmacological agents can offer a promising therapeutic choice for diseases implicated by pathological cell death from BID involvement [2]. Becattini *et al.* developed various 4-phenylsulfanyl-phenylamine derivatives that are capable of binding on the surface of BID resulting to inhibition of tBid-induced SMAC release, caspase-3 activation, and cell death [15]. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) inhibitors have been also reported to induce apoptosis; tumor necrosis factor (TNF) has been linked with cerebral ischemia, atherosclerosis, rheumatoid arthritis, etc. The TWEAK-Fibroblast growth factor-inducible 14 (FN-14) has been identified as potent drug target for the aforementioned diseases [16]. Cytochrome C inhibitors, as Minocycline and methazolamide have shown inhibition of apoptosis. Minocycline revealed inhibition of apoptosis via attenuation of TNF-alpha expression following iNOS/NO induction by lipopolysaccharide in neuron/glia co-cultures [17]. Tian et al. showed that minocycline can inhibit sevoflurane-induced apoptosis [18]. Methazolamide, a carbonic anhydrase has shown prevention of the amyloid β-mediated onset of apoptosis in the mouse brain [19]. Therefore, various apoptotic inhibitors have been developed; however, a great effort is much needed.

A special reference on the drug carriers involved as chemotherapeutic systems inducing apoptosis of cancerous cells is followed due to its importance. Cancer is the second leading cause of death globally [20] and despite the great effort being done by researchers worldwide, its management remains inefficient. Chemotherapy, the most conventional treatment option can lead to serious adverse effects since it can induce the cell death of healthy tissues as well as the cancerous ones [21]. In most cases, the current therapeutic systems involve the use of nanoparticles based on polymeric and inorganic carriers and a combination of them. Nanotechnology-based carriers are of great interest due to their limited size, improved penetration, and functionalization potential resulting to targeting efficiency [22, 23]. The therapeutic

outcome of cancer management strategies mainly depends to the ability of the molecule to induce apoptosis via targeting the overexpressed anti-apoptotic proteins or stimulation of the expression of pro-apoptotic molecules. Nonetheless, cancer cells seem to resist the chemotherapy and apoptosis leading to increased survival rate and the possibility of metastasis. Thus, the combination of drugs or novel strategies involving innovative drug carriers can potentially overcome the chemoresistance [24, 25]. Solid lipid nanoparticles belong to lipid-based carriers and have been designed as potent drug delivery systems for various diseases. As an example, letrozole, a known cytotoxic agent for hormone-dependent breast cancer management was impregnated to folic acid-modified solid lipid nanoparticles in order to induce apoptotic cell death. The modification with folic acid can lead to enhanced targeting efficiency since breast cancer cells overexpressed folate receptors. Inducing of apoptosis performed by employing caspase-3 activity and TUNEL assays. The incorporation of the drug into the folic acid decorated carriers led to *in vitro* cytotoxicity against MCF-7 cancer cells but they were not cytotoxic to MCF-10A normal cells revealing great biocompatibility. It was concluded that the mechanism of cell death was apoptosis based [26]. Similarly, solid lipid nanoparticles were modified with chitosan-coated-trans-resveratrol and ferulic acid and further decorated with folic acid. The developed nano-formulations demonstrated great stability and improved cytotoxicity in the colon cancer cells which led to apoptotic cell death. Thus, the solid lipid nanoparticles can be used for anticancer therapy [27]. Folate modified hydroxyapatite nanorods were used as a matrix for doxorubicin, an anticancer agent, loading. The results showed cytotoxicity against MCF-7 cells while western blot assays revealed that the developed nanocarriers can improve the expression of Bax (a pro-apoptotic protein) and decrease the expression of Bcl-2. Finally, the nanorods improved mitochondrial cytochrome C leakage and activate an apoptotic cell death [28]. In similar skeptic, folic acid conjugated chitosan nanoparticles were able to incorporate the cytotoxic agent, ursolic acid. The targeting affinity improved the local concentration of the drug in cancerous cells MCF-7. According to the studies, the nanoparticles enter the lysosome, released from it while it was localized into mitochondria but not nuclei. Their prolonged retention in mitochondria led to the irreversible apoptosis in cancer cells owing to the overproduction of ROS and the destruction of the mitochondrial membrane. According to the mouse xenograft model, the nanoparticles can hamper breast cancer revealing promising characteristics and potent clinical efficacy [29]. Nano-formulations comprised of amine-functionalized and conjugated with folic acid mesoporous silica nanoparticles were loaded with curcumin, quercetin, and colchicines, known as anticancer prodrugs. The folate decorated nanoparticles incorporating curcumin revealed greater cellular uptake, prolonged intracellular release, and cytotoxicity. It was also reported that the apoptotic cell death was induced through specific signaling molecular pathways (caspase-3, H_2O_2, c-MET, and MCL-1), providing great [30]. In the last years the combination of inorganic nanoparticles, such as mesoporous silica nanoparticles and polymeric materials has been winning the race for effective cancer management. In example, mesoporous silica nanoparticles loaded with topotecan and externally modified with poly (acrylic acid) co-synthesized with chitosan, were investigated for their efficacy against triple-negative breast cancer (MDA-MB-231) and multi-drug resistant MCF-7 cells. The external layer is conjugated also with quercetin as a second drug. Moreover, arginine-glycine-aspartic acid peptide was conjugated on the nanoparticles inducing their uptake from the cancer cells via integrin receptor-mediated endocytosis. It was concluded that the system promoted molecular activation and cell death [31]. Folate modified liposomes loaded with bleomycin were prepared via film hydration and studied for their anticancer activity and apoptosis induction. According to the MTT assay, the nano-liposomal formulations showed

greater efficacy in human cervix carcinoma HeLa, and human breast carcinoma MCF-7 cells. Due to the modification of formulations with folic acid, an improved uptake by HeLa cells was confirmed. Additionally, the folate nano-liposomes with bleomycin effectively promoted apoptotic cell death as well as a cell-cycle arrest in HeLa cells especially at the G2/M phase [32]. Another system composed of modified chitosan nanoparticles and methotrexate was investigated as a potent anticancer system. Two molecules, L-cysteine and folic acid were conjugated to chitosan; the decorated nanoparticles when studied in a reducing environment similar to tumor cells, released the drug as desired. Moreover, the nanoparticles induced anticancer activity on HeLa cells in a dose and time-dependent manner while they demonstrated selective cellular uptake [33]. Another research involved the incorporation of doxorubicin into folic acid-modified lactoglobulin nanoparticles and studied for their anticancer potential against MCF-7 and MDA-MB-231, BC and triple-negative BC cells. It was revealed an important inhibition of cell proliferation and promotion of apoptosis [34].

DR5 which belongs to the TNFR family has been proposed as a potential target for cancer. An interesting study investigated the application of poly(ethylene glycol) decorated poly(lactic-co-glycolic acid) nanoparticles as potent anticancer carriers. The nanoparticles were further conjugated with DR5-specific antibody conatumumab and impregnated with camptothecin. The stealth nanocarriers promoted pro-apoptotic effects of the platform *in vivo* using HCT116 adenocarcinoma xenografts [35]. Another research evaluated the development of nanoparticles comprised from copolymers between poly(ε-caprolactone)-PCL and poly(ethylene glycol)-PEG as well as PEG, PCL, and poly(lactic acid)-PLA as potent carriers of auraptene. The triblock PCL-PEG-PCL and pentablock PLA-PCL-PEG-PCL-PLA copolymers were formulated on nanoparticles and examined for their characteristics. According to the results, the PLA-PCL-PEG-PCL-PLA nanoparticles showed enhanced cellular uptake as well as cytotoxicity. In further, the nano-formulations incorporating auraptene promoted the apoptotic cell death on HT-29 colon cancer cells. The real-time PCR revealed as apoptosis marker the Bax /Bcl2 expression ratio which was increased in the case of pentablock nanoparticles [36]. Nanocarriers based on mPEGylated Dendron conjugated with glycylphenylalanylleucylglycine tetra-peptide spacer and doxorubicin were studied for their efficacy against multidrug resistance of cancer chemotherapy. The *in vitro* studies revealed that the nanoparticles can accumulate in the nuclei of MCF-7/ADR cells and they are potentially cytotoxic leading to apoptosis. Moreover, the nanoparticles showed enhanced therapeutic efficiency against multidrug resistance xenograft tumors and thus they can be applied as potent anticancer carriers that can initiate the lysosomal apoptosis pathway [37]. Nano-formulations based on triphenylphosphine, Pluronic F127, and hyaluronic acid, formulated on nanomicelles able to incorporate paclitaxel, anticancer drug. The nanosystem showed inhibition of A549/ADR cells. Moreover, the nanomicelles entered acidic lysosomes through macropinocytosis, and accumulate in the mitochondria over a day, in A549/ADR cells. The nanomicelles induced the permeabilization of the mitochondrial outer membrane via hindering anti-apoptotic Bcl-2, resulting in the release of cytochrome C as well as caspase-3 and caspase-9 activation. Accordingly, when the nanoformulations studied in A549/ADR xenograft tumor model and a drug-resistant breast cancer mice model with lung metastasis, demonstrated promising cancer targeting and desirable anticancer efficiency [38]. A promising way to initiate cancer cell apoptosis is to targeted deliver cytochrome c, which can mediate apoptotic cell death if released from the mitochondria to the cytoplasm. Thus, an innovative nanosystem based on Cytochrome c was developed in order to promote the apoptotic death of cancer cells when is delivered. The nanocarriers of cytochrome c were modified with poly (lactic-co-glycolic) acid-SH via the

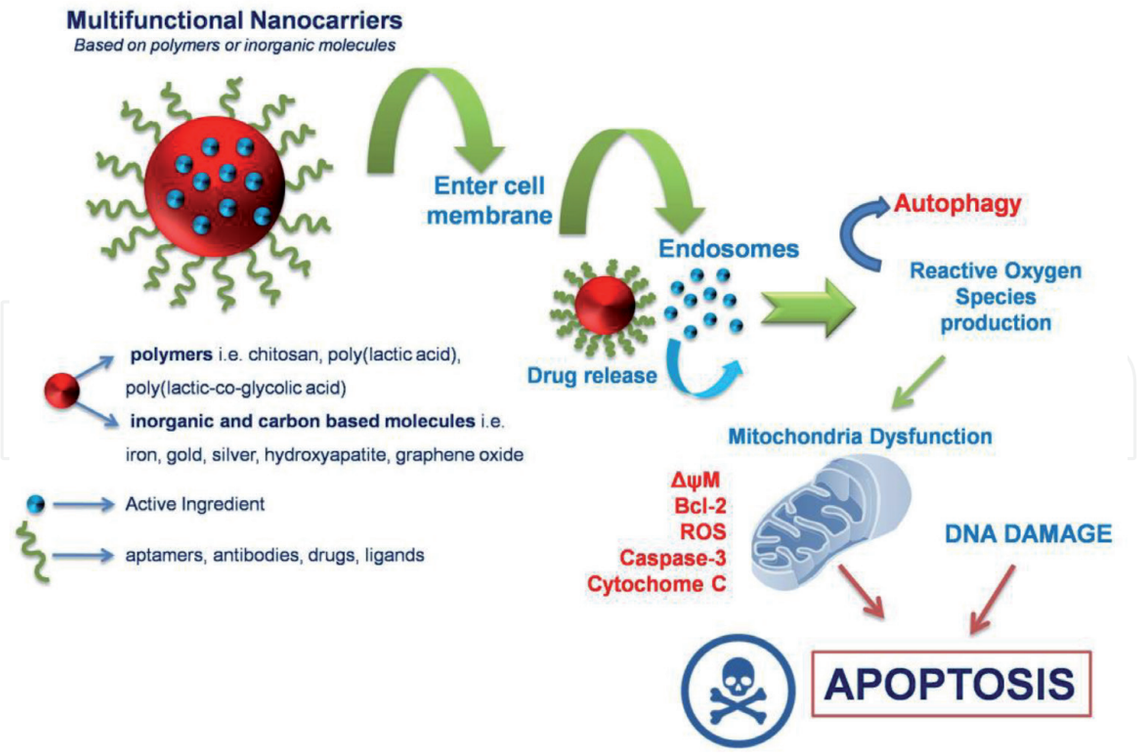


Figure 1.
A summary of multifunctional nanocarriers inducing apoptosis.

linker succinimidyl 3-(2-pyridyldithio) propionate so as to prevent the degradation possibility. The nanoformulations when incubated with HeLa cells exhibited cytotoxicity and the promotion of apoptosis in HeLa cells was also demonstrated [39]. Carbon dots have been widely studied as anticancer systems, *i.e.* carbon dots developed via ultrasonication of sucrose were modified with Gemcitabine and studied for their activity on MCF-7 and HeLa cell lines. The cytocompatible nano-formulations expressed desirable bioactivity and cytotoxicity against the cell lines. Moreover, the nano-formulations did not affect the healthy cells in such extent as they acted against cancerous cells. The most important outcome of the study is that the Gemcitabine conjugated carbon dots promoted early and late apoptotic cell deaths in the MCF-7 and HeLa cancer cell lines [40]. Graphene oxide modified with GE11 peptide was fabricated in order to efficiently targeted deliver oridonin on cancerous cells. The modified graphene oxide showed improved cellular uptake in KYSE-30 and EC109 esophageal cells compared to healthy cells. The oridonin loaded carriers were able to accumulate into lysosomes while they desirably hinder the viability of cancer cells. In addition, the developed system promoted apoptosis of the aforementioned cancerous cell lines [41]. **Figure 1** summarizes the possible mechanisms involving when nanocarriers are delivered to cells and induce apoptosis.

Several active compounds can be used for therapeutic purposes but miRNAs may also be employed for this purpose. The second part focuses on miRNAs as anticancer agents.

3. APOPTOTIC MicroRNAs (miRNA)

3.1 How miRNAs work to silence genes

To generate mature miRNAs, sequential steps are followed. First, RNA Polymerase II transcribes primary miRNAs (abbreviated as pri-miRNA). These

molecules can be translated from both intergenic and intragenic regions [42]. Then in order to generate pre-miRNAs with hairpin precursors, pri-miRNAs are processed by Drosha, an RNase III enzyme and by Pasha, a dsRNA-binding protein [43]. After this step, pre-miRNAs get escorted out of the nucleus with the help of exportin 5 [44]. And the pre-miRNA gets further processed in cytoplasm by Dicer enzyme which is an RNase III endonuclease, this enzyme works to remove the hairpin loop and make a double stranded duplex miRNA [44]. Then this double stranded structure retains the active strand while passenger stand gets degraded. The active strand interacts with RNA-induced silencing complex (abbreviated as RISC) in order to function. RISC is a complex formed by multiple proteins with its key proteins being argonaute 2 (abbreviated as Ago2) and transactivation-responsive RNA-binding protein (abbreviated as TRBP), and it includes miRNA or siRNA in order to use them as a template [45]. With these RNA templates the complex is able to recognize their complementary mRNA. The characteristic features of the target gene for an effective binding can be; seed region, a target sequence that is conserved, 3′ untranslated region of miRNA available for binding but recent studies show the binding of a target may also happen in 5′ untranslated region, promoter regions or open reading frames [45]. The pairing of the miRNA template and its target mRNA differs between plant cells and animal cells. In the plant cells, the pairing is fully complementary between miRNA and mRNA. But in animal cells, this pairing is not fully complementary there are base mismatches even though this base pairing follows a pattern. But there is a small sequence with 2–8 nucleotides of length which is a perfect base pairing that is called seed region [46]. This region is a conserved heptametrical sequence that is always perfectly matched and it is mostly found towards the 5′ end of miRNA [47]. With the binding of mRNA and miRNA, downregulation is tried to be achieved and this can be achieved via enzymatic cleavage of the mRNA leading to its further destruction by the cell or blocking the translation by preventing ribosome subunit from binding to mRNA [48]. And the matching degree of target and miRNA plays a role in the decision of which mechanism will happen for downregulation to occur, if the target is fully complementary then cleavage of mRNA will happen but if it is not fully complementary stability alteration or repression of translation may occur [43].

3.2 miRNAs in apoptosis

miRNAs are known to have a regulatory effect on apoptosis via their regulation on both pro-apoptotic and anti-apoptotic genes. So, miRNAs can work to be both inhibitory and stimulatory depending on the miRNA and the cell context. Also, alteration of the expression of regulatory genes in the apoptotic process by miRNAs is not limited to one of the extrinsic and intrinsic pathways. And the effect of miRNAs can both be direct and indirect. For example, miR-21 is a miRNA that directly affects its target, inhibiting FasL in order to increase apoptosis but miR-130a is a miRNA that affects TRAIL resistance in order to effect other miRNAs that will eventually cause a change in apoptotic process [49].

For their indirect effects, miRNAs can be seen to function in both feedback and feedforward loops. Feedback loop effects can change depending on the cell context, miRNA and transcription factors as the regulators may have the same or opposite effects [50]. And, in feed-forward loops, transcription factors can be seen to regulate both the target gene and miRNA, which also regulates the transcription factor [50]. To regulate genes, miRNAs work together with transcription factors in a highly coordinated manner. Since they can show their effects on mRNAs after the transcription of said mRNA, they usually locate downstream to transcription factors [51].

In the intrinsic pathway, p53 and BCL-2 families play an important role. MiRNAs can alter their expression to regulate the intrinsic pathway. As miRNAs regulate the levels of p53, this tumor suppressor actually has an effect on the miRNAs as well by functioning to regulate miRNA expression and maturation [52]. For an example of p53 regulating miRNAs and how its mutation can cause a change, we can look at miR-16 and miR-143. Their processing is dependent on the interaction between p53 and Drosha complex so if there is a mutation in the DNA binding domain of p53, their processing cannot be achieved and cell proliferation will be suppressed [45]. Activation of p53 is found to be increasing the expression of 30 or more miRNAs including miRNAs like let7a, miR-34a and miR-15a/16 which are tumor suppressors [53]. BCL-2 is an anti-apoptotic protein that is generally overexpressed in tumors. Three pro-apoptotic miRNAs, miR-24, miR-195 and miR-365, work to down-regulate BCL2 expression via their binding to BCL-2 gene's 3′ untranslated region [53]. With this interaction, pro-apoptotic miRNAs lead to apoptosis. Extrinsic pathway is also regulated by miRNAs. Some miRNAs were found to regulate TRAIL-induced apoptosis directly and indirectly [43]. miR-221 and miR-222 can be an example of this regulation since they are found to have altering expressions between TRAIL resistant and sensitive cells, resistant cells being the ones with up-regulation of these miRNAs [43]. Another example can be miR-200c since it directly targets FAP-1, a phosphatase that works to inhibit apoptosis [43].

An example to miRNAs with effects not limited to one site is miR-21. We can observe its effects on both non-small cell lung carcinoma (NSCLC) and diffuse large B-cell lymphoma (DLBCL). In NSCL, miR-21 effects apoptosis via its inhibition on PI3K/Akt/NF-kB pathway and also it is found that miR-21 targets apoptosis-stimulating protein of p53 (ASPP2) which is a protein that functions in tumorigenesis [54]. And it was found that in early-stage samples of NSCL cells, miR-21 expression was increased when compared to the control [55]. The experiments revealed that in NSCL cells, miR-21 down-regulation led to the repression of EMT signaling pathway, cell migration and invasion, and miR-21 inhibition led to triggering of apoptosis [54]. Both *in vitro* and *in vivo*, miR-21 inhibited PI3K/Akt/NF-κB signaling pathway and promoted caspase-dependent pathway of apoptosis. MiR-21 also is known to have high expression levels in B-cell lymphoma. In DLBCL, its effect on apoptosis can be seen via regulation of phosphatase and tensin homolog (PTEN). The expression level of miR-21 in patient samples was found to be more than the healthy samples, and these levels were also negatively correlated with expression level of PTEN [14]. Other miRNAs that have an effect on PTEN are miR-130 family. This family of miRNAs which corresponds to miR-130b, miR-301a and miR-301b, are found to have high expression levels in bladder cancer samples compared to normal ones. Via their regulation upon PTEN they also regulate focal adhesion kinase (FAK) and Akt phosphorylation, and lead to cell migration and invasion increase in bladder cancer. Experiments showed that the inhibition of this family causes down-regulation of FAK and Akt phosphorylation and this effects cell migration and invasion negatively, so it can be said that they have an important role in the progression of bladder cancer [56].

As it can be seen from the examples, the effects of miRNAs are diversifiable depending on the gene they are affecting or their expression level. The alteration of their expression leads to interchangeable role of miRNAs as oncogenes or tumor suppressors. Generally, the miRNAs that are down-regulated in the cancer tissues are considered to be tumor suppressors, as pro-apoptotic miRNAs they work for apoptosis to happen. miR-7, miR335 and miR-608 are examples of this type of miRNAs since they target BCL-2 family, and miR-203 and miR-143 can be other examples as they target PKC family [57]. On the other hand, other miRNA examples

can be seen as upregulated in the cancer tissues, as antiapoptotic miRNAs they induce apoptosis to allow uncontrollable proliferation. miR-197, miR-21 and miR-212 can be the examples of these kind of miRNAs [57].

Our current research based on developing target specific drug candidates over breast cancer cell lines. The array studies indicated that non-coding RNA hsa-miR-215 greatly enhance the inhibitor compound efficiency on MCF-7 and MDA-MB-231 breast cancer cell lines. The expression of hsa-miR-215 decreases in breast cancer cell lines compared to non-cancerous breast MCF10-A cell line. Over expressing this miRNA by transfecting into the cancerous cell lines drive the cells to apoptosis. Therefore, synergetic effect of the inhibitor compound along with hsa-miR-215 mimic augment anticancer treatment. A nanocarrier is being developed with hsa-miR-215 and inhibitor compound (patent pending). This formulation is designed for apoptosis-based therapeutic approach for breast cancer treatment. The utilization of carrier system along with miRNAs and inhibitor compounds introduced in this study for therapeutic purposes has the potential of clinical applications.

4. Future perspectives

Regulated cell death can be employed in cancer treatment since the apoptotic process can restrain survival of abnormal cells. miRNAs regulate distinct pathways and target the pathway's components. Cancer cells metabolic rate is higher and block apoptosis for survival strategy. Factors driving cancer cells to apoptosis can be used for treatment purposes. Recent advances in drug discovery and miRNA handling help these designs. Inhibitor compounds and miRNA-based therapeutics in oncology are promising and although face some challenges.

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