Trends in Biomaterials and Artificial Organs
www.biomaterials.org.in/tibao
ISSN 0971-1198
https://doi.org/10.5281/zenodo.17461923

Review Article

Silver Nanoparticles in Tissue Regeneration: Mechanisms, Cellular Interactions, and Therapeutic Potential

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Received: *1 March 2025*
Accepted: *1 October 2025*
Published online: *28 October 2025*

Keywords: *silver nanoparticles, osteoblasts, osteoclasts, mesenchymal stem cells, tissue engineering*

Tissue regeneration is crucial for restoring damaged cells, promoting organ function, and enhancing overall well-being. Nanotechnology, particularly the use of silver nanoparticles (AgNPs), has revolutionized regenerative medicine by providing targeted therapeutic interventions. AgNPs exhibit unique properties such as antimicrobial activity, osteogenic enhancement, antioxidant effects, and the ability to modulate inflammatory responses, making them valuable in tissue and bone regeneration. Their interactions with key cellular components, including osteoblasts, osteoclasts, and mesenchymal stem cells, further contribute to their regenerative capabilities. This review provides a comprehensive exploration of AgNP-mediated tissue regeneration, including their role in antimicrobial defense, oxidative stress mitigation, angiogenesis, and cell proliferation. Additionally, the influence of AgNP size on cellular uptake and differentiation is examined, alongside the benefits of green synthesis methods for improved biocompatibility. While AgNPs hold great promise in regenerative applications, concerns regarding cytotoxicity and long-term stability necessitate further research. By compiling recent findings, this review aims to provide an up-to-date insight into AgNPs applications in tissue engineering, offering perspectives for future biomedical advancements.

Introduction

Tissue engineering and regenerative medicine (TERM), a multidisciplinary field with constant growth and development is aimed at replacing the lost portion of native tissue/organ as implantable systems. The strategy of TERM combines cells, scaffolds and growth factors to regulate cell growth and differentiation to from tissues [1-3]. Recapitulating tissue microenvironment with appropriate extracellular matrix (ECM) composition requires a nanoscale strategy rather than a macroscopic approach. Bone tissue regeneration is a vital area of research, focusing on repairing or replacing damaged bone tissue, which is essential for addressing various medical conditions and improving quality of life, particularly for individuals suffering from trauma, degenerative diseases such as osteoporosis, osteoarthritis, and rheumatoid arthritis, cancer, and dental and maxillofacial defects [4]. The importance of bone tissue regeneration lies in its potential to restore function and mobility, alleviate pain, and enhance overall well-being. However, this field is fraught with challenges, including the complexity of bone structure and cellular composition, which makes replicating its natural environment difficult [5]. Additionally, controlling stem cell differentiation into bone-forming cells, ensuring adequate vascularization, and ensuring biocompatibility and non-toxicity of materials used for regeneration pose significant hurdles [6,7]. Despite these challenges, researchers are making strides in stem cell therapies, biomaterials and scaffolds, growth factors and cytokines, 3D printing and bioprinting, and gene editing and therapy. For instance, mesenchymal stem cells (MSCs) and induced pluripotent stem cells are being explored for their potential in bone regeneration, while biomaterials such as hydroxyapatite and collagen are being developed to support bone growth [8-10]. Growth factors like bone morphogenetic proteins and vascular endothelial growth factor are also being investigated to enhance regeneration. Moreover, 3D printing and bioprinting techniques are being employed to create customized bone structures, and gene editing tools like CRISPR/Cas9 are being explored to modify genes involved in bone regeneration. However, addressing the existing challenges and translating innovative solutions into clinical practice requires continued collaboration among researchers, clinicians, and industry experts. Successful bone tissue regeneration has the potential to revolutionize treatment outcomes for bone-related disorders, improve quality of life for millions worldwide,

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and reduce healthcare costs associated with bone diseases, underscoring the importance of sustained research and development in this critical field [11-15].

A top-down disassembly of the components of bone reveals the presence of nanostructured collagen and hydroxyapatite crystals highlighting the prevalence of nanodimension in bone tissue. With the advent of nanotechnological approaches it is now possible to create hierarchical structures with appropriate chemistry in a much controllable and predictable manner. Nanosized particles have emerged as a promising tool for bone tissue regeneration, offering enhanced osteoconductivity, osteoinductivity, and osteogenesis due to their unique properties, such as high surface area-to-volume ratio, tunable surface chemistry, and ability to interact with cells at the nanoscale [16-18]. Various types of nanoparticles, including calcium phosphate, hydroxyapatite, silica, titanium dioxide, and polymer-based nanoparticles, have been investigated for their potential in bone regeneration. These nanoparticles can be designed to mimic the natural bone environment, promoting cell adhesion, proliferation, and differentiation, while also providing a scaffold for new bone growth [19]. Nanoparticles are widely employed in scaffolds and hydrogels to modify the surface properties and enhanced the characteristics [20]. Metal nanoparticles, such as gold, silver, titanium, and zinc, have shown great promise in bone tissue regeneration due to their unique physical and chemical properties [21]. These nanoparticles have a high surface area-to-volume ratio, allowing them to interact effectively with biological systems. When integrated into scaffolds or used in drug delivery systems, metal nanoparticles can enhance osteogenesis by stimulating MSCs to differentiate into osteoblasts, thereby promoting bone formation [22]. Titanium nanoparticles, for instance, improve the osteointegration of implants by facilitating cell attachment and growth on the surface [23]. Zinc nanoparticles, on the other hand, promote bone healing by regulating key signaling pathways, including the Wnt/â-catenin pathway [24]. Moreover, their controlled release of metal ions can have therapeutic effects, enhancing tissue healing while minimizing toxicity risks. Functionalizing metal nanoparticles with biomolecules or growth factors further enhances their efficacy in bone tissue engineering, enabling targeted delivery and controlled release of therapeutic agents [25, 26]. While challenges persist, including long-term stability, potential toxicity, and scalability, metal nanoparticles hold significant promise for improving bone repair and regeneration therapies [27]. Silver nanoparticles (AgNPs) have emerged as a valuable tool in bone tissue regeneration, offering a unique combination of antimicrobial activity, biocompatibility, and osteogenic enhancement. By releasing silver ions with potent bactericidal effects, AgNPs effectively prevent infections at bone injury sites, reducing the risk of post-surgical complications. Moreover, AgNPs promote osteoblast proliferation and differentiation, stimulate collagen production, and activate key signaling pathways, such as the BMP pathway, to facilitate bone formation. When incorporated into scaffolds and hydrogels, AgNPs enhance mechanical properties and support cell adhesion, further accelerating bone healing [28-31]. Functionalization of AgNPs with biomolecules or growth factors enables controlled and targeted release, amplifying their therapeutic efficacy [32]. Additionally, AgNPs exhibit anti-inflammatory properties, modulating the healing environment to reduce inflammation and promote tissue repair. While concerns about potential toxicity necessitate careful management, the integration of AgNPs in bone tissue engineering holds significant promise for improving bone regeneration and repair outcomes [33-35]. In this review, we explored the properties of silver nanoparticles that account for successful implication in tissue regeneration and the effect of silver nanoparticles on various types of cells. Although several reports investigated the same, the influence of size of the particle in its application of bone and tissue regeneration is not studied. Recent research investigations in the field were complied to provide readers a detailed insight into the topic

Mechanisms of Action of AgNPs in Tissue Regeneration

Due to the unique physicochemical properties of AgNPs, such as small size, high surface area, and antimicrobial activity, they aid in tissue regeneration [36].

Antimicrobial property

AgNPs play a vital role in tissue regeneration by providing antimicrobial protection at wound sites. Their potent antibacterial properties effectively combat a wide range of pathogens, significantly reducing the risk of infection and promoting successful tissue healing. These nanoparticles have demonstrated efficacy against both gram-positive and gram-negative bacteria, making them a valuable asset in combating a wide range of bacterial infections. The superior physicochemical characteristics of AgNPs, including their small size, high surface area, and unique shape, significantly enhance their anti-pathogenic activity compared to silver ions [37-39]. This enhanced activity can be attributed to the ability of AgNPs to interact with bacterial membranes, facilitating their penetration into the cells and causing substantial disruption to cellular functions. Once inside the bacterial cells, AgNPs induce significant structural damage, ultimately leading to cell death. This multifaceted mechanism of action, involving the disruption of cellular membranes, DNA, and proteins, makes AgNPs a highly effective antibacterial agent (40). The unique properties of AgNPs, including their high antibacterial efficacy, low toxicity, and ability to combat antibiotic-resistant bacteria, make them particularly valuable in the development of novel antibacterial therapies. Furthermore, the potential of AgNPs to be used in conjunction with existing antibiotics to enhance their efficacy and reduce the emergence of antibiotic-resistant bacteria is an area of ongoing research. These exceptional antibacterial properties of AgNPs, combined with their low toxicity and ability to combat antibiotic-resistant bacteria, make them a promising tool in the fight against bacterial infections, especially aiding in tissue regeneration [41, 42].

Antioxidant property

Oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them, can cause cellular damage, inflammation, and delayed tissue repair. AgNPs possess inherent antioxidant properties that help mitigate oxidative damage and promote a conducive environment for tissue regeneration [43-45]. One of the primary mechanisms by which AgNPs exert antioxidant effects is through their ability to scavenge free radicals and ROS, such as hydroxyl radicals and superoxide anions. By interacting with these harmful molecules, AgNPs can neutralize them before they can cause cellular damage [46]. This action is particularly important in protecting cellular components, such as membrane lipids, proteins, and DNA, from oxidative damage that could otherwise impair cellular function and prolong the healing process. The antioxidant activity of AgNPs also helps maintain the integrity of cells involved in tissue repair, such as fibroblasts, endothelial cells, and epithelial cells [47, 48]. By reducing oxidative stress, AgNPs promote the proliferation and migration of these cells to the injury site, thereby facilitating tissue regeneration [49]. Furthermore, AgNPs contribute to the preservation of mitochondrial function, which is essential for cellular energy production. By reducing oxidative damage to mitochondria, AgNPs ensure that cells have sufficient energy to perform vital repair functions. AgNPs are found to modulate the

expression of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase. These enzymes play a critical role in neutralizing ROS and protecting cells from oxidative damage. By enhancing the activity of these enzymes, AgNPs further support cellular defense mechanisms and foster a more favorable environment for tissue regeneration [50-53].

Anti inflammatory property

The reduction of inflammation by AgNPs plays a crucial role in supporting tissue regeneration. Chronic inflammation is a significant barrier to effective tissue repair, often leading to delayed healing, the formation of excessive scar tissue, or even tissue degeneration. AgNPs have demonstrated to modulate the inflammatory response that can help mitigate the detrimental effects of inflammation on tissue regeneration [54]. Research has shown that AgNPs can reduce inflammation by inhibiting the production of key pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). These cytokines are central to initiating and sustaining inflammation, and their downregulation by AgNPs helps alleviate the severity of the inflammatory response. Additionally, AgNPs promote the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which further supports tissue repair and regeneration. The anti-inflammatory effects of AgNPs are thought to result from their interactions with immune cells, including macrophages and neutrophils [55-57]. AgNPs have been shown to modulate immune cell activity, reducing the activation of these cells and consequently limiting the release of pro-inflammatory cytokines. Furthermore, AgNPs are known to encourage the polarization of macrophages toward an anti-inflammatory phenotype, which enhances tissue repair processes and contributes to a regenerative environment [58].

Anticoagulant property

During tissue regeneration, a delicate balance is required where clotting must occur to initially seal the wound. But excessive clotting or fibrosis can obstruct blood flow, leading to tissue hypoxia, inflammation, and ultimately, impaired tissue regeneration. Moreover, blood clots can also provide a physical barrier that prevents the migration of cells, including stem cells, to the injury site, thereby impeding the tissue repair process [59-61]. AgNPs is found to interact with key proteins involved in the clotting cascade, modulating blood coagulation. By preventing abnormal clot formation, AgNPs help ensure that the wound environment remains conducive to regeneration by allowing continued circulation to nourish the damaged tissue. The anticoagulant property of AgNPs is attributed to their ability to interact with blood proteins, such as fibrinogen and thrombin, which are essential for blood clot formation [62].

Angiogenic activity

Angiogenesis, the process of forming new blood vessels, is a crucial step in tissue regeneration, as it provides a means of delivering oxygen and nutrients to the regenerating tissue. Without a sufficient blood supply, tissue regeneration is severely impaired, leading to inadequate healing, tissue damage, and even necrosis. Furthermore, angiogenesis facilitates the removal of waste products and inflammatory mediators, creating a favorable environment for tissue regeneration [63]. AgNPs have been found to promote angiogenesis by increasing the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). These growth factors stimulate the proliferation and migration of endothelial cells, leading to the formation of new blood vessels. Additionally, AgNPs have been shown to enhance the activation of endothelial cells, promoting their migration and organization into tubular structures, a critical step in angiogenesis [64, 65].

Cell proliferation and migration ability

AgNPs have been shown to exhibit a range of biological activities, including antimicrobial, anti-inflammatory, and pro-healing effects. One of the key mechanisms by which AgNPs promote tissue repair is through the enhancement of cell proliferation and migration [66]. Studies have demonstrated that AgNPs can increase cell proliferation rates in a variety of cell types, including fibroblasts, keratinocytes, and endothelial cells. This is thought to be due to the ability of AgNPs to modulate key signaling pathways involved in cell growth and division, such as the PI3K/Akt and MAPK/ERK pathways. Additionally, AgNPs have been shown to increase the expression of genes involved in cell cycle progression, such as cyclin D1 and cyclin E [67]. In addition to promoting cell proliferation, AgNPs have also been shown to enhance cell migration. Cell migration is a critical process involved in tissue repair, as it allows cells to move into areas of damaged tissue and contribute to the repair process. AgNPs have been shown to increase cell migration rates in a variety of cell types, including fibroblasts and keratinocytes. This is thought to be due to the ability of AgNPs to modulate key signaling pathways involved in cell migration, such as the Rho/ROCK pathway [68, 69]. The promotion of cell proliferation and migration by AgNPs has important implications for the development of new therapies for tissue repair and regeneration. AgNPs may be used to enhance the healing of wounds, including chronic wounds that are resistant to healing. Additionally, AgNPs may be used to promote the regeneration of damaged tissues, such as bone and cartilage. Overall, the ability of AgNPs to promote cell proliferation and migration makes them a promising tool for the development of new therapies for tissue repair and regeneration [70].

Ability to improve collagen production

Collagen is a crucial component of the extracellular matrix (ECM) that provides structural support and facilitates cell adhesion, migration, and differentiation. AgNPs have been shown to enhance collagen synthesis by fibroblasts, which are the primary cells responsible for producing collagen in the ECM [71]. The increased collagen synthesis mediated by AgNPs is attributed to their ability to modulate various signaling pathways, including the Smad-dependent and Smad-independent pathways, which are involved in the regulation of collagen gene expression [72]. Furthermore, AgNPs have been shown to increase the expression of collagen-related genes, such as COL1A1 and COL3A1, which encode for type I and type III collagen, respectively. The enhanced collagen synthesis mediated by AgNPs is also accompanied by an increase in the deposition of collagen fibers, which is essential for the formation of a functional ECM that can support tissue regeneration. The collagen synthesis property of AgNPs is particularly important in wound healing, as it facilitates the formation of a strong and resilient ECM that can withstand mechanical stress and promote tissue repair. Moreover, the enhanced collagen synthesis mediated by AgNPs can also promote the differentiation of stem cells into various cell types, including fibroblasts, osteoblasts, and chondrocytes, which are essential for tissue regeneration [73, 74].

Stem cell differentiation

Stem cell differentiation is a pivotal process in tissue regeneration, enabling stem cells to specialize into distinct cell types essential for repairing and replacing damaged tissues. The capacity of stem cells to differentiate into specific cell types, such as fibroblasts, endothelial cells, chondrocytes, and osteoblasts, is crucial for forming functional

tissue structures and restoring tissue integrity [75]. In tissue regeneration, stem cells possess the remarkable ability to not only replenish lost or damaged cells but also to reorganize the extracellular matrix and promote angiogenesis, further contributing to tissue repair [76]. The controlled differentiation of stem cells is particularly vital in addressing injuries or diseases where natural tissue repair mechanisms are inadequate, such as large tissue defects, degenerative conditions, and complex organ injuries. Stem cell-based therapies aim to harness this differentiation ability to promote tissue regeneration, offering promising strategies for healing a variety of damaged tissues, including skin, bone, cartilage, muscle, and nerves [77, 78].

AgNPs holds the ability to influence stem cell behavior, including the differentiation process. AgNPs interact with stem cells, influencing signaling pathways, enhancing the microenvironment, reducing oxidative stress, and promoting angiogenesis and immune modulation. By activating specific signaling pathways, such as TGF-β, BMPs, and Wnt/β-catenin, AgNPs can direct stem cell differentiation toward specific lineages, including osteoblasts, chondrocytes, and endothelial cells. AgNPs also modulate the stem cell microenvironment, influencing ECM organization and integrity, and promoting angiogenesis. Their antioxidant properties protect stem cells from oxidative damage, ensuring their proliferative potential and promoting successful differentiation. Additionally, AgNPs exert anti-inflammatory effects, creating a pro-regenerative environment that favors stem cell differentiation and tissue repair [79-82]. The incorporation of AgNPs into scaffolds and biomaterials provides a localized source of stimulation to guide stem cell differentiation at the injury site. This approach offers a powerful strategy for tissue regeneration, particularly in complex or large-scale tissue injuries. By harnessing the unique properties of AgNPs, it is possible to improve the efficiency and outcomes of stem cell-based therapies, leading to more effective tissue regeneration and restoration of function in damaged tissues [83, 84].

Effect of AgNPs in Osteoblast, Osteoclast and Mesenchymal Stem Cells and Mechanism Involved

As per the discussion it is know that AgNPs promote osteogenesis, which could in turn help in bone fracture healing. Multiple *in vitro* and *in vivo* studies supports the argument. The *in vivo* study by Zhang et al, demonstrated that the AgNPs improved the proliferation and osteogenic activity of MSCs into osteoblast. But the effect of differentiation into chondrocyte and adipocyte by AgNPs was found to be comparatively less. The gene expression study showed that the AgNPs has induced expression of osteoblast differentiation regulator gene *cbfa1* a little earlier. The fracture healing in mouse model was promoted by AgNPs [85]. Qin and coworkers studied the effect of osteogenic differentiation of human urine-derived stem cells. The particles in this study showed minimal dose dependent activity, which was found to be due to the induction of polymerization of actin, activation of RhoA and increment in cytoskeletal tension by AgNPs [86]. Qing et al, conducted gene expression study to find the influence of AgNPs in bone differentiation *in vitro*. The team utilized RNA sequencing technology to evaluate the mechanism involved. The genes responsible of osteogenesis pathway including Fosl1, Bmp4 and Bmp6 were found to be affected by the AgNPs and through which the process was promoted compared to control cells [87]. Implant related infections need a serious discussion, as it remains unsolved. Flores et al, functionalized the AgNPs with citrate and tested the antibacterial efficacy, specifically on titanium substrate as it is the most widely used material for implant. It was concluded that the prepared nanoparticles prevented the formation of biofilm in terms of both bacterial type. Also, the cytotoxic effects were studied *in vitro* on osteoblast cells. The results suggest that at low concentrations, the cytotoxic effect is minimal with high bactericidal effect, making the particle significant as implant material [88]. Similarly, Pauksch et al, constructed polymethylmethacrylate polymer functionalized with AgNPs or loaded with gentamicin. The biocompatibility with the cells that regulate or involved in bone formation was evaluated *in vitro* by studying the cell viability and cell differentiation of MSCs. Both the materials showcased similar cytocompatibility. But the combination of the materials featured decrease in osteogenic differentiation with increase in cell stress. It was concluded that the combination of materials used showed high antibacterial activity with cytocompatibility, which was found to be best suitable for the bone cement material [89]. Research findings indicate that applying nanoparticulate silver coatings to orthopedic implants, particularly those that come into direct contact

Table 1: Compilation of research evidence that reported the use of AgNPs in stimulating osteogenesis and the possible mechanism involved

	Mechanism involved	Concentration used	Ref.
1.	Increase in alkaline phosphatase (ALP) activity, induce osteogenic protein expression, e extracellular matrix mineralization, and activation of autophagy,	2.5 and 5 µg/ml	(92)
2.	Regulation of Rhoa-TAZ axis	25–100 µm	(93)
3.	Bactericidal activity and ROS generation in osteoclasts	10 µg/ml	(94)
4.	RANKL-induced phosphorylation of ERK, JNK, iκbα, and p65	0.01 to 0.05 nm	(95)
5.	Increased oxidative stress and decreased clathrin-dependent endocytosis on mRNA level.	1000 ng/g	(96)
6.	Improved the antimicrobial prophylactic activity	Varying concentrations	(97)
7.	Enhancement in cell calcification and ALP activity	= 50 mol% Pt	(98)
8.	Increased ALP activity and the expression of other osteogenic markers including Runx2, Col-I and OCN	200 ng/ml	(99)
9.	Inhibited pro-inflammatory cytokine expression, induced greater expression of vascular endothelial growth factor (VEGF) and stromal-cell derived factor-1 alpha (SDF-1α)	30.2 ppm	(100)
10.	Upregulation of IL-8 expression via HIF-1a	Varying concentrations	(101)

Table 2: Compilation of research evidence that reported green route of AgNPs synthesis for the application of bone and tissue regeneration

	Details of the source	Size	Ref
1.	*Aspergillus sp.* KF913249	416 nm	(104)
2.	Sil Fibroin	5-12 nm	(105)
3.	*Bauhinia acuminate*	17 nm	(106)
4.	Roasted green tea	19.85 ± 3 nm	(107)
5.	Dimorphocalyx glabellus	22-185 nm	(108)
6.	Agarose	10 to 15 nm	(109)
7.	*Oroxylum indicum*	21.49 ± 0.32 nm	(110)
8.	*Cyperus conglomeratus*	-	(111)
9.	*Flos Sophorae Immaturus*	-	(112)
10.	Trigonella foenm -graecum	118.0 ± 1.7 nm	(113)

with bone, may compromise their biocompatibility. Therefore, additional *in vivo* studies are essential to ensure the safety and efficacy of silver nanoparticle-coated orthopedic implants before they can be widely adopted in clinical practice. Several reports have studied the mechanism involved in this factor. Mahmood et al, found that the AgNP accounted in regulation and expression of miRNA, bone morphogenetic protein 2 (BMP2) and essential transcriptional factors. These processes are crucial for the process of bone cell mineralization and as the AgNPs improves the process, they are best suitable for the application of tissue regeneration [90]. He et al, reported interesting results that explains that the AgNPs enhance not only the osteogenesis but also adipogenesis, which is more compared to osteogenesis. For this study, the group utilized MSCs. The AgNPs upregulated adipogenesis related genes, accumulated high amount of lipid droplets and activated the accumulation of intracellular ROS, which was found to be accountable incase of the enhancement in adipogenesis [91]. Other research reports are given in table 1.

Importance of Green Synthesis and its Application in Bone and Tissue Regeneration

Green synthesized AgNPs offer a sustainable and environmentally friendly alternative to traditional chemical synthesis methods. By utilizing plant extracts, microorganisms, or biopolymers to reduce silver ions, green synthesis eliminates the need for toxic chemicals. The resulting eco-friendly nanoparticles exhibit exceptional antimicrobial properties, making them ideal for medical applications, wound healing, and food preservation. Furthermore, green AgNPs are biocompatible, reducing potential toxicity, and can be tailored for various applications (table 2). The green synthesis process is not only cost-effective and scalable but also aligns with green chemistry principles, promoting a safer and more sustainable approach to nanotechnology [102, 103].

Influence of Size of AgNPs on its Application in Tissue Regeneration

As the properties and activities of nanoparticles are size dependent, it is important to study the influence of size for specific application. While designing AgNPs based orthopedic implant, the understanding of the effect of the particle on the survival rate of osteoblast and osteoclast is crucial as it determines the biocompatibility of the implants [114]. Albers et al, has reported the cytotoxicity of AgNPs on osteoblast and osteoclast for the first time. The *in vitro* study results demonstrated a size dependent activity. The treatment with AgNPs showed decrease in cell viability and differentiation. The results showcased that osteoblast were more affected by the AgNPs treatment than osteoclast. It was also found that the particles that ranged around 50 nm showed strong toxicity, while particle with 3 µm size featured weak toxicity. This was due to the release of silver ions from the particles. The release was found to be dependent on the size and dose. The nanoparticles with 30 nm size showed higher amount of release of silver ions than the silver microparticle that ranged 3mm in Inductively coupled plasma atomic emission spectroscopic analysis [115]. Similar to this result, Rosario et al, studied contribution of release of silver ions at smaller sized particles, in turn influence the properties. For the same, the team developed two different sizes of PVA coated AgNPs, ie, 10 and 20 nm in diameter. From the results, it was shown that the particle in10 nm were reactive leading to the formation of larger aggregates. The study of size dependent activities concluded that the particle in 20 nm arrested the cell cycle and apoptosis, while the particle in 10 nm induced necrosis without any cytostatic effect and adsorption procedure. Hence, from the results, it was demonstrated that the size of the particle plays a important role in cellular uptake and adsorption procedure [116]. With the same PVP coated AgNPs, but with a particle size of 30 nm was subjected to the study of its effect on adipogenic differentiation by He et al. This *in vitro* study with MSCs showed that AgNPs possessed dose and time dependent cytotoxicity. The prepared complex at the particular size showed no influence on the adipogenic differentiation [117]. The study by Sengstock et al, showcased that the particle with the hydrodynamic diameter of 80 nm were more taken up by MSCs. It was found to be accumulated in endolysosomal compartments. When the cells were exposure to subtoxic AgNPs concentrations, it impaired the adipogenic and osteogenic differentiation, while chondrogenic differentiation remained unaffected [118]. Samberg et al, studied the influence of copolymer with AgNPs on osteoblast differentiation, where the spherical shaped particles ranging between 10-20 nm showed mild toxicity on adipose-derived stem cells at particular concentration. This was studied by providing the cells with the single dose for 24 h. This *in vitro* study results demonstrated that particles are particular size can penetrate the cells and exhibit different mechanism for differentiation [119]. Similarly, Hackenberg et al, reported that the spherical and elongated AgNPs at the size of around 45 nm showed high toxicity in the cell viability of adipose-derived stem cells [120].

Toxicity of AgNPs

AgNPs have garnered significant attention for their potential biomedical applications due to their multifaceted properties. However, concerns regarding their toxicity have sparked intense research. Despite humans naturally ingesting small amounts of silver daily, the effects of AgNPs on biological systems remain unclear [121]. Numerous *in vitro* and *in vivo* studies have yielded contradictory results, with some reporting toxic effects on various cell types, including rat hepatocytes, neuronal cells, and human lung epithelial cells. AgNP exposure has been linked to mitochondrial dysfunction, oxidative stress, and DNA damage, leading to apoptosis, necrosis, or inflammation [122]. The mechanisms behind AgNP toxicity are complex, involving factors such as surface charge, size, morphology, concentration, and dispersion rate. The zeta potential, a measure of surface charge, influences cellular uptake, translocation to tissues, and cytotoxicity. Surface functionalization can significantly impact AgNP toxicity. Further research is necessary to fully understand the toxic effects of AgNPs in both cellular and animal models. In vivo studies have demonstrated that AgNPs can cause structural and physiological

changes in vital organs, including the lungs, liver, kidney, and nervous system [123]. The transformation of AgNPs in biological and environmental conditions, including interactions with biological molecules, surface oxidation, and the release of silver ions, also influences their toxicity. Distinguishing between the toxicity associated with nanosilver and ionic silver is crucial [124, 125]. To better comprehend the risks associated with AgNP exposure, further studies in nanotoxicology are necessary to provide more coherent and meaningful findings. Pauksch et al, evaluated the biocompatibility of AgNPs of MSCs and osteoblast. The *in vitro* study results demonstrated dose dependent cytotoxicity. Though the mechanism of cell stress induction and dentrimental effects remain unexplored, this was predicted to be due to the production of ROS [126]. Xie et al, also reported that exposing AgNPs to osteoblast-like cells showed adverse effect on the osteogenic activity even at low concentration. Hence, it is proved that the AgNPs interfere in the formation of bone cells and may affect the mechanism leading to toxic effect [127]. These study results continuously suggest that AgNPs application in bone implant needs attention.

Conclusion

The pursuit of advanced therapies in tissue regeneration has been relentless, and this review has delved into the complex field, covering topics such as the mechanisms of silver nanoparticles (AgNPs) in tissue regeneration, their impact on specific tissue types, and the influence of size on bone formation by regulating osteoblast differentiation, osteoclasts, and other cells. AgNPs have emerged as promising candidates for efficient tissue regeneration due to their extraordinary modes of action and broad applications, demonstrating potential to reduce infection rates, minimize discomfort, and accelerate the healing process in various therapeutic situations. However, challenges such as cytotoxicity concerns and evolving regulatory issues must be addressed to realize the revolutionary promise of AgNPs in tissue regeneration, ensuring patient safety and responsible clinical implementation. As the world of tissue regeneration stands on the cusp of transformation, the integration of AgNPs presents a compelling route for innovation, and this study aims to inspire researchers to harness the potential of AgNPs to improve tissue regeneration and secure a better future for patients in need.

Acknowledgement

The authors acknowledge Saveetha Institute of Medical and Technical Sciences, Chennai for all their support.

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