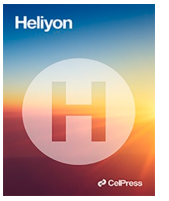
Heliyon 10 (2024) e23679

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Mutuality of epigenetic and nanoparticles: two sides of a coin

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ARTICLE INFO

Keywords:
Nanotechnology
Epigenetic
Epi-drugs
Nanoparticles
Drug delivery

ABSTRACT

Nowadays nanoparticles (NPs) due to their multidimensional applications in enormous different fields, has become an exciting research topic. In particular, they could attract a noticeable interest as drug deliver with increased bioavailability, therapeutic efficacy and drug specificity. Epigenetic can be considered as a complex network of molecular mechanism which are engaged in gene expression and have a vital role in regulation of environmental effects on ethology of different disorders like neurological disorders, cancers and cardiovascular diseases. For many of them epigenetic therapy was proposed although its application accompanied with limitations, due to drug toxicity. In this review we evaluate two aspects to epigenetic in the field of NPs: firstly, the role of epigenetic in regulation of nanotoxicity and secondly application of NPs as potential carriers for epidrugs.

1. background

Epigenetics is almost a new emerging science defined as somatic heritable modifications in gene expression that are not attended with modifications in the DNA sequence and comprise DNA and RNA methylation, histone changes epigenetics, regulation using noncoding RNAs, and nucleosome positioning [1,2]. Such epigenetic changes are associated with the emergence and progression of many medical conditions and diseases. A typical representation of DNA Methylation is Methylation at the C5 position of cytosine nucleotides (5-mC) which almost occurs on cytosine phosphate guanine (CpG) islands, by DNA methyltransferases, a decrease in CpG island occurs which is associated with transcriptional activation of DNA [3]. The main histone tail modifications are acetylation and methylation of histones H3 and H4 at lysine residues that can regulate gene expression by converting chromatin into an uncondensed active state or into a condensed inactive state non-coding RNAs can repress gene expression by two paths; MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [4]. They aim to silence genes by degrading target mRNAs or declining the efficiency of mRNA translation or identifying nuclear construction or remodeling chromatin, etc [3]. These epigenetic modulations have a crucial role in adjusting expression of genes in response to internal or external triggers [1]. Furthermore, epigenetic regulation include complex interacting structures that, together with the genetic information in DNA, enable sophisticated time and tissue specific control of gene expression, both in normal and pathological development have a profound impact on cell fate decisions [2].

Albeit it is broadly proposed that epigenetic mechanisms are mainly regulators of gene transcription and have the capacity to respond to environmental cue [3]. The role of individual epigenetic processes and their role in health and disease remain unclear [5].

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https://doi.org/10.1016/j.heliyon.2023.e23679
Received 12 June 2023; Received in revised form 26 November 2023; Accepted 9 December 2023
Available online 13 December 2023

However, comprehensive epidemiological investigations have shown that disease risk in adults is related to adverse environmental conditions in early development [5]. Heijmans and et al. [5] demonstrated that people who were before birth exposed to starvation during the severe Dutch Hunger Winter, less DNA methylation of the imprinted IGF2 gene compared to their not exposed, same-sexsiblings.

A limitation of present epigenetic medications is their cytotoxicity, owing to the everywhere expression of their targets. Consequently, a specific targeting of epi-drugs would be very favorable [6]. Undoubtedly, delivering a drug to the specific site of a disease is a big challenge in pharmacology. Actually, the small percentage of the drug reaches the target organ, and an even smaller percentage targets the selected cell type. The typical solution is to raise the dose of the drugs to assure adequate amount at the target organ [6]. One strategy to delivery drugs to target site is to employ NPs as delivery systems [7].

Turning to the nanotechnology, a wide variety of nanomaterial (NM) are produced and employed not just in industry, that can used

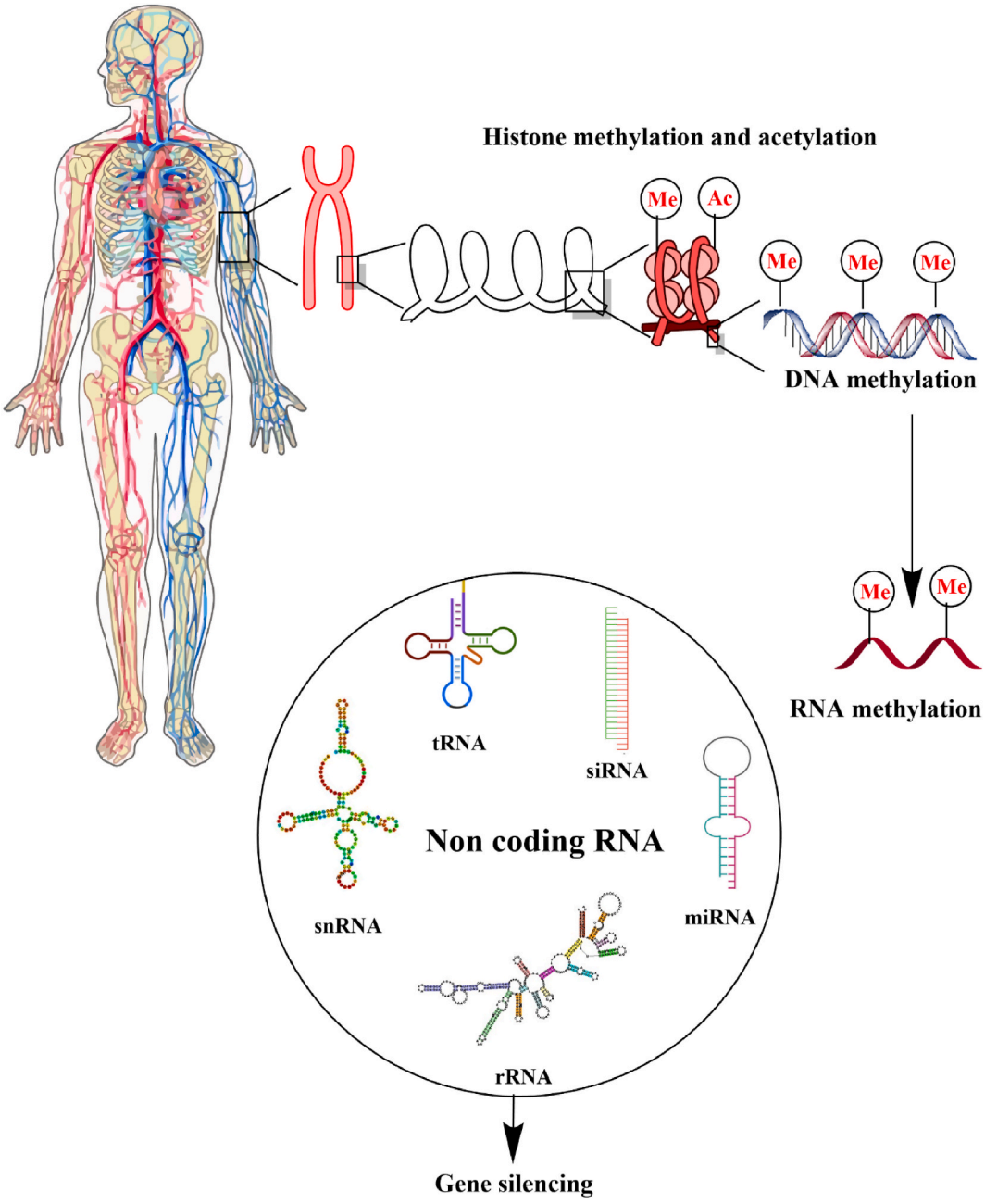

Fig. 1. The three main epigenetic mechanisms are DNA methylation, histone modifications (acetylation, methylation, etc.) and RNA (including tRNA, siRNA, miRNA, rRNA and snRNA) methylation. These three mechanisms are distinct but are interrelated and control gene expression.

in medicine, biology, pharmacology and everyday life. Several NPs are presently in usage or are being investigated for their potential applications as drug and gene transporter and for the production of biocompatible materials, also for medical monitoring, infection treatment, in vitro and in vivo diagnostics, and tumor therapy [8–10]. Due to this fact that the rise of nanotechnology has become an integral part of our daily lives our environment, recently, some online repositories, the Nano Database, Nanowerk, and StatNano list thousands of financially fabricated nanotechnology products [11,12].

Furthermore, NM display specific properties involving quantum size effect, quantum tunneling, small size and dielectric confinement, they owe specific physical properties including acoustic, optical, electrical, thermal and magnetic properties which cause them to be used in biomedical applications such as molecular imaging, targeted therapy, drug or gene delivery, and tissue engineering, and as immunological adjuvants (is a substance that enhances the immune system's response) [13]. Albeit, due to their ability to enter the human body through breathing and also transpire via skin, interrelate with intracellular structures consequently. Concerns about NPs potential toxicity to workers and the end user were so high that many studies have been conducted to evaluate their potential toxicity [12,14]. Due to the fact that usage of NM and NPs has become so prevalent these days, so many studies have been encouraged to evaluate the biological effects and toxicity of them on different organisms [15–17]. With the exception of epigenome (comprise of a record of the chemical modifications to the DNA and histone proteins), of which effects still need to be more investigated and researched in the field of nanotoxicology, because of their indeterminate and narrow outcomes, in addition to the various questions without definite answers [18]. Several studies have affirmed that environmental stimuli, including toxins, can contribute to a phenotype or a disease in an individual or even subsequent offspring through epigenetic changes [13]. Therefore, to assess the toxicity of NM or to diagnose diseases at an early stage, epigenetic biomarkers that correlate with exposure to NM are needed [18]. Moreover, because of the ever-growing application of NM in medicine, the study of their epigenetic changes in cells can provide another understanding of their therapeutic mechanisms. Evolution of NM epigenetics could assist us in two vital ways: firstly, help researchers who want to gain a deeper understanding of the potential destruction caused by NM and their therapeutic process. Secondly, guide end-users in choosing NM with good biocompatibility [19]. The connection between epigenetics and NPs is a relatively new field of study. In this study, we review two aspects of epigenetics and nanotechnology correlation. Present study explores the impact of NPs on epigenetic modifications and also NPs as specific targeting systems for delivery of epi drug for battling the current limitations which prevent their application, on the other hand with the aim of giving more comprehensive perspective about the utilization of NPs and their effects on the body.

The limitations of present study including: While the field of nanotoxicology is rapidly growing, the number of studies focusing on the epigenetic effects of NPs is still relatively limited. On the other, many studies exploring the relationship between epigenetics and NPs were performed in vitro or with animal models. While these investigations provide valuable insights, it is important to consider that human responses may considerably different that requires human studies. The purpose of this study is encouraging discussions among specialists about the improvements that the investigation of epigenetics in the field of nanotechnology can bring to both disciplines and to inspire young researchers to this fascinating technology.

2. Epigenetic mechanisms

Over the past decade we have witnessed an ever growing field of epigenetics that has brought about novel comprehension about gene expression mechanisms in normal as well as abnormal states [20]. Regulating of the impact of environmental elements on phenotype through transcriptional modulation, epigenetic phenomenon can change the processes have been found to be deregulated throughout underlying cellular events including the cell cycle, DNA repair and cell differentiation, causing in a range of human diseases (cancer, neurological diseases, and heart failure) and developmental disorders [1,2].

As its mentioned earlier, epigenetics involves inherited DNA regulation that cannot alter the DNA sequence although it might have an impact on expression of genes [2].

Surprisingly, epigenetic changes not only occur in disorders but also happen during several normal cellular processes, such as cell growth and differentiation. If DNA is like a hard drive containing the information to control every cell function, then epigenetic modulation acts like software, regulating DNA packaging to increase the potential of gene expression patterns. Epigenetic control directs the fate of cell types during embryogenesis and adult cell renewal [21].

The most common epigenetic mechanisms which have been reported so far are: DNA methylation, histone modification, and ncRNA -associated gene silencing and RNA methylation (Fig. 1) [22].

2.1. DNA methylation

DNA methylation is catalyzed by DNA methyltransferase enzymes and involves the direct addition of methyl groups to the fifth carbon of cytosine nucleotides within CpG sequences. It is often surrounded by other CpGs forming CpG islands. CpG islands, especially those within promoter regions, are common targets of epigenetic DNA methylation. In fact, approximately 70 % of gene promoter regions have been reported to reside within his CpG islands [22]. At the promoter region, Methylated cytosines can cause reduction in DNA and transcription factors by employing gene repressor proteins. Since methylation of the cytosine also promotes heterochromatin constitution, transcription machinery is prevented from DNA interaction by nucleosome condensation. Therefore, gene silencing happens by DNA methylation inside the promoter region. Hyper and hypo methylation of tumor suppressor genes and proto-oncogenes respectively, are caused usually by Cancers and both of them have a role in tumor oncogenesis [23,24]. Since, inasmuch, the process of active deamination (regulated by AID/APOBEC-family cytosine de aminases) can eliminate the methyl group of 5 mC and/or oxidation (mediated by ten–eleven translocation enzymes) of 5-methylcytosine which result in to the foundation of 5-hydroxymethylcytosine

that, in turn, is transformed to 5-formylcytosine and 5-carboxylcytosine, DNA methylation can be a reversible epigenetic mechanism [25]. Meanwhile, both of these adjusted bases through the base excision repair pathway are substitute with cytosines. In addition, declined 5-hydroxymethylcytosine levels and mutations which cause loss of function in TET proteins could possibly influence malignant transmutation [1]. It is noteworthy to say that, DNA hydroxymethylation can be considered as an epigenetic mark and when this regulation happens in the body and enhancer region of a gene, can enhance transcription, and thus has a crucial role in regulating transcription through development and also so many diseases including congenital abnormalities and heart disease, cancer and intellectual disability [3]. Furthermore, a hallmark of cancer can be aberrant DNA methylation, known as hypermethylation which is described as methylation of normally unmethylated CpG promoters and can result in inactivation of tumor silencer genes and thus as a potential indicator can be used for early diagnosis and prognosis of cancer [4,21]. In addition, genome-wide DNA hypomethylation, found in several cancers, can cause genome instability. For example 368 uniquely differentially methylated CpG region in BC tumors that recognized by De Almeida et al. [21] were compared with normal breast tissue. It was found that hypermethylated CpG region were mainly located in the upstream promoter zone (56 %) while hypomethylated CpG region found in the body of gene mostly (66 %) [21]. However, zones with low aggregation of CpG in many CpG island shores, which have common borders with traditional CpG islands (up to 2 kb apart) display unique subtype-specific methylation effects. Hypermethylation of more than 100 genes has recently been identified in breast cancer. They have fundamental roles in several process in cells including DNA repair (e.g. MGMT, BRCA1, MLH1), cell cycle modulation (e.g. CCND2, AK5, FOXA2), apoptosis (e.g. BCL2, APC), cell adherence (e.g. CDH1), tissue incursion and metastasis (e.g. RASSF1A, RARβ, TWIST, HIN1), and hormone-mediated cellular signaling (ESR1, ESR2 and THRB) [26].

2.2. Histone modifications

The next epigenetic mechanism is histone protein modifications, of which enzyme-catalyzed acetylation, methylation, phosphorylation, and ubiquitination are the most fundamental variations [1]. DNA-histone interactions in nucleosomes would be altered by all of them. To be more precise, nucleosomes are constituent components of chromatin which is a dynamic structure. Histones are cornerstone subunits of nucleosomes. These alkaline proteins form an octamer composed of two equal subunits, each of them consists of four histones: H2A, H2B, H3, and H4. The main part of the nucleosome comprises 147 bp. a DNA sequence wrapped around a histone octamer with almost two supercoils [27]. In general, post-translationally modulated at the amino acid residues in their C- and N-terminal ends, histones are proteins which remain highly conserved. Post-translational histone modifications (PTMs) can have an impact on gene expression by reconstructing chromatin from an uncompacted transcriptionally active situation (euchromatin) to a condensed passive condition (heterochromatin) but do not affect DNA sequence but can influence expression of gene [28]. Histone regulations happen on particular amino acid residues, which are located mostly on the amino-terminal tails of histones. So far, acetylation and methylation are the most examined modifications in histone acetylation that usually happens at lysine residues which are positively charged, to loosen the DNA and histone interaction, which can open up chromatin and facilitate transcription [26]. For instance, acetylation of histone 3 at 9th and 27th lysines (H3K9ac and H3K27ac, respectively) which are related to transcriptional activation [21]. Methylation of histone is more complicated which may contribute to the excess of 1–3 and 1–2 methyl groups to lysine and arginine respectively. This modification does not alter the charge of histone protein. For example, methylation of histone 3 lysine 4 (H3K4me), as an instance, is correlated with activation of transcriptional process, while tri methylation of histone 3 lysine 27 (H3K27me3) can suppress the mentioned process [27,28]. Increasing a negative phosphate group to the tail region of histone, named histone phosphorylation, plays a role in DNA damage response and following repair. However, its function is not well known as H2A. Various enzymes catalyze histone PTMs, such as histone deacetylases (HDACs), histone methyltransferases, demethylases, and histone acetyltransferases, which remove acetyl groups. At least 18 HDACs have been identified in humans and categorized into four sets. Molecular changes affecting the expression of enzymes which are involved in modifications of histone may also confer cancer development and progression [27–29].

2.3. RNA methylation

RNA methylation, including N6-methyladenosine, N1-methyladenosine, 5-methylcytosine, N7-methylguanosine, N4-acetylcytidine, and 2′-*O*-methylation are involved in cell proliferation, immunity, DNA damage, and calcium signaling which are novel epigenetic modifications [30,31]. M^6A is one of the most plentiful post-transcriptional RNA modifications in eukaryotes which was first identified in 1974. M^6A methylation results from the addition of a methyl group donated by S-adenosylmethionine to the N6 site of adenosine in the RRACH RNA sequence (R = purine, A = M^6A and H = A, C or U). On average, there are 1–2 M^6A mRNA residues per 1000 nucleotides [32–34]. M^6A RNA methylation is mediated by methyltransferases (METTL16, METTL14, METTL3, RBM15/15B, ZC3H13, KIAA1429, and WTAP), YTH domain proteins, or YT521-B homology (YTHDF1, YTHDF 2, YTHDF3, YTHDC1, and YTHDC2) and demethylases (ALKBH5 and FTO) and can affect a variety of biological processes, including mRNA processing or stability, gene expression, and regulation of functional proteins [32,35].

2.4. Non-coding RNAs (ncRNAs)

Another epigenetic mechanism which recently illuminated is noncoding RNA-associated gene silencing. To be more detailed, functional RNA molecules that are transcribed but not translated into protein are called ncRNA. Recent evidence proposed that ncRNA molecules play a vital role in epigenetic gene expression, although in the past thought to be a non-functional part of the genome. Despite this similarity in the encoded proteins, they are widely distributed between species and suggest that it is likely responsible for

the large phenotypic differences within human populations [36]. Noncoding RNAs can be categorized based on their length: short ncRNAs with less than 200 nucleotides and long ncRNAs with more than 200 nucleotides. MiRNAs, small interfering RNAs (siRNAs), and PIWI interacting RNA are considered as components of short ncRNAs. Small RNAs 19–25 nucleotides in length are currently the most studied compared to the other non-coding mRNAs (miRNA) [37]. Degradation or prevention from being translated to proteins by microRNAs may happen by combining 30 untranslated zone (30-UTR) of marked mRNAs and that can regulate expression of the gene. Thus, regulation of cell cycle including proliferation, differentiation, survival and death, can modulate by microRNAs as a more heterogeneous group of ncRNAs, called IncRNAs, may modulate gene expression through a variety of mechanisms and have been found to have vital functions in modulating growth process, cellular homeostasis, as well as pathogenesis [38]. With the exception of ncRNAs, which act on mRNAs in the post-transcriptional phase, DNA methylation and histone modifications, can control expression of gene by regulating chromatin structure and adjusting biological processes that are based on DNA including availability of transcription parts to promoters and transcription progress, which all of these epigenetic markers act in a coordinated manner in determining the transcriptional status of a gene in a very substantial way [3,4,39].

3. Epigenetic effects of NPs

Several experimental studies in vitro and in vivo have recorded a relation between cytotoxicity and epigenetic changes after exposure to particular NM and NPs, from them it can be concluded that epigenetic changes can be worthy indexes of NM and NPs toxicity and possible translational biomarkers to detect detrimental impacts of NM on humans [40]. Recent research is mainly related to DNA methylation and miRNA expression induced by nanostructures, researchs should not stop at this stage; more research to investigate the mechanisms associated with these genes in biological pathways should be needed [41]. Although the European Commission reported; NM must be in nano range (size range 1–100 nm) with a specific surface area greater than 60 m2/cm3, the term "NM" in nanomedicine is broader and includes particles with sizes up to 1000 nm. All three dimensions need to be in nanoscale range according to the definition of the International Organization for Standardization to be considered as a NM [19,42,43]. Albeit these different definitions and classifications provide a wide range of interpretations. Specifically, the possibility of having advantageous or possibly harmful effects of NM for the surroundings as well as human wellbeing according to their features; either chemical or physical including shape, composition, size, surface charge, and electron transfer [19]. Noxious impacts of NPs to which we are regularly exposed through the application of textile products, food packaging, dietary supplements, electronic devices, hygiene and cosmetic products, can lead to the production of reactive oxygen species (ROS) or to directly react with biomolecules comprising lipids, proteins and nucleic acids. The mechanisms of epigenetic toxicity induced by NPs is not well realized though, thus further investigation needs to be performed. So in the first step, lipid peroxidation, mitochondrial dysfunction, DNA damage and protein denaturation that are resulting from the overproduction of ROS may cause cytotoxicity and genetic toxicity [44,45]. The physicochemical components of the NPs (including size, shape, charge, chemical combination, solubility, and ability to create aggregates or agglomerates) as well as surrounding elements which may impact on their function and on the cell type that NPs expose with can determine the quantity of ROS which generated and its consequent cell destruction [42]. As an instance, smaller the NPs are with the same chemical composition, can have better reaction with biological molecules to generate reactive oxygen species. In the second step, the reaction of NPs with biomolecules changes the work of the cell membrane and organelles for example lysosomes, mitochondria or cell nucleus [38]. Regarding the cytoplasm, during the mitosis procedure or through the nuclear pores, NPs are able to penetrate via diffusion mechanism to the nucleus, inadvertently. In the nucleus, binding to DNA in a direct way or to nuclear proteins can disturb their performance [37, 38].

3.1. NPs and DNA methylation

Most studies that review the epigenetic effects of NPs evaluate DNA methylation [46,47]. For example, treatment of the HaCaT cell line (human epidermal keratinocytes) with silica NPs (SiO2 NPs) causes hypomethylation related with a decline in the expression levels of Dnmt1, Dnmt3a and NPs on the one hand MBD2, and on the other hand, increased DNA methylation in the promoter of the poly (ADP-ribose) polymerase (PARP-1) gene, causing its suppression. PARP-1 has a fundamental role in the primary cellular response to DNA destruction, and its inactivation resulted in the lack of stability in genomic and following apoptosis [48]. Suppression of PARP-1 has also been explained in treated adenocarcinoma cells with TiO2 which is another example of DNA methylation effects [2]. MRC5 lung fibroblasts which were treated with varying concentrations of titanium dioxide (TiO2) and zinc oxide (ZnO) NPs were also indicated declines in the global DNA methylation profile and in DNA methyltransferase activities (Dnmt1, Dnmt3a, and Dnmt3b). In contrast with that, treatment with NPs (fullerenes, multi-walled carbon nanotubes, single-walled carbon nanotubes) globally enhancement of methylation in DNA which happen in A549 human lung cells [19]. Furthermore, it has been proposed that multi walled carbon nanotubes induce toxicity of lung, which can advance inflammation by reducing methylation of the promoter TNFα, an important immune response gene, and also facilitate fibrosis initiation by methylation of the TNFα promoter [40]. And also, THY-1, a gene implicated in idiopathic pulmonary fibrosis. Eventually, hypermethylation of promoters of genes which encodes telangiectasia ataxia (ATM), cycle-dependent kinase and glutathione reductase, causing by administration of 60 nm gold NPs (AuNPs) intratracheally in BALB/c mice and on the contrary, in lung tissue hypo methylation in the glutathione peroxidase (Gpx) promoter. AuNPs can stimulate size and dose-dependent hypermethylation of the promoter zone of the tumor suppressor protein P53 as well (trp53) [19].

3.2. NPs and RNA methylation

The fundamental roles of M^6A RNA modification have been considered in several substantial cellular mechanisms, such as the fate of mRNA, the maintenance of stemness and even tumorigenesis, as a result of impressive discoveries in transcriptome sequencing of M^6A over the last few years [44]. According to recent studies, M^6A RNA modification is known to involve "writers", "erasers" and "readers", which is a dynamic process for adding or removing a methyl group. At adenosine and generally happens in the RRACH sequence of adenine. The "writers", "erasers" and "readers" involved in M^6A RNA change have been related to particular disorders [49, 50], including infertility, obesity, dysplasia and even cancer. Given its ubiquity in mRNA and lncRNA, further regulatory figures for M^6A RNA modulation as well as the discovery of supplementary M^6A -related proteins are expected [45]. The M^6A RNA modifications are considered steady and unaltered for a long period of time, due to the deficiency of M^6A -related proteins and the short half-life of most RNAs. This countdown was solved by discovery of the first authentic M^6A demethylase, a protein associated with fat mass and obesity (FTO) and exhibited that M^6A RNA transformation is a dynamic process tightly regulated [44]. Study of nephrotoxicity of black phosphorus quantum dots (BPQDs) has shown remarkable endoplasmic reticulum (ER) stress and insulin sensitivity caused by BPQD in the kidney. Moreover, on the investigation of lung cells exposed to BPQDs, M^6A level elevation was found in lung cells [48]. There is also evidence of relation between abnormal increase of M^6A level and a malefic expression of genes which are responsible for ferroptosis engaged in ER stress, iron homeostasis and iron homeostasis. These genes are verified by evidence of iron overload, lipid peroxidation, GPX4 down regulation and glutathione evacuation [51]. Another study revealed that Carbon black NPs CB exposure can influence some organs such as reproductive system and lung. In CB induced pulmonary fibrosis, the PI3K–AKT–mTOR pathway can be activated by declining the M^6A level of pri-miRNA-126 and it's binding with DGCR8 [44]. Furthermore, another study has claimed being in contact with CBNP pending gestational period affects maternal behaviors and causes unusual neuro behaviors to a limited extent and the progress of the reproductive system in next generation, all of which have correlation to decreased level of M^6A RNA modification [51,52].

3.3. NPs and histone modifications

DNA packaging strength depends on other epigenetic markers collectively known as histone modifications. There are many types of these chemical markers (acetylation, methylation, and phosphorylation), all of which alter the amino tails of histones, altering the degree of tightness or weakness of DNA packing [8]. Generally, a gene can have access to the transcriptional machinery of cells only when the envelope is lost, on the contrary, in the presence of a tight envelope gene cannot be available and so less expressed [3]. NPs can regulate different cellular mechanisms according to the site of the affected chromatin when penetrate into the cell nucleus; although NPs can only have a slight effect on euchromatin (is a lightly packed form of chromatin and enriched in genes) regulation, heterochromatin-induced NPs modifications lead to marked nuclear shrinkage [37]. The effect of nanoscale materials on post-translational changes of histones has been many fewer studied than their influence on DNA methylation. Nevertheless, some primary investigations propose that histone modification is also an important molecular target for different types of NPs [35]. As an instance, recently it was shown in one study that the cells' nuclei of human breast cancer undergo condensation of chromatin and total histone reductions in acetylation after being treated with quantum dot cadmium telluride, a present NPs which are being considered as potential tools for diagnosis, treatment and imaging [40]. Global reduction of histone H3 acetylation and decreased transcription of MCF-7 cells gene can happen after 4–24 h treating with cadmium telluride quantum dot. Interestingly, treatment with quantum dots increases the several apoptotic genes' expression via p53 activation [53]. Regarding silver NPs, they have also been recently suggested that can have effect on histones at post-translational level. Application of these compounds are remarkably increasing in a variety of arenas and can be considered as properties of antibacterial coatings, antistatic materials, superconductors, and biosensors. Silver NPs when penetrated into the nucleus can have effects on different enzymes such as histone deacetylase which are engaged in remodeling of chromatin [54]. Recently it was demonstrated in a study that sub lethal concentrations of silver NPs in red blood cells caused a decline in hemoglobin concentration in Rats, possibly due to decreased H3K4me3 and H3K79me1 methylation. Although the underlying molecular mechanisms were not fully unknown, later published data from that study proposed that this effect may be regulated by particular methyl-converters that inhibit histones or even by the association of silver NPs with histones H3 and H4 [19]. Micro and NM topography are used as a scaffold for biological and medical applications and appear to influence cellular epigenetics, notably via histone changes [37]. Moreover, it is more efficient to reprogram vegetative cells into pluripotent stem cells using biotechnological substrates. In support of this view, cell differentiation and reprogramming were shown in a recent study that can be regulated by cell substrate topography. Adoption of methods is still unknown. The molecular mechanisms, the microscopic groove surface leading to increased acetylation and methylation of histone H3, are believed to have a crucial role in the modulating of differentiation and reprogramming process of cells [55]. Disposal to cadmium telluride quantum dots (QD) for a short period of time induces global down regulation of MCF-7 histones and following chromatin compaction in human MCF7 breast cancer cells [56]. Treating with a histone deacetylase (HDAC) inhibitor, trichostatin A, histone regulation was reversed. Albeit, it remains unclear whether histone acetylation is a consequence of this NP's direct effect on the specific mechanisms involved in histone acetylation. Interestingly, silver NPs (AgNPs) significantly reduced the overall level of histone H3 methylation in red blood cells by attaching to histones H3 and H4, which found to catalyze H3- and H4 in mouse and prevent methylation [57,58]. In addition, treating with gold NPs (AuNPs), human small airway epithelial cells exhibit a decline in tri methylation of lysine 27 on H3K27me3. With regard to histone phosphorylation, AgNPs can induce histone H3 phosphorylation on serine 10 (H3S10) in human lung adenocarcinoma cells A549, leading to full cascade activation by NPs which release MAPK by Ag ions [59]. The previous investigations studied the effects of NPs on a single epigenetic regulation while, there are others that aim to examine the impacts of NPs on the modification's crosstalk

histones [59]. Arsenic trioxide NPs (As2O3 NPs) were found to cause decreased H3K9 and increased H3K9 in human prostate cancer cell lines (LNCaP and PC-3) [60]. Furthermore, HaCaT cell line that was treated with zinc NPs (ZnO NPs), not only induced cell cycle arrest at the G2/M checkpoint, but also resulted in an increase lysine 9 dimethylated (H3K9me2) of histone H3, while reducing histone H4 acetylation of lysine 5 (H4K5), identifying an epigenetic marker involved in condensation of chromatin [49,61]. Accompanying by increased expression of two histone methyl-transfer enzymes, G9a and GLP, that catalyze mono- and di-methylation of histone H3 lysine 9, these epigenetic alterations regulate decreased expression of various acetyl histone transducers including GCN5, P300 and CBP. Such epigenetic variation may result from the generation of ZnO NP being concentrated in the peri nuclear zones that may interact with the nucleus in a direct way by disrupting its structure or producing ROS by this set [49].

3.4. Effect of NPs on non-coding RNAs

A study performed on PC12 neuronal cells exposed to supermagnetic iron dioxide NPs (SPION) a widely used material for the purpose of magnetic resonance imaging, revealed a remarkable alteration in the expression of several miRNAs in cells. This study demonstrated that microRNAs repress the expression of the N-methyl-D aspartate receptor and vital genes involved in neuronal plasticity, growth and survival, and their suppression induced apoptosis in neuronal cells [62]. Treatment with TiO2 NPs induced considerable down regulation of miRNA-21 and miRNA-30a, in human lung cells A549, important regulators of autophagy, while the treatment of NIH3T3 mouse fibroblasts using CdTe quantum dots were able to induce notable modifications in the expression of 51 miRNAs, of which 16 were down-regulated and 35 up-regulated [49]. Evaluation of the in vivo effects of NPs on miRNAs has been performed by a considerable number of studies [63]. As an instance, noticeable changes were illustrated in the expression of 16 miRNAs in the lungs by exposing adult mice which were female C57BL/6BomTac to surface-coated titanium dioxide NPs (TiO2 NPs). Among them, miR-1 was up-regulated 6-fold, miR-449a 2.6-fold, and miR-135b 60-fold in comparison with mouse not exposed to NPs [51]. It has also been shown that 100 nm gold NPs (AuNPs) can cause altered expression of so many miRNAs (e.g., up regulation of Let-7a and miR-183) in the livers and lungs of mouse fetuses [64]. There are also other studies which have indicated that certain NPs can induce changes in the levels of certain miRNAs in the blood, proposing that, based on circulating content, they can be considered as markers of biological toxicity for this NP [48]. Mice gold NPs induce a time-dependent change in miRNA expression patterns in blood cells and the treatment of mice with 70 nm SiO2 NPs (nSP70) induced liver injury along with an elevation in the number of two liver-specific miRNAs (miR-122 and miR-192). Because miR-122 levels differed more than miR-192, and because the sensitivity of this miRNA to liver damage was consistent with other markers of this abnormality, it has been suggested that miR-122 might be a novel indicator of damage in liver caused by SiO2 NPs and other NM [65]. Moreover, to the best of our knowledge, studies on the influence of NPs on chromatin reconstructing multiplex have not been conducted to date, while investigation on the epigenetic impacts of NPs on deregulation of non-coding RNAs, and on microRNAs specifically, are growing [66]. Silver NP (AuNP) treatment was found to alter the expression of 63-miRNAs in human T-Jurkat cells [6]. Among them, miR-504, miR-33, and miR-302 might play a role in regulating damage of DNA and apoptosis caused by these NPs. PC12 neuronal cells exposed to super magnetic iron dioxide (SPION) NPs were investigated in a study, a material commonly used to perform magnetic resonance imaging, and a considerable modifications in the expression of several miRNAs in cells was witnessed [67]. Thus, managing the functional significance and recognizing epigenetic changes caused using different types of NP (as biomarkers) are significant challenges for the future [47].

4. Epigenetic therapy

At the molecular level, epigenetics involves a series of extremely complex and dynamically reversible structural regulations in the nucleosome components such as nucleic acids and histone proteins [4]. These chemical changes are catalyzed by enzymes, often called writers that add entities of varying sizes, from single methyl groups with molecular weight 15 Da to proteins such as ubiquitin with molecular weight 8.5 kDa. These molecular decorations can directly affect the affinity between DNA and histone proteins, and attract partner macromolecules such as ncRNAs and chromatin remodelers as well [68]. Conjuncting interactions are governed by so called "reader" domains that identify particular characteristics of modified nucleic acids and proteins, chemically. Last but not least, to certify the reversibility of the process, a series of “eraser” enzymes catalyze the deletion of recorded information, warranting a dynamic trait [69]. Etiology and progression of a variety of illnesses, comprising developmental diseases, cancer, neurological diseases, and cardiovascular disease (such as heart failure and atherosclerosis) can be related with alterations in epigenetic mechanisms. For instance, the loss of methylation in the heterochromatin zone of DNA in cancer cells leads to either loss of chromosomal stability or stochastic expression of the context of these regions of genes [70,71]. These two phenomena, which underlie tumor cell heterogeneity, are among the basic reasons of tumor resistance to chemotherapy. Turning to neurological diseases, engagement of epigenetic processes in different perspectives of the progress of these diseases has been described: Mutations in epigenetic components can stimulate multiple neurodevelopmental disorders. A severe neurodevelopmental disorder that primarily has an impact on females occurs when mutations in the encoding gene of the methyl-CpG binding protein happens [64]. These mutations mediated by exposure to environmental risk factors and RETT syndrome, can be considered as the best example of neurodevelopmental disorders [72]. Eventually, recent discoveries have demonstrated that there are so many different fundamental epigenetic phenomenon that contribute to cardiovascular disorders: in heart failure, the transcriptional program underlying cardiac hypertrophy results from changes in the epigenome, and with the same situation, in atherosclerosis, epigenetic damage may be involved in the development and progression of atherosclerosis with plaques [65]. Owing to the reversible nature of the epigenetic mechanisms, several therapeutic strategies have been suggested for many of these diseases according to the concept that epidrugs can disrupt the epigenetic alterations responsible for the disorders by recovering the correct epigenetic prospect in diseased cells [3,64]. However, the use of these drugs has been suggested to treat a range

of diseases, Including: DNA methylation inhibitors, histone deacetylase inhibitors and histone methyltransferase inhibitors [62,73]. One of the great distinguishing characteristics of epigenetics is the fact that, unlike genetic abnormalities, epigenetic modifications are reversible, allowing the function of affected genes to be restored with a normal DNA sequence. Aim of these treatments are to reprogram cancer cells into a more normal state. During normal development, the epigenome is mobile, allowing for changes in cellular phenotypes from the embryonic to the differentiated state [30]. Regarding to cancer, aberrant epigenetic states can help lock in cellular states that exclude the ability of cells to abandon self-renewal and differentiate normally. As an instance, during colonic oncogenes is, the cells of the crypts of the colon retain a more primitive, embryonic cell type. These stages of reprogramming likely develop over many years after cancer onset and progression [74]. The potential to reverse epigenetic changes began in the late 1970s with the discovery of drugs that reverse DNA methylation. However, these drugs only became established in clinical studies in the 1990s, especially in the treatment of hematological malignancies and in particular the preleukemic myelodysplastic syndrome [75]. Their effectiveness was demonstrated when doses of epigenetic drugs were reduced, improving patient tolerance and possibly the specificity of reprogramming. DNA demethylating agents are currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS, and there is ongoing evidence that lower doses of the drug are effective in treating solid tumors development of many new epigenetic therapeutics are due to dramatic progress in our understanding of epigenome legislation [68]. The most important ones are resistance in both forms of primary and secondary as well as rare reactions in solid tumors. Lack of specific target site and non-chromatin effects are also major disadvantages of traditional epigenetic preparations. In order to dominate these issues, identification of more effective approaches for searching epigenetic drugs and to progress combination therapies in an effective way for existing drugs it's necessary [76]. In the past decade, several epidrugs have received USFDA approval for the treatment of blood-borne cancers: 5-aza-2′-deoxycytidine, 5Azacytidine, Belinostat, Vorinostat, Panobinostat, Romidepsin, and Hidamide [13]. In addition to the drugs mentioned above, chidamide, an anilide type HDAC inhibitor, has also been approved using China Food and Drug Administration (CFDA) to treat patients with refractory Peripheral T-Cell Lymphoma [77]. Albeit, with the exception of one FDA approved drug, tazemetostat, in 2020 for locally advanced or metastatic epithelial sarcoma, there are no approved epigenetic therapies for solid tumors, which have more complexity in their epigenetical structure. In addition, they demonstrate abnormal angiogenesis, tumor-specific microenvironment, and more differentiated cells with reduced reprogramming in epigenetic field. The logical discovery of epi drugs using confirmed targets is a recent phenomenon [13]. Primarily, knowledge about molecular targets was not so extended to help improvement and advancement of epi drugs, hence efficacy and phenotypic witnessing were two factors that were implicated [78]. To be more detailed on the feature of epi drugs, the impact of the environment on the epigenetic genome has intriguing and profound implications for public health: the fact that an individual's behavior can affect the next two generations are rarely taken into account. The implications for environmental factor research, especially in common case-control studies, are enormous [55]. Likewise, if environmental factors can influence susceptibility to disease, then treatments (after all, environmental factors themselves) can also change disease progression [54]. Due to the plasticity and the reversible nature of epigenetic changes can be considered as promising potential drug targets for anticancer therapy, as they enable repair of the cancer epigenome [44]. Epidrugs can be categorized based on the enzyme of the target [56]. Considering limitation of epigenetic therapy, potential disadvantages of many epidrug due to ubiquitously expressed of targets. In addition to that some epidrugs have low bioavailability, poor stability, and short half-lives. Regarding suberoylanilide hydroxamic acid as an instance, also known as vorinostat, is a potent HDACS class I inhibitor that is used to the treatment of cutaneous T-cell lymphoma. It cannot be neglected that, its limitations due to poor solubility and permeability reduce its clinical application [57]. Battling these problems "smart epi drugs" can be generated, on the one hand, are able to release (figs just in cells which get involved in disease process and, on the other hand, improve their pharmacokinetics. In the "smart foreign drug" generation, potential improvement can appear in the area of NP [48]. Indeed, in recent years, many biocompatible NPs have been developed with physical and chemical properties that make them capable of delivering drugs to the desired site and controlling diffusion of drug and lunch them. These NPs immobilize the drug on their external layer or inside of themselves, and thus preventing from premature activation. To achieve this aim application of NPs for this reason could also improve the pharmacokinetics (including absorption, distribution, metabolism and elimination) and the drug specificity, declining the quantity of drug needed and detriments of the drug [59].

4.1. Nanotechnologies as a promising strategy to epigenetic therapy

Nanomedicine implements the conception of materials science and nano biotechnology to healthcare so that enhance the whole steps involved in a therapeutic process from diagnosis, imaging, monitoring, prevention to treatment efficacy and safety as well as recovery [50]. In first step, despite ever increasing advances, application of epigenetic in medical field still encounter many challenges. Lack of specificity for particular target bring about side effects with consequent high level of substance toxicity and not being able to elicit a reaction for a long period of time. Furthermore, the low solvability and permeability of these epigenetic agents and their lowly pharmacokinetic properties, including lack of stability and bioavailability, pose remarkable disadvantages for their broader clinical use [69]. Therefore, to realize the clinical capacity of these drugs completely, it is very important to purify target specificity and enhance drug stability and delivery efficiency [2]. In second step, delivery systems in nano size scale and prodrugs could prevail some of the clinical limitation of current epigenetic drugs as they can prevent them premature hydrolysis, increase bioavailability, and enhance cellular penetration and tumor delivery [2,3]. Second generation nucleoside analogues (demethylating elements) are currently being tested to cover stability and selectivity obstacles [35]. The therapeutic efficacy of demethylating agents can be improved by Nanoscale delivery systems. NP delivery systems can be designed to prevent demethylating drugs degradation, in order to enhance permeability and target specificity, and minimize disadvanteges [37].

4.2. Nano materials for drug delivery of epi-drug

NPs must be in the range of 10–200 nm in size in order not to be eliminate by kidney or following uptake by spleen and liver pre maturely in systematic administration. All biomedical NM have these imperative properties: biocompatibility and low level of systematic as well as immunological toxicity and in order to be approved by FDA for clinical use, they must undergo extensive preclinical and clinical trial so that their biosafety is confirmed [40]. Preclinical studies have shown some evidences that encapsulation of existing epidrugs in various formulations enhances stability and improves targeted delivery while minimizing side effects. Currently, the range of nano-based delivery systems is expanding. Liposomes, solid lipid NPs, polymeric NPs, polymeric micelles, dendrimers, nano-emulsions, and polymer-lipid hybrid NPs were used as targeted drug delivery vehicles (Fig. 2) [79]. Nanostructures were frequently used to encapsulate low-soluble drugs with poor absorption capacity to reach controlled and sustained drug release. Nevertheless, the effectiveness of these drug-delivery systems relies on diverse factors such as their shape, size, surface properties, hydrophobicity and other biophysical and chemical characteristics. NMs show improved biocompatibility; biodegradation properties are regarded ideal drug delivery strategies for medical applications [80]. Epigenetic agents have the potential to be highly effective treatments for a variety of diseases, especially cancer and neurological disorders [59]. Although the usage of NM for medical purposes has unique benefits, the potential health hazards are not well understood at this time. Their potentially wide biomedical application reflects the growing need to assess their health effects prior to use nowadays, polymer-based NPs, lipid-based NPs, and inorganic NPs. Are the most commonly used NPs as drug delivery systems [48]. Although these NPs provide sustained and controlled drug release, some of them, like liposomes, are usually easily identified by the reticulo-endothelial system and therefore removed, a major disadvantage [81]. Entering in an organism, the NPs become concealed with a variety of proteins, such as opsonins, that change their properties and make them easier to remove [44]. Therefore, it is crucial that drug delivery systems remain circulating for extended periods of time without opsonization and hence phagocytosis. Achieving this aim, a number of coatings have been expanded recently that can prevent NPs from being opsonized, permitting them to avoid the immune surveillance system and enhancement half-life from the bloodstream [49]. These coatings can be divided into two classes: artificial polymers (such as PEG, POX and polywitterions) and “self-labels” (e.g., CD47). NPs to tumors using abnormal vasculature of the tumor and the lack of a normal lymphatic system (increased permeability and retention - EPR effect), creating Nanodrugs which are smaller than 200 nm it’s essential for optimal implication of the EPR effect in

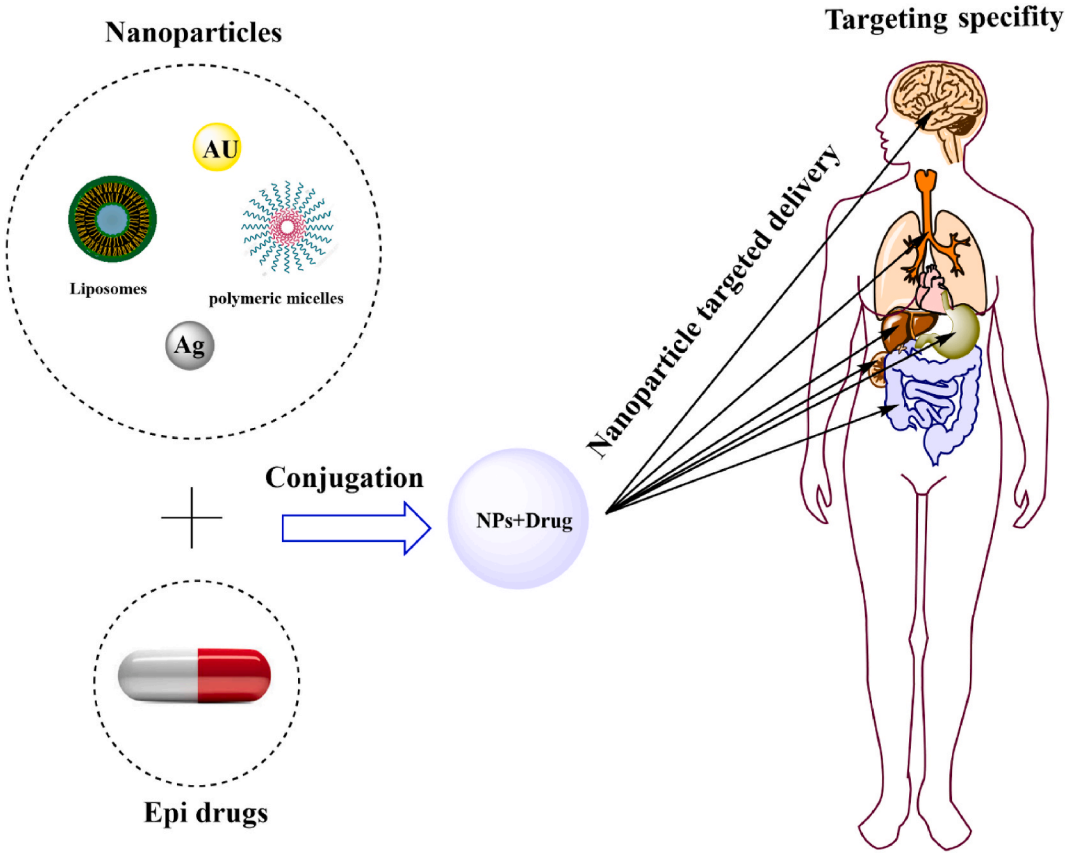

Fig. 2. Schematic diagrams of various nanostructure, including liposomes (a small artificial vesicle, spherical in shape, having at least one lipid bilayer), metallic NPs (Ag, Au, etc.) and polymeric micelles (Self-assembling nanoscopic core-shell structures of amphiphilic block copolymers) can be used for targeted drug delivery of epi-drugs.

tumors, due to this fact that the large NPs can't pass through the windows of tumor vessels. So the size of the nanodrug is very important for permeation in the tumor [56,57,59] turning to other side of the coin, nanodrugs with the size of 6 nm or smaller, are easily eliminated from the circulation for renal excretion without time to act at the tumor level [55]. Accordingly, the physicochemical features of NPs are very fundamental for efficient drug delivery to the site of interest as well as ensuring controlled release. As an instance, polylactic acid NPs (PLA) that have been suggested for topical treatment of skin disorders as a drug delivery agent: PLA NPs are destabilized upon contact with sebum and therefore release their charge particularly at the level of hair follicles and sebaceous glands [82]. Magnetic NPs are another example for deliver a drug to a particular tissue when affected by a disease utilizing a magnetic field [83]. Dimer captosuccinic acid (DMSA)-coated magnetic NPs used for activation and infiltration tumor-specific T cells and macrophages in tumors. Implementing this delivery system for the first time was demonstrated that can stimulate inhibition of tumor angiogenesis [84]. Using mentioned NPs in an external magnetic field in a mouse models with cancer study that were targeted to tumor tissue, showed an increase in the level of IFN-γ release at the site of the tumor in comparison with what was discovered in mouse treated with non-NP-conjugated IFN-γ: leading to a more effective anti-tumor immune response and a significant reduction in tumor progression [85]. Another interesting category is inorganic NPs have been used as nano delivery for epi-drugs. An instance for these kinds of NPs is polyethylene glycol-conjugated gold NPs can transport and release some HDACs (vorinostat) into tumors, resulting in decreased tumor growth. The advantage of these nanocarriers is that they easily cross the endothelium, which allows the drug to diffuse quickly via the bloodstream [86]. Furthermore, it has been found that the SiO2 NPs MCM-41-VOR and MSMs can have a remarkable effect on enhancing the solubility and permeability of vorinostat, and this effect would be even more in combination with especially when combine with amino and phosphonate groups [87]. Analyzes performed on colorectal (HCT 116) and cutaneous T-cell lymphoma (CTCL) cell lines demonstrated that the drug encapsulating the drug in amino-functionalized SiO2 NPs caused boosted antitumor performance than the free drug [88]. These days cancer treatment occupy golden position in the medical use of nano-products, with the several scientific articles and product approvals with regulatory organizations [55]. Traditional cytotoxic therapy of cancer which usually has two disadvantage, firstly poor therapeutic efficacy and secondly elevated systemic toxicity [55]. Chemo-therapy substances can cause common symptom by affect rapidly dividing non-cancerous cells as well as systemic toxicity such as cardio toxicity, neurotoxicity, nephrotoxicity by drug-specific diseases side effects. Turning to the next issue, various guarding mechanisms against the effects of chemotherapy which are toxic in tumor cells the most important of which is multidrug persistence due to overexpression of ATP-dependent drain pumps with broad drug specificity [60]. NPs as innovative materials and because of their incomparable components can be considered as possible vehicles for standard and experimental anticancer drugs, that have several advantages [59]. They allow encapsulation of hydrophobic and lipophilic molecules, and consequently improving their pharmacokinetics and circulation time in the body, resulting in elevated aggregation of the drug at the location of tumor due to inactive selecting by the EPR effect. In addition, they can be binded to specific ligands in order to bypass biological barriers and carry a high quantity of drug to the selected tissue through active targeting. They also induce steady and controlled diffusion of the drug caused by pH, temperature, redox potential, etc [49].

4.3. Nano materials for combination therapy of epi-drug

It has also been reported that NPs increase the selectivity of current epigenetic drugs. Indeed, due to the ubiquitous expression of epigenetic enzymes, one of the main restrictions of therapy with epigenetic drug, toxicity, can occur. A promising strategy to prevail this issue and to achieve greater therapeutic benefit seems to be compound therapy with epidrug-loaded NPs and either a chemo-therapeutic encapsulated nanocarrier, standard free anticancer drugs, or the co-packaging of epidrugs and anticancer drugs in a single nano component platform [49]. The combination of NPs loaded with epigenetic targets and a chemotherapeutic agent is emerging as an ideal approach to reach more significant therapeutic benefit and reduce side effects [62]. The development of epigenetic drugs capable of simultaneously inhibiting two or more epigenetic enzymes, which are therefore unregulated in diseased cells, might be a potential goal for the development of selective epigenetic drugs for disease pathways. NPs can be used in combination with different epi-drugs to enhance their therapeutic influence and selectivity [6]. For example in One study decitabine (DAC), an inhibitor of DNA hypermethylation, as a cancer drug was combined with doxorubicin (DOX) to improve upon composition of the two drugs with biodegradable MPEG-b-PLA NPs to obtain NPDAC and NPDOX respectively, can be considered as a proof of concept for this strategy [89]. Introduction of these NPs into the MB-MDA-231 xenograft mouse model demonstrated that they could carry these drugs to the transplanted breast more efficiently, thereby contributing to the inhibition of breast cancer cell growth by inducing tumor cell apoptosis. The potential to combine more than one drug in a NP has enabled the development of nanocarriers that can carry a compound of epigenetic drugs in combination with a drug of a second type (e.g., a cell cycle progression inhibitor) to boost their therapeutic effects [90]. As an instance, the drug paclitaxel (PTX), which was used for the treatment of ovarian cancer as a chemo-therapy drug, at the present time, has some resistance-related limitations due to activation of the EGFR/ERK mechanism. Overcoming this obstacle, NPs that carry PTX and miR-7 at the same time, inhibitors of the EGFR/ERK pathway, were developed. Anti-oncogenic effects of DOX: miR34a inhibit the expression of resistance-associated genes and BCL2, a pro-oncogene with anti-apoptotic activity [91]. Another example is the combination of DAC and arsenic trioxide (ATO) that is shown to boost each other's effect in the treatment of MDS. The co-packaging of DAC and ATO into bone-targeting alendronate-conjugated NPs (BTNPs) simultaneously compounds the benefits of both polymeric NPs and liposomes to provide regulated and tissue specific release of co-delivered drugs. BTNPs consist of a poly (D,L-lactide-*co*-glycolide)-cholesterol polymer that releases drugs in a governed manner, within an alendronate-PEG lipid envelope that targets the bone marrow [49]. Substances that exhibit limited tissue penetration or are rapidly turning to passive phase, can use red blood cells, as safe and biocompatible carriers. An instance is erythromagnetic hemagglutinin virosomes (EMHV), an erythrocyte-based system for delivering drug that compounds super paramagnetic NPs with a heme-agglutinin fusion protein that has

been employed as a carrier for 5-aza-2′-dC [62]. The magnetic character of this delivery method makes them a very tissue-specific carrier with high selectivity, in an external magnetic field, while the presence of a fusogenic glycoprotein on the EMHV membrane allows for efficient intracellular drug release [67]. Using the EMHV delivery method, the pharmacokinetics/pharmacodynamics of decitabine significantly improved in mouse prostate cancer xenograft models and enforced a remarkable decrease in tumor mass at much lower concentrations compare to its typical medicinal dose [64].

5. Conclusions

Nanoparticles have the capacity to be utilized as epigenetic therapy; however, some nanoparticles can also have toxic properties for epigenetics. On one side, the assays commonly employed to determine toxicity are not able to evaluate latent nanotoxicity. The need for more research on the mechanisms of the toxicity of nanoparticles, such as whether the changes it causes have a direct effect on DNA or miRNA. There is still a need for deeper research in this field to make better use of nanomaterials. On the other side, NPs are appearing as potential carriers for epidrugs. Nevertheless, the nanocarriers currently known for epi-drugs are exclusively available for different kinds of cancers and have low selectivity. Thus, there is a critical requirement for nanocarriers competent of delivering epi-drugs with more significant selectivity, and to cells involved in different illnesses, where the medicinal potential of epigenetic therapies has been demonstrated (for example, neurological and cardiovascular diseases).

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Maryam sanei: Investigation, Resources, Writing – original draft, Writing – review & editing. **Bagher Amirheidari:** Supervision, Writing – review & editing. **Naghmeh Satarzadeh:** Investigation, Project administration, Software, Writing – review & editing, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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