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EXPLORING THE INTERPLAY OF EPIGENETICS AND NANOTECHNOLOGY IN OPTIMIZING STEM CELL THERAPY FOR TISSUE REGENERATION

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ABSTRACT

Stem cell therapy offers promising effects in tissue regeneration and respective functional restoration. Particularly, in regenerative medicine, it is a transformative approach. However, despite its therapeutic potential, its translation in clinical setup faces several challenges such as tumorigenicity, poor cellular retention and ineffective differentiation. To address those limitations, alternative approach has been studied since decades by integrating it with nanotechnology and epigenetics. Nanotechnology holds promise in regulating stem cell microenvironment aided by tailored nano surfaces. Moreover, nanostructures offer effective real time monitoring of therapeutic output and the development of precise medications. Nanostructured cargos can deliver specific therapeutic compounds owing the potential to inhibit and promote respective stem cell differentiation, making it more precise. Integrated epigenetic modifications also offer therapeutic applications by regulating gene expression without making any changes in DNA sequences. Primarily studied modifications such as DNA methylation and histone modifications reported to offer effective result in cellular reprogramming, stem cell differentiation and survival. In regenerative pharmacology, reprogramme a cell to become an induced pluripotent stem (iPS) cell can be done by transcription factors, mRNA, proteins, or small compounds. CRISPR-based editing creates genome-wide reprogrammable transcriptional memory and shows potential for therapeutic gene editing. This review explores novel strategies such as CRISPR-dCas9-based reprogramming, epigenetic modulators, and gene regulation mediated by nanoparticles. Associated challenges with clinical translation, epigenetic stability, and nanomaterial toxicity were also discussed. Advances in stem cell therapy, personalized regenerative medicine, and more potent treatments for degenerative diseases could be made possible by the multidisciplinary synergy between nanotechnology and epigenetics.

Keywords: *Epigenetics, microenvironment, nanotechnology, regenerative medicine, stem cell therapy, tissue regeneration, tumorigenicity.*

1. INTRODUCTION

Recent studies put light on the importance stem cells to encourage tissue repair and regeneration. Stem cell-based therapies proved to be effective in treating chronic wounds and accelerating healing process by releasing growth factors and cytokines [1]. Advancements in understanding the mechanisms of differentiation in stem cells laid the foundation for targeted therapies [2]. Stem cell therapy in tissue regeneration is a transformative approach to treat several diseases. Stem cells in practical applications face certain challenges. Firstly, the potential of stem cells to convert into tumor, referred as tumorigenicity. Secondly, transportation of these delicate cells required proper handling and specific physiological condition e.g. temperature for preservation, lastly, low retention and restricted differentiation is the main hurdle. Nevertheless, integration of stem cells therapy with advance technologies such as epigenetics and nanotechnology offers great results in improving its therapeutic application [3]. The term nanotechnology refers to the use of nano-scale material in various fields of science and engineering, particularly in treating cancer. [4]. Although chemotherapy is frequently used to treat cancer, but there are associated side-effects such as poor solubility, toxicity, and lack of selectivity. By utilizing tumor-specific mechanisms like Enhanced Permeability and Retention (EPR) effect and targeted delivery of drug increases the efficacy by regulating release rates and minimizing side effects [5]. Nanotechnology can influence stem cell differentiation through engineered nano surfaces mimicking the extracellular matrix (ECM). These surfaces can guide stem cells biochemically for specific differentiation, enhancing regenerative potential [6]. Furthermore, NPs can deliver epigenetic modifiers to alter expression patterns of gene in stem cells, promoting to activate or deactivate desired differentiation pathways. Real-time stem cell tracking can be made possible by the applications of NPs. Superparamagnetic iron oxide nanoparticles can be used in magnetic resonance imaging (MRI) techniques to visualize the behaviour and location of stem cells in the body [7]. In addition, encapsulate genes or growth factors support stem cell survival and activity, thus, increasing the therapeutic efficacy [8].

The application of stem cell therapy in tissue regeneration represents a significant advancement in regenerative medicine, focusing on the potential of stem cells to repair or replace damaged tissues and organs. Heritable modification in genome without making any changes in underlying DNA sequence is known as epigenetics [9]. For instance, Histone/DNA methylation, acetylation, ubiquitination and phosphorylation, are type of those modifications. Recent research reported the crucial role of epigenetics in treating wide range of diseases such as cancer, neurological, metabolic, and cardiovascular disorders. Since epigenetic events are reversible, scientists believed that, inhibiting those modifications may have important therapeutic implications [10, 11].

Integrating nanotechnology and epigenetic in stem cells can improve capacity to differentiate in cell types needed for tissue repair [12]. The well-known epigenetic modification is to add methyl group in the DNA molecule, which typically effects by suppressing gene expression [13]. Histone modification chemically alters the degree with which DNA wraps around histone to affect the accessibility of specific genes. Those changes have long-term effects on cellular growth and function [14]. This interdisciplinary approach may result in more effective treatments for several diseases by improving delivery mechanisms, tracking capabilities, differentiation modulation, and safety.

2. NANOTECHNOLOGY IN STEM CELL THERAPY

Recent development in the field of stem cell research has greatly influenced the biomedical science. Medicinal drugs can be delivered directly to organs using targeted drug delivery systems by employing nanoscale carriers like liposomes and nanoparticles [15]. Nanomaterials have been utilised extensively to modify cell behaviour because of their tiny size, feasible synthesis and surface functionalisation. The average diameter of drug delivery nanoparticles (NPs) is less than 300 nano-meters. Many types of nanomaterials have been thoroughly investigated for biological and medicinal applications. They can be made from natural or synthetic polymers, such as polyethylene glycol (PEG), polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), dextran, chitosan [16], silica nanoparticles, titanium dioxide nanoparticles (TiO_2), iron oxide nanoparticles (IONPs), gold nanoparticles (AuNPs), iron oxide nanoparticles (AgNPs), liposomes, quantum dots, carbon nanotubes (CNTs), graphene (GR), and DNA nanostructures [17]. Those substances are potent enough to control stem cell activity and encourage tissue regeneration [18].

2.1. Targeted delivery of growth factors and drugs

Efficient targeted delivery can be improved by increasing the retention times. Growth factors, DNA, and tiny molecules as medicinal substances can be encapsulated in NP. Their tiny size can increase bioavailability and facilitate effective cellular absorption. Nanoparticles (NPs) enhance stem cell survival and proliferation via following mechanisms: Firstly, encapsulated therapeutic medicines can be internalized more readily due to effective permeability of NPs. Secondly, by modifying NPs to release their cargo in a regulated way, stem cells can be exposed to growth factors to support survival and proliferation over an extended period [19]. Applications of nanoparticle in several diseases are as follow.

2.1.1. Neurodegenerative Diseases: NPs have been utilized to deliver neurogenic factors to improve neural stem cell differentiation into neurons, which may help patients to recover from diseases like Alzheimer's [20].

2.1.2. Cardiovascular Diseases: By delivering protective chemicals to lessen the ischemia damage, NPs can improve the survival of cardiac stem cells after transplantation [21].

2.1.3. Bone Regeneration: Mesenchymal stem cells can undergo osteogenic differentiation when exposed to nanoparticles, which speeds up the healing process [22]

2.2. Types of Nanoparticles used for stem cells

In stem cell therapy, various kinds of nanoparticles were employed, each with special characteristics, those are as follow;

2.2.1. Polymeric Nanoparticles: These are type of biodegradable polymers, such as polylactic-co-glycolic acid (PLGA), which is biocompatible and enable regulated release of the drug [23].

2.2.2. Metallic Nanoparticles: The potential of gold and silver nanoparticles to improve cellular signalling pathways that encourage stem cell proliferation has been investigated [24].

2.2.3. Liposomes: These lipid-based vehicles offer a variety of drug delivery options by encapsulating both hydrophilic and hydrophobic medications [25].

3. NANOMATERIALS AND STEM CELL ENGINEERING

3.1. Nanofibers and Scaffolds for Tissue Regeneration

Scaffolds made of nanoparticles enhance tissue repair and cell proliferation by mimicking the natural tissue architectures. Scaffolds are biodegradable and porous; they allow efficient waste and nutrient exchange. scaffolds made up of nanofibers, can effectively mimic extracellular matrix and improve tissue growth and cell adhesion. Tissue scaffolds can be fabricated by variety of techniques, such as phase separation, electrospinning, and self-assembly. This has led to the development of tissue scaffoldings made up of biomaterials in the form of nano-fibres [26]. Nanofiber scaffoldings are extensively common in engineering of many soft and hard tissues [27]. Previously reported, engineered nanomaterials, materials with at least one dimension are less than 100 nm [28], act as promising candidates for creating scaffolds and can be effectively replace damaged tissues and resemble natural extracellular matrix (ECM). Nanofibers and nanotubes were investigated extensively in terms of modifying the stem cells. Nanostructures reported to play a crucial role to support stem cell proliferation [29] and differentiation [30]. It has been reported that the addition of nanofibers in a traditional micro-scale scaffold can boost up cellular functions, improve the activity of alkaline phosphatase (ALP) as well as cellular viability, [31], attachment [32], proliferation, [33] and differentiation [34]. It has been found that an engineered scaffold made of self-assembling peptide nanofibers promote regeneration of axons [35]. It was observed that aligned nanofibers provide strong support for mouse neural stem cell growth and, in contrast to the microfibers, enhanced the neurite development [34]. It has been proposed that isotropic or aligned nano-textures may stimulate neurite outgrowth both in *in-vivo* and *in-vitro* settings. Conclusively, cell differentiated was reported to improve by nano-fibrous structures [29].

3.2. Nano-biomaterials for Stem Cell Differentiation

Nanoparticles can effortlessly transport through cells membranes and influence certain cellular signalling pathways to regulate differentiation [36]. Studies have shown that nanomaterials can effectively guide stem cell differentiation by modifying the substrate properties, such as stiffness, surface chemistry, and alignment. Aligned carbon nanotubes (CNTs) improve proliferation and osteogenic differentiation of human mesenchymal stem cells by mimicking the natural extracellular matrix's structure. Nanomaterials with specific geometric features are also promising for advancing stem cell differentiation in regenerative medicine [37, 38]. Similarly, 3D nanomaterials are even more effective for differentiation of osteogenic, neural, chondrogenic and odontogenic stem cells. 3D models allow cells to experience tissue like environment [39, 40]. There are certain factors affecting the cellular uptake of engineered nanostructures such as size and shape, can influence stem cell differentiation. For example, nanospheres absorbed more readily as compared to nanorods of similar size. Moreover, physical characteristics of nanoparticles not only influence cellular uptake but also affect signalling to guide stem cell differentiation [41, 42]. Lastly, functional groups like amines (–NH_2), hydroxyl (–OH), and carboxyl (–COOH) significantly influence proliferation and differentiation. As gold nanoparticles with carboxyl groups can inhibit bone cell development, while amine or hydroxyl groups assist this process. Charge on nanoparticles affects its absorption in cells. Positively charged particles although easily taken up but, cause greater cytotoxicity. All those factors affect in integrated manner [42-44].

4. EPIGENETICS IN STEM CELL REGULATION

DNA methylation and histone modification can control the accessibility of regulatory elements in the genome, thereby affecting gene expression and subsequent biological processes without altering the core genetic sequence. There are different types of epigenetic modifiers such as DNA Methyltransferases (DNMTs), enzymes which adds methyl groups to DNA, usually at cytosine to block the transcription factors from accessing the DNA, this mechanism often suppresses gene expression. Ten-eleven translocation (TET) enzymes can turn on a silenced gene by removing methyl groups from DNA and changing 5-methylcytosine into 5-hydroxymethylcytosine and other forms [45]. There are also histone modifiers as Histone Deacetylases (HDACs) reduced gene expression and tight DNA wrapping around by removing acetyl groups from histones. Methyltransferases can stimulate or suppress gene expression by adding methyl groups to histones. Histone Acetyltransferases (HATs) enzymes add histones acetyl groups to relaxes the chromatin structure and boosts gene expression [46]. RNA Methyltransferases modify the RNA molecules, influencing their stability, localization, and translation into proteins. Demethylases remove the methyl groups from RNA, affecting gene expression at the post-transcriptional level [22]. Disruption in the processes of epigenetic alteration can result in aberrant gene activity and lead to several illnesses, such as cancer, metabolic diseases, and neurodevelopmental abnormalities. Comprehending these modifications creates opportunities for treatment approaches that focus on epigenetic pathways [47].

4.1. Epigenetic modulation of stem cell fate

There is growing evidence that epigenetic modifications are required for nuclear reprogramming and cell-fate conversion. Recent advances in epigenetics suggested that cell fates can be reset by the alteration of epigenetic marks on histones or DNA, those converted cells will only be functional if transplanted *in-vivo*. Combination of epigenetic regulators have shown to ensure that multiple adult stem cell types, including hematopoietic, mammary, intestinal, and muscle, are given precise instructions to activate or suppress transcription, maintaining their inherent stemness [48], guiding lineage specification, enabling specific transcriptional routes while blocking others [49]. Alterations of chromatin accessibility can induce transcriptional changes in hematopoietic stem and progenitor cells (HSPCs), resulting in an imbalanced production of mature cells [48].

Experimental data suggested that epigenetic modifications might permit the generation of new neuronal SCs (stem cells) and neurons from non-neuronal SCs. It was reported that, addition of either valproic acid, a histone deacetylase inhibitor, or 5-azacytidine (5-AzaC), a DNA methylation inhibitor, can convert bone marrow stromal cells to NSCs. In addition, very early evidence points out that chromatin remodelling factors such as ISWI and Brg1 can reset the somatic nuclei transplanted into Xenopus eggs and modify the histone codes during the nuclear reprogramming [50].

4.1.1. DNA Methylation

DNA methylation is the process of adding a methyl group at 5th carbon of cytosine forming 5-methylcytosine (5mC), primarily common in CpG dinucleotides in mammalian genome. Approximately, 70–80% of CpG dinucleotides are methylated, but CpG clusters linked to gene regulatory regions known as CpG islands (CGIs) remain largely unmethylated. Usually, this alteration results in the silencing of genes by preventing transcription factors from attaching to gene regulatory regions or by attracting proteins to compress the chromatin. De novo DNA methylation is carried out by enzymes, Dnmt3a and Dnmt3b. It is necessary to establish DNA methylation patterns. Those patterns maintained throughout cell division by Dnmt1, a hemi-methylation-favouring maintenance methyltransferase. DNA methylation is a critical process during gametogenesis that generates parental-specific imprinting and silence genes of the inactive X chromosome and retrotransposons [51].

4.1.2. Histone Modification

Chemical alterations in histone proteins, such as acetylation, methylation, and phosphorylation, are referred as histone modifications. These changes alter the accessibility and structure of chromatin to either stimulate or repress gene expression. Histone phosphorylation is to adds phosphate groups to serine, threonine and tyrosine residues on histone tails, and in histone acetylation, adds acetyl groups to lysine residues. Transcriptional activation is linked to both modifications. Adding methyl groups to lysine or arginine residues is known as histone methylation, and the process of gene on and off depend on methylation of specific amino acid residue and the number of methyl groups added. [52]. For example, H3K4me3 (trimethylation of lysine 4 on histone H3) is linked with active transcription, whereas H3K27me3 (trimethylation of lysine 27 on histone H3) is related to gene suppression. These epigenetic processes work in concert to create a sophisticated regulatory network that affects differentiation and development by mediating gene expression. Comprehending these mechanisms provides insight of the regulation of gene expression to determine of cell fate [53].

The post-translational changes of histones, such as acetylation and methylation of conserved lysine residues on the amino terminal tail, are dynamically regulated by similar enzymes affecting chromatin with opposing activity [48]. The idea that two opposing activities produce two contrasting states on the chromatin, is the foundation of the "histone code" theory. Lysine acetylation, carried out by histone acetyltransferases (HATs), typically indicates regions of active transcription. On the contrary, acetyl groups are eliminated by histone deacetylases (HDACs), resulting in hypoacetylated histones that are associated with inactivation of chromatin. Lysine 4 on histone H3 (H3-K4) is methylated and its methylation is typically present in promoter regions. For instance, Drosophila trithorax (trx) and its mammalian counterpart, mixed lineage leukaemia (MLL), add three methyle H3-K4, whereas the histone methyltransferase Set7/9 add one methyle on H3-K4 [48]. In tissue-specific stem cells and differentiated cells, DNA methylation is common in the silencing of alternative lineage differentiation genes. On the other hand, in embryonic stem cells (ESCs), histone modifications promote self-renewal and the suppression of genes relevant to lineage differentiation through pluripotent-related transcription factors such as the Oct4-Nanog-Sox2 complex [48].

4.2. Epigenetic Reprogramming for Enhanced Regenerative Potential

Tissue engineering and gene therapy are used in regenerative pharmacology to repair damaged organs or tissues. To attain regeneration, there are three primary methods such as reprogramming, restoring pluripotency and the ability of a specialised cell to behave as a stem cell [54]. The direct conversion of one type of cell into another (brain stem cells into blood cells) known as transdifferentiation. Reverting a fully specialised cell to a less specialised state is known as dedifferentiation. One intriguing method for regenerating tissues or organs is to reprogramme a cell to become an induced pluripotent stem (iPS) cell utilising transcription factors, mRNA, proteins, or small compounds. This is accomplished by altering the chromatin and gene packaging without altering the DNA sequence itself [54]. Currently, a multitude of clinical experiments utilizing reprogrammed cells are in progress, exhibiting encouraging outcomes. Somatic cell nuclear transfer (SCNT), cell fusion, ectopic production of transcription factors, micro-RNAs, and utilisation of small signalling molecules are some of the reprogramming techniques [54].

4.2.1. CRISPR-Cas9-based genomic editing for reprogramming

Recent studies reported the importance CRISPR and catalytically inactive dCas9 for cell reprogramming. This system is highly versatile, enabling correction of disease-causing mutations, and regulation of gene expression through activation or repression of specific genes. A new method utilizing CRISPR-based editing to create genome-wide reprogrammable transcriptional memory shows potential for therapeutic gene editing [55]. CRISPR-dCas9 was used to activate Octamer-binding transcription factor 4 (Oct4), SRY-box transcription factor 2(Sox2), K ruppel-like factor 4(Klf4), c-Myc (proto-oncogene), and Lin28 promoters, which convert human fibroblasts into Induced Pluripotent Stem Cells (iPSCs). Targeting Alu-motif enhanced reprogramming efficiency [56]. CRISPR can alter DNA methylation by fusing with DNA (Cytosine-5)-Methyltransferase 3 Alpha (Dnmt3a), Ten-Eleven Translocation Methylcytosine Dioxygenase 1(Tet1). Controlled gene expression influence cell fate and reprogramming. For example, Tet1-Cas9 activated the Myo enhancer, converting fibroblasts into myoblasts [57]. CRISPR targeted the Sox1 gene in neural progenitor cells (NPCs) to enhance reprogramming efficiency and differentiation potential by increasing Sox1 expression [58]. It also induced the simultaneous activation of Brain-specific Homeobox/POU Domain Protein 2 (Brn2), Achaete-Scute Family BHLH Transcription Factor 1(Ascl1), and Myelin Transcription Factor 1 Like (Myt1l) promoters, converting mouse fibroblasts into neurons. This method, employed chromatin remodelling, resulted in more efficient and stable neuron reprogramming compared to other methods [59].

5. ROLE OF NON-CODING RNAS IN STEM CELL BIOLOGY

Non-coding RNAs (ncRNs) are transcripts of untranslated region of genome. Human genome contain many ncRNAs and majority of these have been linked with regulating cellular homeostasis. Several studies reported the role of microRNAs and long non-coding RNAs in stem cell differentiation (Fig. 1) [60].

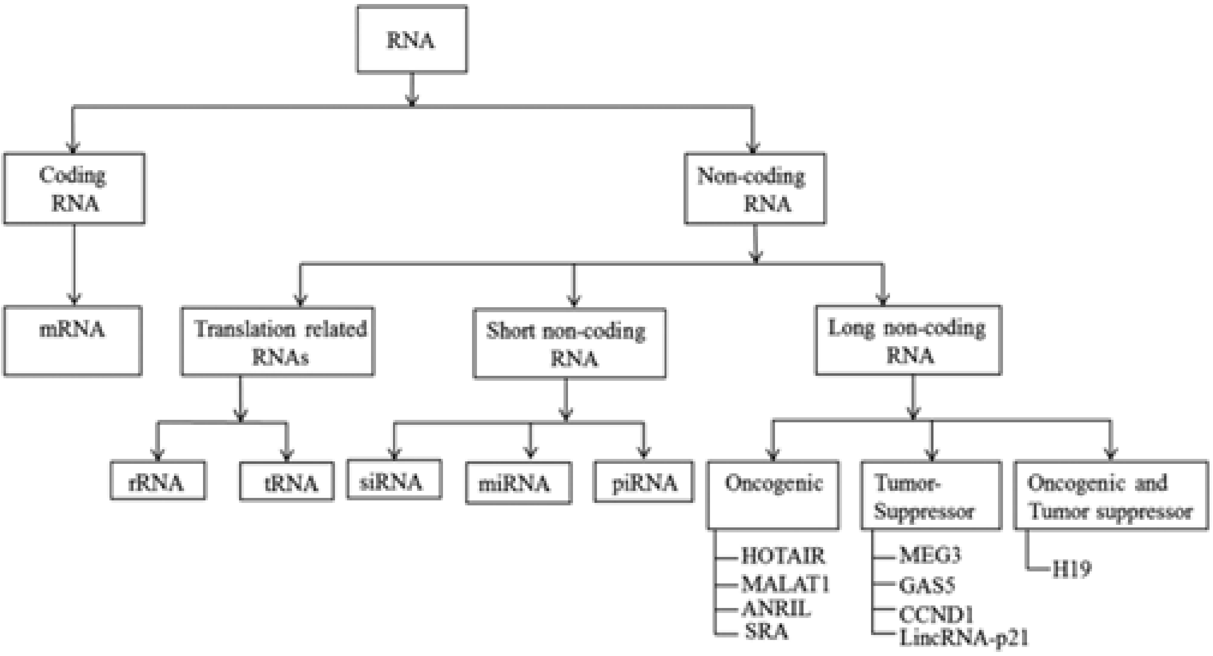

Fig. 1. A taxonomy of RNA types illustrating the vast array of RNAs that modulate gene expression through antisense and miRNA-mediated regulation, hence playing significant roles in a variety of biological processes [60].

5.1. Role of microRNAs (miRNA) in differentiation

miRNAs can regulate gene expression by their integration into the RNA-induced silencing complex (RISC). They may consequently decrease the expression of their intended targets. They degrade mRNA, depending on how closely the miRNA and target sequences resemble in sequence [61]. Certain miRNAs supporting stemness and self-renewal in embryonic stem cells (ESCs) are downregulated during differentiation into human neural stem cells (hNSCs), whilst those, prevent self-renewal are increased. Some reported miRNAs promoting self-renewal in human ESCs are miR-200 family, miR-302/367 cluster, and miR-372, are specifically downregulated. In the meantime, renewal-suppressive, let-7a, elevated. Such alteration of ESCs to hNSCs is regulated by SOX2-Lin28 transcriptional factor [62, 63]. Those ESC-specific cell cycle-regulating miRNAs induce dedifferentiation in somatic cells by inhibiting the TGF-β-induced epithelial-mesenchymal transition (EMT) [64]. Many miRNA clusters exhibit changes during differentiation to neural stem cells, hepatocyte stem cells, hematopoietic stem cells and muscle stem cells. Stem-cell differentiation-associated miRNAs are regulated through a complex network of transcriptional, epigenetic, and/or post-transcriptional mechanisms. For example, ESC-associated transcription factors (TFs) such as Oct3/4, Sox2, and Rex1, promote pluripotent stem cell formation or self-renewal, regulated miR-362/367 cluster [65].

miRNA expression during the development of embryonic stem cells (ESCs) is significantly influenced by epigenetic regulation, particularly, by epigenetically modified chromatin [66]. Epigenetically controlled miRNAs during lymphopoiesis were discovered during small-RNA sequencing (sRNA-seq) and chromatin immunoprecipitation sequencing (ChIP-seq) of histone modifications. For instance, PRC1 mediates histone 3 lysine 27 tri-methylation (H3K27me3), which regulates miRNAs specific to lymphocytes. H3K27me3 reduction caused miR-139 and miR-147 to be elevated in ProB and PreB cells, whereas miR-152 miR-152 miR-152 miR-152 miR-152 were downregulated [66]. Furthermore, miR-302 expression inhibited the histone 3 lysine 9 demethylase (JMJD1C), to supress neural differentiation. Neural differentiation can be triggered by downregulating JMJD1C [67].

After examining the miRNA signature in healthy human bone marrow, it was discovered that there are more than 30 miRNAs in CD34+ hematopoietic stem-progenitor cells (HSPCs). One important miRNA, shown to be involved in controlling both erythropoiesis and myelopoiesis is miR-155, reduces the development of erythroid and myeloid colonies from HSPCs [68]. Another study explained how different miRNA families regulate the self-renewal and differentiation of hematopoietic stem cells (HSCs) by investigating each stage of HSC differentiation, marked by a unique miRNA profile. Significantly elevated miRNAs in long-term HSCs (LT-HSCs) were miR-125a, miR-125b, miR-155, miR-99a, miR-126, miR-196b, miR-130a, miR-542–5p, miR-181c, miR-193b, and let-7e. While miR-196b, miR-181c, let-7e, and miR-542–5p showed opposing effect, indicating that these miRNAs regulate HSC homeostasis rather than directly influencing specific differentiation pathways. Higher expression of miR-125b–5p, miR-126-3p and miR-155 in bone marrow cells enhanced competitive engraftment across lineages [69].

5.2. Epigenetic regulation by lncRNAs in tissue regeneration

Tissue engineering with the regulation of lncRNA holds promise for the prevention and treatment of numerous diseases. lncRNAs play a part in cellular senescence in addition to their functions in a variety of illnesses, such as cancer, metabolic disorders, neurological, and cardiovascular systems [70]. It has been demonstrated that cellular senescence programs are significantly influenced by long noncoding RNAs (lncRNAs), making them promising agents for precise regulation [71]. Both differentiation and pluripotency can be influenced by lncRNAs. [72]. Those type of RNAs increase transcription, as well as they can act as signals, decoys, scaffolds, and can guide to control gene expression directly or indirectly by enlisting regulatory molecules [73]. Ectoderm, mesoderm and endoderm appears during the beginning of gastrulation. When endoderm progenitors reach the primitive streak, the definitive endoderm (DE) layer develops underneath the epiblast. Together with BMP signalling pathways, key pluripotency factors, Wnt/β-catenin, Activin/Nodal, and NANOG create a regulatory network to shifts cells from maintaining pluripotency to developing endoderm. One crucial step in this process is the reduction of SOX2, which initially preserves stemness but later promotes ectoderm growth. its reduction enables the activation of markers such as EOMES, FOXA2, and SOX17 that are essential for the development of DE. Studies have shown that how lncRNAs regulate this mechanism [72].

A study discovered a lncRNA, dynamically regulated during the development of pancreatic lineages. An analysis of lncRNA expression in human embryonic stem cells (hESCs), definitive endoderm (DE), pancreatic progenitors and endocrine cells revealed that many cytoplasmic lncRNAs have expression levels similar coding mRNAs transcripts with open reading frames (ORFs) to synthesize microproteins. One such lncRNA, necessary for the development of cells and produce insulin, is LINC00261 (DEANR1). Despite being primarily cytoplasmic, experiments such as frameshift mutations showed that LINC00261 play a role in pancreatic endocrine cell development independent of its microproteins [74]. Numerous physiological and pathological processes involve lncRNA, MALAT1, has recently suggested that it has new role in hepatic differentiation [22]. Furthermore, A sequential differentiation process that begins with hESCs or hiPSCs and proceeds through the development of definitive endoderm (DE), anteriorization of the foregut endoderm, and ultimately differentiation into distal and proximal lung epithelial cells can be used to duplicate lung morphogenesis. The adjacent gene PITX2, which affects lung morphogenesis by interacting with the WNT signalling pathway, is regulated by the lncRNA, RP11-380D23.2 in distal lung differentiation. PITX2 expression is modulated by PARP1 binding to the genomic sequence of RP11-380D23.2, which downregulates its expression [75].

5.2.1. Neurodegeneration

Numerous preclinical investigations have shown that altering the amounts of particular lncRNAs in nervous system cells may reverse senescence, useful strategy for postponing neurodegeneration. Another study showed that exposure to the HIV trans activator of transcription caused human primary astrocytes to become senescent. The elevation of taurine-upregulated gene 1 (TUG1) lncRNA was linked with elevated senescence levels [76]. It is interesting to note that TUG1 downregulation reduced senescence marker levels. It has been suggested that lncRNAs could be used as biomarkers to diagnose Parkinson's disease. Study suggested that downregulating its antisense lncRNA could be a treatment approach. This neurodegeneration disease is characterized by α-synuclein overexpression and aggregation [77]. The transcription of synuclein alpha antisense 1 (SNCA-AS1), an antisense lncRNA of the α-synuclein-coding gene, increased the amounts of α-synuclein mRNA and protein. In cultured cells, SNCA-AS1 overexpression raised the RNA levels of most of the senescence markers. The effects of SNCA-AS1 knockdown were contrary [78]. In conclusion, level of lncRNA reported to fluctuate by age and regulated to postpone the senescence of nervous system cells. Thus, having an impact in promoting regeneration and lessening neurodegeneration.

5.2.2. Osteoarthritis and Osteoporosis

Those disorders involve the senescence of bone or cartilage cells. lncRNA up/downregulation promotes bone healing and is a promising technique against osteoarthritis and osteoporosis. They are prospective therapeutic targets against osteoporosis because they mediate osteoblast differentiation and migration to the bone forming sites, as well as osteoclast differentiation [79]. In addition to mediating osteoblast migration and differentiation, which are essential for the production and repair of bone mass, lncRNAs also control the gene expression which influence the cartilage health [79].

Reduced chondrocyte levels of the zinc finger homeobox 2 (lncZFHX2) lncRNA also linked with osteoarthritis as its removal resulted the senescence of those cells. In human and mouse cartilage chondrocytes, LncZFHX2 was elevated under physiological hypoxia; however, in mice, lncZfhx2 levels was naturally declined with age, raising the risk of osteoarthritis [79]. The lncRNA AC006064.4-201, which was downregulated in senescent human cartilage, prevented osteoarthritis and reduced chondrocyte senescence. Whereas downregulation stabilizes the mRNA coding for cyclin-dependent kinase inhibitor 1B, which promotes senescence [80]. Conclusively, increasing the expression of lncRNAs reduce senescence risk, which would otherwise lead to osteoarthritis or osteoporosis [81].

5.2.3. Cardiovascular Diseases

lncRNAs influence the vascular aging particularly, regulating endothelial senescence [82]. it was reported that cardiomyocyte senescence was accelerated by lncRNA-SMAL, and its suppression protect the heart. H19 level rose in senescent cardiomyocytes and aged mice hearts. The H19 lncRNA typically acts as a microRNA sponge to regulate gene expression in aging and inflammatory conditions. Its reduced levels lessen the senescence of cardiomyocytes [83]. It was also shown that in aging human bone-marrow-derived mesenchymal stem cells, lnc-CYP7A1-1 level increased. Those aged MCS were implanted in myocardial infarction induced mice. Moreover, before implantation, lncRNA level was reduced. Downregulation of lnc-CYP7A1-1 in those cells reduced senescence and improved cardiac function [84]. Aged mice aortas and vascular smooth muscle cells exhibited lower levels of ENSMUST00000218874 lncRNA, which may indicate an anti-senescence function, investigated by knockdown [34].

In human vascular endothelial cells, overexpression of SIRT1 Antisense RNA (SIRT1-AS) increase silent information regulator 1 (SIRT1) mRNA (SIRT1) levels, to prevent senescence. Its reduced level was reported in deep vein thrombosis condition which is therapeutic target to treat this condition [85]. According to those research, aging and senescence are associated with specific level of lncRNAs in cardiac cells.

5.2.4. Skin Aging

It has been reported that lncRNA regulation can reverse the aging of skin cells and encourage their regeneration. Aged Human dermal fibroblasts showed lower level of H19 lncRNAs. Their overexpression improved cell viability, reduced senescence and help in wound healing [86]. In aged adipose-derived stem cells, overexpression of the lncRNA senescence-associated noncoding RNA (SAN) was reported. Its knockdown improved function of cell and prevented their senescence. Additionally, rats wound healed quickly after receiving a transplant of SAN-depleted adipose-derived stem cells. As adipose-derived mesenchymal stem cells are transplanted, lncRNA modulation in these cells may increase wound repair [87]. However, still there in need to investigate this hypothesis detail how this process works.

5.2.5. Liver Diseases

Notably, several lncRNAs have demonstrated protective functions against the detrimental effects of senescence on liver cells particularly, with non-alcoholic fatty liver disease. Livers of NAFLD patients and the hepatic endothelium of obese mice showed elevated levels of maternally expressed gene 3 (Meg3) lncRNA. In diet-induced obese mice, Meg3 knockdown resulted in decreased glucose metabolism, insulin resistance, and hepatic endothelium senescence. lncRNA is the potential strategies for reducing liver cell senescence, restoring liver function, and shield against cellular senescence. The hepatic endothelium p53 knocked out to reversed those effects [29].

Table 1. Epigenetic Regulation by lncRNAs in Tissue Regeneration

Category	lncRNA	Effect/Function
Neurodegeneration	TUG1	Elevated in senescent astrocytes due to HIV transcription factor; downregulation reduces senescence markers and delays neurodegeneration.
	SNCA-AS1	Overexpression increases α-synuclein and senescence markers; knockdown improves synaptic markers. Potential target for Parkinson's disease treatment.
Osteoarthritis & Osteoporosis	lncZFHX2	Elevated under hypoxia; decline with age accelerates chondrocyte senescence, increasing osteoarthritis risk.
	FER1L4	Downregulated in osteoarthritis; levels decline with aging.
	AC006064.4-201	Prevents osteoarthritis by reducing chondrocyte senescence and stabilizing cyclin-dependent kinase inhibitor mRNA.
Cardiovascular Diseases	H19	Elevated in senescent cardiomyocytes; suppression reduces senescence.
	lnc-CYP7A1-1	Downregulation in aged mesenchymal stem cells prevents senescence and improves cardiac function after myocardial infarction.
	SIRT1-AS	Overexpression increases SIRT1 levels, reduces endothelial senescence, and prevents deep vein thrombosis.
	ENSMUST00000218874	Downregulation linked to vascular aging; knockdown indicates anti-senescence properties.
Skin Aging	H19	Overexpression in dermal fibroblasts improves viability and prevents senescence.
	SAN	Knockdown in aged adipose-derived stem cells improves functionality, promotes wound healing in transplanted cells.

Liver Diseases	Meg3	Elevated in NAFLD; knockdown reduces glucose metabolism issues, insulin resistance, and hepatic endothelial senescence.

6. INTERPLAY BETWEEN NANOTECHNOLOGY AND EPIGENETICS IN STEM CELL THERAPY

6.1. Targeted Delivery of Epigenetic Modifiers

Epigenetic modulators like histone deacetylase and DNA methyltransferase inhibitors can be delivered directly to target cells by nanocarriers [88]. Epigenetic-based nano-medicine can successfully transform cold tumor into hot tumor, thus improving the efficacy of immunotherapies [22].

As epigenetic drugs degrade rapidly in the body due to action of enzymes, thus, special delivery methods are often needed. For example, decitabine is rapidly broken down by cytidine deaminase, an enzyme found in high concentration in organs such as in stomach and liver. Because decitabine cannot strongly bind to proteins, it is quickly cleared from the body and must be continuously given via intravenous infusion. Once the infusion stops, drug level in body become almost negligible after 30 minutes [89].

Target cells must overexpress transcription factors (TFs) like OSKM to induce pluripotent stem cells (iPS cells). Certain molecular alterations are linked to this reprogramming process. Studies have demonstrated that, molecularly and functionally, reprogrammed iPS cells displayed transcriptional patterns strikingly comparable to those of embryonic stem cells (ESCs). This suggests that TF overexpression-driven epigenetic modifications are essential for cells to reach a pluripotent state [90].

6.2. Nanocarrier-based epigenetic reprogramming

Transfection works better if integrated with nanocarriers as they can transport genetic material, with low immunogenicity (little immune response), and facilitate transfection rather easily. In several genetic engineering initiatives, nanoparticles have been used successfully in place of viral vectors, which carry a risk of insertional mutagenesis or gene integration. Nevertheless, the primary disadvantage of nanocarriers is their reduced efficiency [91].

6.2.1. Limposome-Based Reprograming

Liposomes are mostly use for cellular transfection, especially cationic liposomes. they are amphiphilic vesicles that can interact with both lipid and water environments as consist of phospholipid bilayer. Positively charged cationic liposomes can enter negatively charged cell membranes by endocytosis or related mechanisms [92]. Lipofectamine is frequently used as the gold standard for transfection. Additional lipid-based formulations, such as TransIT and DharmaFECT1, have also been effectively utilised to reprogram cells to become pluripotent [93]. Lipid-based formulations distribute synthetic messenger RNA (mRNA), which is responsible for encoding the transcription factors (TFs) required for reprogramming [94].

6.2.2. Nonliposomal Transfection Reagent

Plasmid delivery for reprogramming to produce induced pluripotent stem (iPS) cells was pioneered by Shinya Yamanaka and his colleagues. They used plasmid to transport four essential components (Oct3/4, Sox2, Klf4, and c-Myc) collectively known as OSKM, required for reprogramming [91]. Two constructed plasmids were transfected into mouse embryonic fibroblasts (MEFs) using the non-lipid-based reagent FuGENE 6: one plasmid having the genes for Oct3/4, Sox2, and Klf4, and another plasmid with c-Myc gene. This technique effectively converted the MEFs into iPS cells without integrating the plasmid into genome, while lowering the possibility of insertional mutations. Those iPS cells were shown to be functional once transplantation into mice, they developed teratomas (a tumour type, capacity to specialise into several tissues) and helped to generate adult chimaeras, thereby validating their stem cell-like characteristics [91].

6.3. Polymers based regenerative medicine

Polymers (natural or synthetic) have gained popularity in regenerative medicine attributed to respective greater efficiency, low risk of immunological reactions, biodegradability and biocompatibility. They are in use since a decade to transport a variety of therapeutic agents, including proteins, vaccines, hydrophobic and hydrophilic medicines, and nucleic acids (siRNA for gene knockdown) [95].

Poly (β-amino ester) nanoparticles (PBAEs) are positively charged, biodegradable polymers, can be chemically modify for specific purposed. They are easily synthesised by conjugating amines with diacrylates. They work very well for transfection, even with challenging cells like human mesenchymal stem cells (hMSCs). Successful gene transfer is aided by PBAEs' ability to form stable complexes with nucleic acids which void endosomal destruction. PBAEs have been widely employed by researchers for effective gene delivery, which makes them useful instruments for regenerative medicine and other for therapeutic purposes [96].

6.4. Cell-Penetrating peptides (CPPs) based reprogramming

Exogenous proteins cannot enter the cells unaided. Plasmid DNA encounters a similar problem. Drug delivery devices can condense these molecules and shield them from enzymatic breakdown to promote their uptake [97]. Certain naturally occurring peptide have been reported to exhibit the ability to cross the plasma membrane, known as cell-penetrating peptides (CPPs). Those peptides consist of arginine or lysine rich residues [98]. Peptide Transfer Domain (PTD) called 11R, consists of 11 consecutive arginines residues, able to transport any desired protein into cells with sufficient potency [99].

Therefore, protein transduction domains (PTDs) offer unique and successful drug delivery method. In a previous study researchers integrated the C-terminal ends of four transcription factors (TFs: OSKM) to 11R. After being expressed in Escherichia Coli, proteins were separated and refined. The stability and permeability of the resultant recombinant proteins in mouse embryonic fibroblast (MEF) cells was investigated and it was shown that those tagged proteins effectively crossed the cell membrane. The cells were treated with the proteins over the course of four cycles, along with a histone deacetylase (HDAC) inhibitor, such as valproic acid (VPA), which is known to affect histone acetylation, to improve the reprogramming efficiency of MEFs into iPS cells [100].

6.5. Carbonate Apatite

Apatite is the collective term for phosphate minerals. Hydroxyapatite is the term for apatite consist of higher concentrations of hydroxide ions (OH^-). Carbonate apatite is the result of crystal development inhibition caused by carbonate ions present in the apatite structure. Body contains higher amounts of phosphate, especially in the bones and teeth. One form of calcium phosphate, an essential inorganic crystal in those tissues, is hydroxyapatite [23]. The production of calcium phosphate crystals as nanocarriers has been thoroughly investigated, and efforts have been made to increase their effectiveness. pH-dependent carbonate apatite nanocrystals have been investigated in recent work for efficient and targeted gene delivery, with an emphasis on obtaining cell-specific targeting for therapeutic purposes [23].

7. CLINICAL POTENTIAL OF CELLULAR REPROGRAMMING

Significant advancements in cellular reprogramming have demonstrated clinical potential. Some examples are as follow:

7.1. Corneal Transplant: A Japanese woman's vision was enhanced by a cornea made from iPSCs. Reprogrammed donor skin cells became induced pluripotent stem cells (iPSCs) and developed into corneal cells, providing a way around the scarcity of corneal tissue for transplantation from donor's eye [101].

7.2. Treatment for Parkinson's Disease: A patient in Japan received implanted reprogrammed neural precursors. To potentially treat symptoms like tremors, skin cells were transformed into induced pluripotent stem cells (iPSCs) and subsequently differentiated into dopamine-producing neurons [102].

7.3. Heart Disease Therapy: Trials are being conducted to treat heart disease using cardiac tissues produced from iPSCs. iPSC-derived cardiac muscle sheets are grafted into damaged heart with the goal of accelerating tissue regeneration through the production of growth factors [103].

7.4. Spinal Cord Injury: Treatments using progenitor neurons produced from iPSCs are being investigated for spinal cord injuries. After being injected into spinal cords of monkey model, these neurons may grow into glial cells and other neurons to aid in healing [104]. iPSCs were first used to create muscle cells by MyoD activation to treat Duchenne Muscular Dystrophy DMD. With the help of HDAC inhibitors, the reprogrammed cells should be able to rebuild muscle tissue in patients with DMD-related muscular degeneration [105].

8. ADVANCEMENTS IN NANOTECHNOLOGY-DRIVEN STEM CELL THERAPY

8.1. Tissue Engineering

Stem cell nanotechnology is rapidly advancing as modulated nano materials exhibited stem-cell labelling, tracking, gene transport, differentiation, transplantation, and their cytotoxic potential [106]. Biodegradable nanoparticles in targeted delivery, therapy, and stem cell regeneration are quite promising [107]. *In-vivo* stem-cell tracking using magnetic nanoparticles (NPs) is becoming more and more common, particularly in stem cell-based tissue regeneration treatments. Modified magnetic iron oxide nanoparticles, or Superparamagnetic Iron Oxide Nanoparticles (SPIONs), exhibited good results in MRI analysis [108]. Since large quantity of conventional transfection agents can be hazardous to stem cells. Nanoparticles coated with dextrans, as the commercially available products, Endorem, Feridex, and Sinerem, promote cellular absorption without causing any toxicity [109]. Mesenchymal stem cells (MSCs) and embryonic stem cells (ESCs) can be more effectively labelled by modifying the surface of Superparamagnetic Iron Oxide Nanoparticles (SPIONs) with ligands/fluorescent and isotope [110].

8.2. Nanoparticle scaffolds

Recent developments, including 3D scaffold culture systems, shown better structural organization than conventional 2D cultures. In 2D cell culture, growth factors, hormones, and composition of extracellular matrix affect the stem cell development. This opens new avenues for bone regeneration and improves heart disease therapy choices by using bioartificial constructions [111, 112].

8.3. NanoDevices

Bioreactors, biosensors, and bio-capsules are examples of advanced microfabrication products known as nanodevices. Smart capsules that can perform real-time analysis and diagnostics are integrated into biocapsules, which are intended for the regulated administration and isolation of molecules. Bioreactors integrate BioMEMS for large-scale applications while maintaining ideal conditions for the growth of cells and tissues. High sensitivity nanosensors, such carbon nanotubes and quantum dots, track chemical and biological interactions to enable accurate control and diagnosis in regenerative medicine [113].

9. ADVANCEMENT IN EMERGING EPIGENETIC DRUGS AND THERAPIES

9.1. Methylation inhibiting drugs

The earliest class of methylation inhibitors are nucleoside-like chemical compounds, some of which are FDA approved against specific cancers. 5-Azazacytidine (Aza; brand name Vidaza) shown to be cytotoxic to cancer cells since 1968, but its exact mode of action was still unknown [114]. It is an analogue of cytidine, marked by the substitution of a nitrogen atom at position 5. It became phosphorylated once inside the cell and integrated into the DNA during replication. Normal methyl transfer proceeds when DNA methyltransferase 1 (DNMT1), but the nitrogen substitution creates a long-lasting DNMT1-aza bond. Degradation of DNMT1 and decreased methylation levels are the results of this connection. Those medications work well against cancer cells which are dividing quickly, because it needs to be combined with DNA during the replication process. Moreover, pose adverse effects if taken orally [114].

Another cytidine analogue that works in a similar way is zebularine, inhibits DNA methylation by creating a covalent link with DNMT1. Zebularine has demonstrated encouraging outcomes in mouse models, indicating that it can suppress methylation and reinstate the expression of suppressed genes when taken orally [10]. Zebularine is more stable than aza and has the potential to be an anticancer medication in future because of its oral bioavailability. Inhibiting methylation is another application of antisense oligonucleotides. A 20-base pair antisense oligonucleotide called MG98 binds to the 3′ untranslated region of DNMT1, blocking the gene from being transcribed. It was shown to be effective for renal cell carcinoma in clinical trials The most positive results were obtained from a trial which combined the use of MG98 with the well-known chemotherapeutic medication Roferon-A. With negligible MG98 toxicity, decreased DNMT1 levels were seen with delayed tumor growth [10].

9.2. Chemical inhibitors for reprogramming

9.2.1. Inhibitors and bromodomain

Histone acetyltransferases (HATs) and other chromatin-modifying proteins contain conserved structural regions called bromodomains. There are 61 distinct varieties of bromodomains which serve as readers of epigenetic modifications by identifying acetylated lysine residues, an essential phase in the remodelling of chromatin. BRD4 and other bromodomain and extra-terminal (BET) proteins interact with RNA Polymerase II (RNAPII) and acetylated chromatin to facilitate transcriptional elongation. BRD4 reported to have role in many disease conditions. For instance, a BRD4 fusion protein causes transcriptional inhibition and hypoacetylation in NUT-midline cancer. It regulates the expression of human HPV oncogenes and is also overexpressed in plasma cell leukaemia [115].
Bromodomain inhibitors obstruct the connection between BET proteins and acetylated histones, hence downregulating c-Myc, a gene commonly linked to cancer. For example, studies of the bromodomain inhibitor JQ1 was conducted in mouse models with multiple myeloma, a c-Myc dependent malignancy. Reduced expression of c-Myc and related proteins results from JQ1 binding to acetylated lysines and pushing BET proteins out of histones [116]. I-BET726, a tiny molecule, works as an inhibitor of BET proteins by attaching on acetyl-lysine recognition sites. It competes with histone peptides for BRD2, BRD3, and BRD4 sites, for which it has a strong affinity. I-BET726 has also been shown to be effective in preventing the formation of neuroblastoma tumors by regulating the expression of BCL2, an anti-apoptotic gene which extensively expressed in a variety of malignancies. As those inhibitors are unique to BET family proteins, they offer a promising new approach to targeted cancer therapy [117].

9.2.2. Protein methyltransferase inhibitors

One important mechanism in controlling the transcription of genes is the methylation of arginine and lysine residues by protein methyltransferases (PMTs). Numerous illnesses, including cancer, neurological ailments, and inflammatory problems were reported to have link with those enzymes. It has been demonstrated that blocking PMTs may stop these pathological alterations. Although BIX-01294 the first selective inhibitor of lysine methyltransferases effectively prevents protein-protein interactions [118]. The 7-alkoxyamine-tethered quinazoline core is one structural modification used in recent inhibitors, such as UNC321 and E72, to increase their therapeutic effect. While UNC0638 stands out for its efficacy, selectivity, and minimal cell toxicity, making it a strong candidate for PMT inhibition in therapeutic situations, UNC0646, another medication, exhibits a favourable balance between toxicity and function in some cell line. Second generation inhibitors, E72 and UNC321, present promising possibilities for addressing illnesses caused by changes in methylation. 5′-azacytidine (5′-azaC) promote a partial to complete reprogramming and improves OSKM-induced reprogramming in a dose-dependent manner [118]. BIX, an inhibitor of G9a histone methyltransferase, is more effective in reprogramming when combined with another inhibitor, RG108 [119].

9.2.3. Histone methylation inhibitors

Genes that are typically regulated during development have been found to be reactivated by recently identified histone methylation inhibitors. One such inhibitor, 3-deazaneplanocin A (DZNep), has been found to selectively inhibit the trimethylation of lysine 27 on histone H3 (H3K27me3) and lysine 20 on histone H4 (H4K20me3). DZNep has been successful in reactivating genes that were silenced in cancer cells by focusing on these alterations. Significantly, research has demonstrated that these inhibitors can change the expression of developmental genes that are not regulated by DNA methylation, suggesting that they may have therapeutic uses in the treatment of cancer [120]. HMT G9a inhibitor BIX-01294 increases the efficacy of reprogramming in neural progenitor cells (NPCs) by inhibiting H3K9me2 methylation and by triggering Oct4 expression [119]. CHIR99021, an inhibitor of GSK-3, and parnate, an LSD1 inhibitor, human keratinocytes can be reprogrammed into iPSCs by overexpressing Oct4/Klf4 [120]. Through the activation of genes linked to the inner cell mass, parnate also partially transforms epiblast stem cells into embryonic stem cells [121].

9.2.4. EHDAC inhibitors

Like HDAC proteins, HDACi exhibited variety of structural variations. Structure-wise, HDACi can be divided into several classes, such as benzamides, hydroxamic acids, epoxyketones, and short-chain fatty acids. Hydroxamic acid inhibitors, which target Class I and II histone deacetylases (HDACs), have shown significant potential as cancer treatments. Among these, at nanomolar concentrations, aminosuberoyl hydroxamic acids, such suberanilohydroxamic acid (SAHA), also marketed under the name Vorinostat, have shown the capacity to inhibit HDAC activity and inhibit cell proliferation. Vorinostat approved in 2006 by FDA to treat cutaneous T-cell lymphoma, particularly given to patients gone through two rounds of chemotherapy and disease is in progressing, chronic, or recurrent state [122]. Combining epigenetic medications with other cytotoxic drugs is an innovative approach reduce toxic side effects and enhance therapeutic selectivity against cancer cells. According to a recent study, calpeptin, TRAIL, and telomere homolog oligonucleotides can sensitize breast and ovarian cancer cell lines to HDAC inhibition. It is interesting to note that HDAC inhibitors have also been demonstrated to demethylate tumor-suppressor genes which have been repressed by downregulating DNMT1 [123]. HDACi also proven potent in treating neurological and mental disorders. Numerous studies have demonstrated its neuroprotective function such as its effective in reducing memory-loss. For instance, one study demonstrated that treatment with valproic acid after cerebral ischemia significantly reduced infarct size and neurological deficiency, indicating the potential of HDAC inhibitors as a therapeutic option to prevent irreversible brain damage followed by a stroke. When paired with OSKM factors, histone deacetylase (HDAC) inhibitors acid can dramatically increase the effectiveness of reprogramming even in the absence of cMyc overexpression. It has been demonstrated that Valproic Acid (VPA) improved mouse embryonic fibroblast (MEFs) ability to produce pluripotent stem cells (piPSCs) [121]. Moreover, MEF reprogramming efficiency is enhanced by other HDAC inhibitors such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA). Sodium butyrate, another HDAC inhibitor, enhances reprogramming of human iPSCs by promoting pluripotency gene expression through promoter demethylation [124]. It was discovered that in Oct4 and Klf4-based reprogramming, butyrate works better than VPA. Reprogramming astrocytes into neurons and directly converting fibroblasts into neurons and cardiomyocytes was accomplished using VPA and related inhibitors [22].

Table 2. Chemical inhibitors

Category	Inhibitor	Application/Effect
DNA Methyltransferase Inhibitors	5′-azacytidine (5′-azaC)	Promotes partial to complete cell reprogramming; improves OSKM-induced reprogramming dose-dependently.
	BIX (G9a histone methyltransferase inhibitor) + RG108	More effective reprogramming when combined with RG108.
HDAC Inhibitors	Valproic Acid (VPA)	Enhances reprogramming efficiency with OSKM factors, even without cMyc; improves MEF reprogramming to pluripotent stem cells.
	Trichostatin A (TSA) & SAHA	Improve MEF reprogramming efficiency.
	Sodium Butyrate	Promotes human iPSC reprogramming via pluripotency gene expression and promoter demethylation; better than VPA in Oct4/Klf4-based reprogramming.
	VPA and related inhibitors	Successfully reprogram astrocytes into neurons and convert fibroblasts into neurons or cardiomyocytes.
Histone Methyltransferase Inhibitors	BIX-01294 (HMT G9a inhibitor)	Increases reprogramming efficiency in NPCs by inhibiting H3K9me2 methylation and triggering Oct4 expression.
Histone Demethylase Inhibitors	CHIR99021 (GSK-3 inhibitor) + Parnate (LSD1 inhibitor)	Reprograms human keratinocytes into iPSCs with Oct4/Klf4 overexpression; partially transforms epiblast stem cells into embryonic stem cells by activating inner cell mass genes.

9.3. Future of epigenetic drugs

Studies showed clear connection between histone modifications and DNA methylation at CpG sites, indicating the cooperative action of several epigenetic processes in controlling gene expression [123]. This connection gives rise to the idea of "epigenetic code," which may function as a switch to turn on or off certain cellular processes and gene expression. There is potential for precise control over this switch when epigenetic medications are developed for increased specificity and efficacy. If these medications are given early in the course of the disease, it may be possible to reverse disease phenotypes by reprogramming epigenome. It has been suggested that those treatments could stop cancer progenitor cells from growing while eradicating drug-resistant cancer. [125]. Subsequent research endeavours will yield insights into the extent to which various diseases can be prevented and treated by epigenetic events [126].

10. PERSONALIZED APPROACHES IN STEM CELL THERAPY

Autologous and allogeneic stem cell therapies are the two main types currently utilized in medical interventions. Since they prevent the possibility of tissue rejection and the requirement for immunosuppressive medications as they produced from the patient's own cells offer a safer alternative [127]. The benefits of personalized autologous stem cell therapy, such as the prevention of immunological rejection and the removal of immunosuppressants frequently used to prevent graft-versus-host disease (GVHD), have shown great promise in the field of cellular therapy. Furthermore, there is better accessibility with autologous transplantation. Haematological diseases, myelomas and malignant lymphoma, shown positive results with this therapy. In autologous transplants, the patient's stem cells are removed, cryopreserved, and then re-administered to preserve the stem cell population prior to chemotherapy. Developing transplantation techniques appropriate for personalized therapy still requires a thorough investigation to study mechanisms causing GVHD [54].

The development of clinical grade raw materials, large-scale expansion of desired stem cells, well-controlled clinical trials conducted under standard conditions, and identification of the best source of stem cells have all contributed to the significant global effort to evaluate the safety and potential risks of stem cell therapy. The efficacy and safety of cell-based therapies have been guaranteed by this precise evaluation, which also portends well for the treatment of terminal illnesses in the future [15]. Those evaluations are crucial to ensure the safety and effectiveness of cell-based treatments, which provide new hope for treating fatal diseases [128]. For autologous stem cells employed in customized cell-based therapies, human adipose-derived stem cells (ADSCs) are the most suitable resource. Due to their immunomodulatory feature, and ease of availability with little ethical concern, ADSCs seems to be the perfect for stem cells for applied regenerative therapy. It has been demonstrated that ADSCs, a type of progenitor adult stem cells, can differentiate in vitro into osteogenic, chondrogenic, neurogenic, and myogenic tissues [129]. Minimally invasive method of producing multipotent autologous ADSCs makes them a good option for regenerative treatment.

Many regenerative and personalized medicine expected to use ADSCs instead of bone marrow mesenchymal stem cells as the alternative solution [130]. Additionally, autologous stem cells help to avoid risk of transplant rejection, thus can reduce the patient care cost [131]. The banking of ADSCs hold great promise to advance customized and regenerative medicine [132].

11. CHALLENGES

11.1. Toxicity of Nanomaterials

Nanoparticles alter their binding property based on the biological system in which they are present. Cells can absorb NPs through active or passive processes but still need thorough investigation to comprehend uptake mechanism. Small variation in surface coating, charge, or size can make hazard assessment even more challenging as nanotoxicology lacks standard testing and dose measurement protocols. Nanoparticles, smaller then 50 nm may adopt viral like endocytotic route underscoring the importance of toxicological risks [133].

11.1.1 Cytotoxicity

The cytotoxicity and pattern of (NPs) delivery vary across different organs such as the liver, skin, and lungs, evaluating the cytotoxicity of commonly used NPs including silica (SiO_2), metal oxides, polymeric NPs, and quantum dots [34], has been the focus of research in Nanotechnology. As it was reported that NPs impaired the phagocytotic activity of macrophages of lungs, therefore affecting the lungs' ability to fight with foreign particles. To address this issue biocompatible polymers like PLGA show potential in lowering cytotoxicity and improving drug delivery for pulmonary disorders [134].

Skin is the body's primary barrier against dermal exposure. Although toxicity studies yield inconsistent results, research on gold nanoparticles (AuNPs) and titanium dioxide (TiO_2) shows that NPs can collect in hair follicles as penetrate in epidermal layers. TiO_2 block UV-blocking radiation thus common in sunscreen products, however its penetration is limited [135]. Conversely, gold nanoparticles demonstrate permeability based on size and effective for transdermal application [136]. Though smaller AuNPs are more readily absorbed, the cytotoxic effects of varies with particle size and concentration, indicating the need of comprehensive study on safety profiles prior their clinical application.

Liver plays a crucial role in first-pass metabolism, thus more vulnerable to NP induced damage. Although quantum dots (QDs) exhibited promising effects in biomedical applications, but the release of metal ions from core causes cytotoxicity. Adding surface modifications such as adding zinc sulfide on QDs can reduce toxicity.

However, coated QDs may present the risk of toxicity underscoring the significance of using appropriate coating [137]. Recently biocompatible nanomaterial such as polymeric oligohedral silsesquioxane (POSS) reported to reduce the ion leakage [138].

11.1.2. Neurotoxicity

Nanoparticles (NPs) which can cross the blood-brain barrier (BBB) carry the risk of inducing to have neurotoxic effects in central nervous system (CNS). Most used nanoparticle having the capacity to cross the BBB are pegylated and polysorbate 80-coated nanoparticles. However, their exact of mechanism of action is unknown. Moreover, superparamagnetic iron oxide nanoparticles (SPIONs) can stimulate the production reactive oxygen species (ROS) and inflict cellular damage [139]. Superparamagnetic Iron Oxide Nanoparticle (SPIONs) contain iron oxide core with modified surface which infleunce cellular uptake and circulation time. According to research, the surface coating and particle size have a major impact on how well macrophages absorb and retain the particles in the body. Studies reported the potential risk associated with those nanoparticles such as mitochondrial dysfunction due to and oxidative stress [140].

Research comparing various SPIONs' surface coating and size has shown that these characteristics affect toxicity levels. For instance, compared with coated variants, untreated SPIONs showed increased toxicity, while certain coated particles even encouraged proliferation [141]. Even though SPIONs offer promising medical applications, more study is needed comprehend their neurotoxic potential and guarantee their safe implementation in clinical settings.

11.1.3. Nanosilver

The toxicity of nanosilver is strongly associated with its respective transformation in biological, such as surface oxidation, silver ion release, and interactions with biological macromolecules [142]. Nano-silver inhibits signalling pathways by interacting with membrane proteins [143]. Silver nanoparticles can enter the cells via diffusion or endocytosi and promote mitochondrial dysfunction by producing reactive oxygen species (ROS). This, in turn, can damage cellular proteins and nucleic acids, ultimately inhibiting cell proliferation [144, 145]

11.2. Biocompatibility of nanoparticles

In early stages of research, researchers assess the cytotoxic effects of newly nanomaterials to identify any potential risk associated with the disruptions to fundamental cellular functions. However, the absence of cytotoxicity does not guarantee biocompatibility, which must be assessed independently. Biocompatibility refers to a material's capacity to interact with biological systems without eliciting toxic or immune responses. Generally, a biocompatible material does not cause negative effects like oxidative stress, DNA damage, mutagenesis, or cell death [146].

11.2.1. Hemocompatibility

Recent research endeavours to comprehend the blood compatibility of foreign materials, and their analysis has demonstrated that the blood compatibility was influenced by diverse material surface features. Blood's response with the materials relies on physiochemical features like the surface area, surface charge, hydrophobicity/hydrophilicity etc [147].

11.2.3. Histocompatibility

The biocompatibility of many nanomaterials, including gold nanoparticles (AuNPs), dendrimers, silica nanoparticles, and SPIONs, varies, which makes them interesting for targeted medication administration and diagnostics. SPIONs are generally biocompatible [148]. The toxicity of dendrimers is dependent on their production method and surface charge; cationic forms exhibit increased toxicity, yet this can be mitigated by modifications such as PEG. Functionalized silica nanoparticles can carry genes and facilitate imaging. AuNPs are useful in a variety of biological contexts, but they frequently elicit little immune response unless they are coated with peptides, which can set off reactions. To create safe and useful nanomaterials for medical applications, it is imperative to assess these interactions [149, 150].

12. CHALLENGES IN STABILITY OF EPIGENETIC MODIFIERS

Histone acetylation and DNA methylation might be chemically unstable. These alterations may be lost or altered because of environmental variables like oxidative stress or pH variations. For example, hydroxymethylation can alter gene regulation by destabilizing DNA structures [22].

The activity of the enzymes that add or remove epigenetic marks, such as histone deacetylases and DNA methyltransferases, can vary depending on the state of the cell. The exact regulation of gene expression may become more difficult because of heterogeneity, which may result in irregular epigenetic states [45]. The cellular environment frequently affects epigenetic modifiers. Different cell types may react differently to the same epigenetic change. When using epigenetic therapy, this diversity makes outcome prediction more difficult [52].

The reversible nature of many epigenetic changes can have both positive and negative effects. This makes it possible to react dynamically in different environment, but it also makes it difficult to sustain steady patterns of gene expression over time [22]. Some changes are temporary, which could cause therapeutic applications to lose their intended effects. Epigenetic modifiers interact with different cellular pathways rather than functioning alone. Histone changes, for instance, might affect or be affected by other post-translational changes, forming a complicated regulatory network which can make it more difficult to accomplish desired gene expression. The use of pharmaceuticals intended to alter epigenetic states carries the danger of off-target consequences, in which genes that are not intended are altered. Negative effects could result from this, such as oncogene activation or tumor suppressor gene suppression [47].

13. CONCLUSION

The combination of nanotechnology and epigenetics offers revolutionary approach to improve stem cell therapy for tissue regeneration. Precision, survival, and development of stem cells in regenerative medicine can be improves by nanomaterials and nanoparticle-based delivery systems. Concurrently, epigenetic modification via non-coding RNAs, histone modifications, and DNA methylation provides an additional degree of control over stem cells fate and their capacity for regeneration.

The convergence of these domains, especially through epigenetic modification mediated by nanoparticles, hold promise to develop personalized and efficient treatments. Despite notable progress, challenges remain such as instability of epigenetic modifiers and the biocompatibility of nanomaterials. To completely achieve the potential of this interdisciplinary approach in clinical settings, future research focused needs to focus on overcoming these obstacles.

CONFLICT OF INTEREST

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