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REVIEW

Gold Nanoparticle-Based Therapy for Muscle Inflammation and Oxidative Stress

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Abstract: Proinflammatory cytokines and reactive oxygen species are released after muscle damage, and although they are necessary for the muscle regeneration process, an excess of these substances leads to the destruction of biomolecules and impairment of the repair system. Several drugs have emerged in recent years to control the muscle inflammatory response, and studies have shown that gold nanoparticles (AuNPs) have anti-inflammatory and antioxidant properties. This review reveals the effects of AuNPs on the inflammatory and redox mechanisms of muscles. We assessed the results of several studies published in different journals over the last 20 years, with a focus on the effects of AuNPs on possible aspects of muscle regeneration or recovery, namely, inflammatory processes and redox system mechanisms. A systematic database search was conducted using PubMed, Medline, Bireme, Web of Science, and Google Scholar to identify peer-reviewed studies from the 2000s. Combinations of keywords related to muscle damage, regeneration or repair, AuNPs, oxidative stress, and antioxidants were used in the search. This review did not address other variables, such as specific diseases or other biological effects; however, these variables should be considered for a complete understanding of the effects of AuNPs on skeletal muscles.

Keywords: gold nanoparticles, redox homeostasis, antioxidant, muscle regeneration, inflammation, nanomaterials, oxidative stress

Introduction

In the last decade, gold nanoparticles (AuNPs) have been widely explored as tools with applications in the medical field. Several studies performed by our group and other researchers have revealed the potential application of AuNPs in the medical field based on their optical, anti-inflammatory, antioxidant, and anti-cancer properties. Paula et al[1] revealed that N-acetylcysteine (NAC) plus AuNPs promotes pronounced anti-inflammatory and antioxidant effects under conditions associated with lung inflammation. Haupenthal et al[2] showed that chronic administration of AuNPs in Mdx mice increased the antioxidant potential and reduced inflammation in the gastrocnemius muscle. Tartuce et al[3] also demonstrated the potential anti-inflammatory and antioxidant activities of AuNPs by conjugating AuNPs with 2-methoxy-isobutyl-isonitrile, which improved the redox and inflammatory profiles in infarcted rats. Other studies have indicated the efficacy of AuNPs as anticancer drug nanocarriers[4–6] and in disease diagnosis.[7]

Based on their demonstrated properties and effectiveness, AuNPs have become the focus of numerous studies in the research and development of new tools for applications in numerous diseases. However, for applications in the medical field, the physical and chemical properties of AuNPs need to be precisely controlled[8,9] because these properties have a direct influence on the interaction of AuNPs with biological cells/tissues,[10,11] as represented in Figure 1. The intracellular release rate of AuNPs can affect their associated toxicity depending on the dose, size, shape, and/or surface charge,[6,12–15] and different routes of administration can result in various effects on the biodistribution of drug carriers.[16] Different sizes and shapes of AuNPs tend to induce different responses when applied in biological media.[11,17] In vitro

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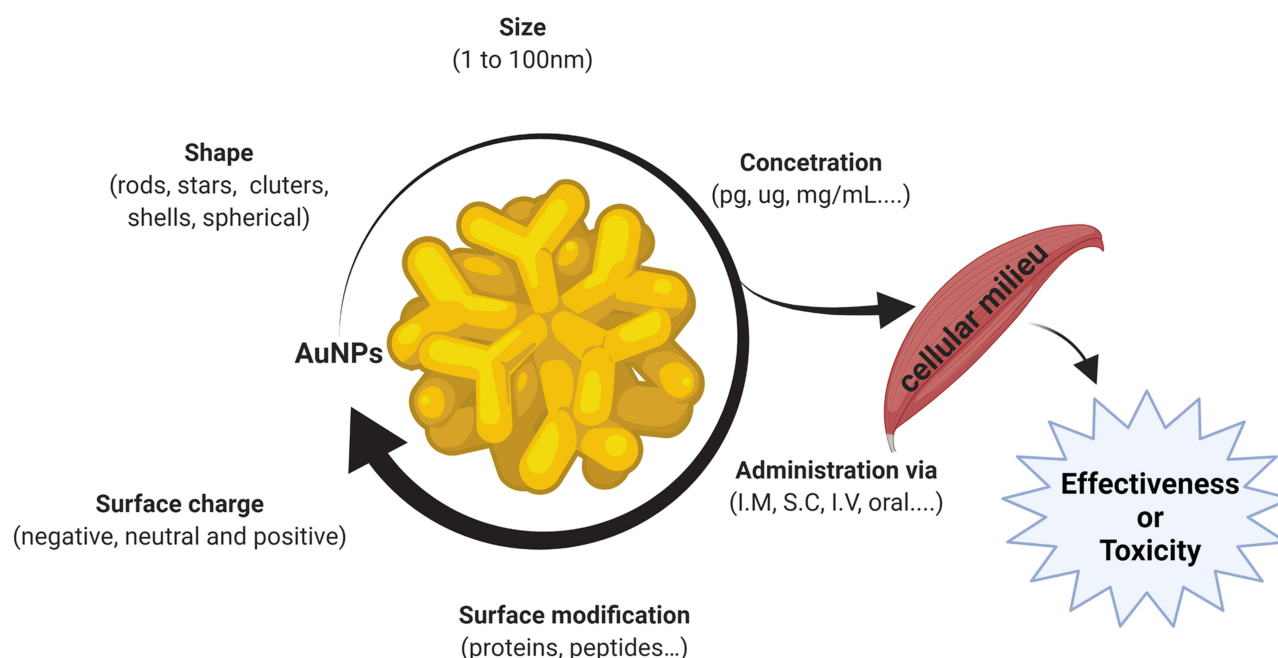
Figure I Critical factors for gold nanoparticles in muscle cells. The structural and physicochemical characteristics of gold nanoparticles, including the size, shape, charge, and surface modifications, as well as the concentration and administration route are determinants of the therapeutic effectiveness or toxicity to muscle cells.
Abbreviations: M, intramuscular; SC, subcutaneous; IV, intravenous.

studies have revealed that AuNPs present concentration-dependent cytotoxic effects, including increased reactive oxygen species (ROS) production and consequent oxidative damage.[18,19] However the complexity of a whole organism is much greater than that of a single cell, thus suggesting that a broad analysis is required that includes general health indicators and possible tissue toxicities.[20] For example, Chen et al[21] studied the in vivo effects of different concentrations of AuNPs and observed that concentrations of 3, 5, 50, and 100 nm did not show harmful effects; however, the intermediate size range of 8–37 nm had lethal effects on mice and induced severe sickness, clinical changes, and shorter average lifespans.

In relation to their shape, spherical AuNPs are the most commonly used because they easily synthesize and produce nanoparticles with different physicochemical properties.[22] Several studies have shown that these properties of AuNPs have direct implications in biological media.[10,11,23,24] The study of Della Vechia et al[11] demonstrated that particle size directly influences biological behavior. In this study, the authors showed that small variations in size (10–30 nm) could directly influence therapeutic efficacy as well as toxicity. Other studies have demonstrated that the shape of AuNPs is essential for their effectiveness when applied in biological media.[6,25] Xie et al[25] demonstrated that different AuNP shapes induced different cellular uptake mechanisms; and Xia et al[26] showed that the cellular uptake of AuNPs in human hepatoma cells (HepG2 cells) was dependent on their size and shape. The results showed that spherical AuNPs presented a higher uptake and star-shaped AuNPs presented lower uptake by HepG2 cells.

Another important property of AuNPs for application in the medical field is the surface charge. In conjunction with the size and shape, the surface charge can also directly affect the efficiency and cellular uptake of AuNPs. AuNPs can be positively and negatively charged or have a neutral charge. Gupta and Rai[27] evaluated the effect of the size and surface charge of AuNPs on skin permeability and showed that neutral AuNPs (2 nm) presented maximum permeability while cationic AuNPs (3 nm) exhibited the lowest permeability. In general, negatively charged AuNPs exhibit lower toxicity than positively charged AuNPs. AuNPs tend to disrupt cell membrane integrity, leading to increased toxicity.[28,29]

The surface of AuNPs can be easily linked with different types of ligands/biomolecules depending on the application, thereby ensuring the higher effectiveness of these nanoparticles.[30] The surface chemistry of AuNPs and surface modifications with biomolecules can significantly improve the permeability of these particles in cells/tissues, thereby increasing the effectiveness of AuNPs for the treatment and diagnosis of diseases.[31–34] The surface chemistry of AuNPs is considered a key factor in the toxicity of the particles. Özçiçek et al[35] showed that the surface chemistry of the AuNPs

was a more important parameter than the size in terms of in vivo histological toxicity. Surface modifications of AuNPs can induce a synergistic effect, thereby potentiating the performance of these particles for biomedical applications.[33]

All of these properties mentioned above are critical parameters for the effective application of nanomaterials in the medical field. However, the effectiveness and toxicity of AuNPs are also related to cell or tissue type, the concentration used, and the administration route.[11,26,36] In summary, spherical AuNPs with sized ≥50 nm tend to present an improved interaction with the biological medium and thus present higher effectiveness and lower toxicity.[6,29] Table 1 summarizes a number of the influences of physicochemical properties on the effectiveness of nanoparticles from in vitro and in vivo studies.

Gold Nanomaterials Alter ROS Function and Support Redox Homeostasis in the Muscle

From a historical perspective, the effect of oxidizing free radicals in various biological samples and the mechanism that induces toxicity and injury were first verified in the 1950s.[37,38] The effect of reactive oxygen species (ROS) on aging was discovered by Harman.[39] At that time, it was believed that ROS induced aging. Another milestone study confirmed the presence of ROS in living organisms by isolating superoxide dismutase (SOD) from bovine erythrocytes.[40] However, subsequent studies by Murad et al revealed the importance of ROS in biological functions; in particular, the role of nitric oxide (NO) in the vascular endothelial system revealed the importance of ROS as a secondary messenger in cell signaling to regulate various cellular functions.[41] As a result, several extraordinary studies on free radical biology have been conducted. Studies have well established that ROS and reactive nitrogen species (RNS) are crucial in regulating various cellular functions by acting as messengers in biological systems during cellular metabolism. Almost every cellular event, including survival, has been linked with the removal and acceptance of electrons (called redox), which sometimes impacts other molecules and causes oxidative stress during physiological and pathological events. High levels of ROS formation create an "oxidative distress" environment during the pathological event instead of oxidative stress, and various cellular and molecular functions are organized.[42] In addition, the level and steady-state of endogenous antioxidants determine the toxicity of these molecules. Indeed, exogenous antioxidant research has demonstrated for several decades the need to scavenge ROS. As a result, several molecules from natural products or synthesized products have been approved for treating various diseases, including cardiovascular and inflammatory diseases. However, addressing the limitations of these small molecules, such as their nonspecific distribution and low delivery efficiency, is difficult. The development of the nanotechnology field has significantly reduced the aforementioned burdens and could ultimately advance the field of antioxidant therapy.

Most importantly, several nanomaterials have been shown to efficiently increase the stability of endogenous antioxidants and improve their functions by protecting them from decay under harsh pH conditions in the cellular environment.[43,44] Furthermore, nanomaterials can act as artificial redox systems by mimicking various antioxidants or delivering antioxidants to targeted tissues, which can significantly combat ROS-induced damage.[45] However, the delivery of single antioxidants with nanomaterial doping can induce additional oxidative injury. For example, SOD-doped nanoparticles may be able to stop superoxide-induced oxidative damage but not concurrently induced hydrogen peroxide (H_2O_2)-mediated oxidative damage,[46] suggesting that nanomaterials must not only break the free radical chain but also prevent ROS-induced damage. Although studies have demonstrated that nanomaterials with doping molecules can affect ROS scavenging activity in vitro, transferring these findings to clinical trials has been limited by the low biocompatibility, biodegradability, hydrophobicity, and hydrophilicity of loading molecules.[46] Therefore, these factors should be considered when selecting nanomaterials with loading molecules to facilitate the treatment of ROS-mediated diseases. In this context, the use of gold materials, such as gold nanosheets, gold nanoconjugates, and AuNPs, has been reported to be effective in the treatment of various diseases, either with doping materials or AuNPs alone; however, the ability of such materials to affect ROS responses is the ultimate indicator of their benefits.[47] Based on their size, shape, and oxidation state, AuNPs induce ROS production or prevent ROS formation. In addition, AuNPs alter various redox signaling pathways, including threonine-protein kinase B (AKT), by supporting the controlled release of ROS. For example, bioconjugated AuNPs regulate ROS formation and corresponding signaling pathways to induce angiogenesis without

Table 1 Influence of the Physicochemical Properties of AuNPs on Their Effectiveness from in vitro and in vivo Studies

AuNP Characteristics	Surface Chemistry/ Modification	Methods	Findings	Reference
20 nm, spherical, positive surface	Citrate/N-acetylcysteine)	In vivo administration of AuNPs into the pleural cavity of male Wistar rats immediately after surgery	Anti-inflammatory and antioxidant effects on the lung	Paula et al[1]
20 nm, spherical, negative surface	Citrate	In vivo chronic subcutaneously administered AuNPs	Anti-inflammatory and antioxidant effects in the gastrocnemius	Haupenthal et al[2]
20 nm, spherical, negative surface	Citrate/ 2-methoxy-isobutyl -isonitrile	In vivo chronic administration study	Anti-inflammatory and antioxidant effects in the gastrocnemius	Tartuce et al[3]
10, 20, and 30 nm, spherical and near-spherical, negative surface	Citrate	In vitro cytotoxicity study of HeLa, NIH3T3, and human erythrocyte cells	20 nm AuNPs presented lower cytotoxic effects on NIH3T3 and higher cytotoxic effects on HeLa cells.	Della Vechia et al[11]
10 to 100 nm, spherical and rod-shaped, negative surface	Citrate	In vitro cellular uptake study of HeLa cells	50 nm and spherical AuNPs presented higher cellular uptake into HeLa cells.	Chithrani et al[13]
60 to 90 nm, star-, triangle-, and rod-shaped	HEPES, CTAB, and CTAC/methyl polyethylene glycol	In vitro cellular uptake study of RAW 264.7 cells	Triangle-shaped AuNPs exhibited the highest cellular uptake in RAW 264.7 cells, followed by rod- and star-shaped. All three shapes induced cellular uptake via the clathrin-mediated endocytic pathway	Xie et al[25]
5, 20, and 50 nm, spherical, negative surface	Citrate	In vivo study of BALB/c mice	50 nm AuNPs showed the longest blood circulation and highest distribution in the liver and spleen; 5 nm AuNPs increased neutrophils and slightly increased hepatotoxicity.	Xia et al[26]
2 to 5 nm, neutral, anionic, and cationic surface	Different surfaces	In vitro study of the interaction with skin lipid membranes	2 nm AuNPs with a neutral surface presented maximum permeability, and 3 nm AuNPs with a cationic surface presented minimal permeability.	Gupta and Rai[27]
25 nm	PVA	In vivo study of the influence of AuNP administration route on Wistar rats	Via oral administration, only a small amount of AuNPs was absorbed. Intravenous administration showed that the AuNPs are accumulated in the liver, lungs, and spleen and only slightly removed from the body via urine and feces.	Bednarski et al[36]

6 and 15 nm, neutral, anionic, and cationic surface	Citrate, lecithin, dodecanethiol, and cetrimide	In vitro study on human skin penetration of AuNPs with different surface modifications, sizes, vehicles, and concentrations	Dodecanethiol and cetrimide AuNPs were able to penetrate deeper layers of skin, while citrate-coated AuNPs were not detected	Labouta et al[14]
30, 60, and 100 nm	Citrate/PEG and IL4	In vivo study of female C57BL/6J mice to assess whether the association between IL-4 and AuNPs can direct the polarization of M2a Mφ.	AuNPs were able to deliver a cytokine to direct M2 macrophage polarization following muscle injury. The polarization shift promoted regeneration and increased muscle strength.	Raimondo and Mooney[15]
85 nm and 22 nm, rod-shaped, and positively charge	CTAB/BSA	In vitro cellular uptake study of RAW 264.7 cells	BSA-coated AuNPs were more stable and more easily uptaken.	Li et al[34]

Abbreviations: HEPES, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid); CTAB, cetrimonium bromide; CTAC, cetyltrimethylammonium chloride; BSA, bovine serum albumin; PEG, polyethylene glycol; IL4, interleukin 4; PVA, polyvinyl alcohol.

altering inflammatory cascades in human umbilical vein endothelial cells.[48] The use of gold-coated nanoparticles upregulates cluster of differentiation 163 (CD163) in macrophages in atherosclerosis.[49] Moreover, CD163 plays a crucial role in detoxifying ROS and preventing oxidative stress.[50]

Physical and Chemical Properties of AuNPs in the Formation of ROS and Oxidative Stress

The size of the AuNPs alters their impact on oxidative stress. For example, smaller-sized AuNPs promoted greater ROS formation, with approximately 2 nm AuNPs significantly increasing ROS by decreasing intracellular glutathione.[51] In contrast, 5 nm AuNPs increased cell survival under normoxic conditions compared to hypoxic conditions,[52] which may be due to the higher uptake efficiency and increased endocytosis facilitating less exposure to the cellular environment and extending the half-life.[53,54] At the molecular level, 1 and 3 h of AuNP treatment activated extracellular signal-regulated kinase (ERK) signaling in response to oxidative stress.[55] In addition to size, the shape of the AuNPs affects the formation of ROS and associated damage. For example, hexagonal AuNPs increase ROS formation compared to triangular and spherical AuNPs.[56] Other shapes, such as gold nanorods, significantly increased ROS formation compared to gold nanospheres, indicating that hexagonal and spherical AuNPs are more crucial for forming ROS. The surface chemistry of AuNPs affects the formation of ROS. Studies have shown that positively charged AuNPs with an approximate size of 1.5 nm increase apoptosis,[57] whereas other studies have shown that negatively charged AuNPs induce apoptosis in neutrophils.[58]

Neutral-charged AuNPs have also been shown to cause necrosis,[57] and AuNP-induced ROS could be a significant factor underlying apoptosis. However, AuNP-induced ROS formation may be due to the different AuNP sizes, cell types, and ligand structures. For example, AuNPs with suitable ligands can modify the redox properties of particles, which may enhance the redox-mediated cellular actions either by decreasing or increasing ROS. Previous studies have reported that PNP ligands and carbanionic ligands alter the redox properties of gold.[59,60] In addition, ligands could facilitate the internalization of AuNPs at the cellular level, which may occur through the endocytosis process.[61] Although ligands help stabilize nanoparticles during their synthesis and facilitate their internalization, their presence in cells mainly affects the catalytic activity of their substrate. Furthermore, removing the ligands influences the AuNP size, which in turn modifies the specific function of the AuNPs.[62] Such changes could eventually limit the redox-mediated benefits in the cells and cause ROS formation and oxidative stress. Developing a procedure to remove ligands that does not affect the size and morphology of the AuNPs would possibly enhance the redox properties of AuNPs.

In addition, the chiral structure of gold influences the formation of ROS. For example, a study showed that D-glutathione-decorated AuNPs increased ROS levels and depolarization of mitochondria compared to L-glutathione-decorated AuNPs in the human gastric cancer cell line 803 (MGC-803) cells.[63] Other metallic and non-metallic coated AuNPs also significantly influence ROS formation, such as platinum-coated gold nanorods and mesoporous silica nanoparticles with gold nanorods. Furthermore, AuNPs affect ROS-mediated autophagy according to their physicochemical properties. A possible mechanism is that ROS-activated adenosine monophosphate-activated protein kinase (AMPK) may inhibit the mammalian target of rapamycin (mTOR) and promote autophagy activation.[64] Another possible mechanism is that increased ROS formation inactivates autophagy-related proteins (Atg), particularly Atg4, consequently inducing autophagy,[65] suggesting that AuNPs induce autophagy in response to oxidative damage. On the other hand, this mechanism causes lysosome alkalinization, which results in the inhibition of autophagy and further cell death. In summary, all of these processes are associated with AuNP-induced ROS production and oxidative stress.

AuNPs with Endogenous Antioxidant Properties

As previously mentioned, nanoparticles have been exploited as artificial redox systems in nanomedicine in recent years. For example, cerium oxide nanoparticles mimic SOD and catalase (CAT) and display higher catalytic rates than inherent antioxidants.[66,67] Similarly, AuNPs exhibit CAT mimetic activity, which may be due to the mixed valence state of AuNPs that permits them to react with superoxide and hydrogen peroxide to detoxify ROS. However, coating the materials with AuNPs prevents an increase in the stability of the antioxidants. For example, Pt nanoparticles showed excellent

glutathione peroxidase (GPx) and SOD-activating abilities along with CAT activity, thus promoting the maintenance of ROS at a physiological concentration,[68] and Pt-coated AuNPs would efficiently stabilize this activity. A previous study showed that Pt-coated gold nanorods effectively detoxify ROS to prevent oxidative damage during plasmonic photo-thermal therapy.[68] In addition, AuNPs with antioxidants could alter the deoxyribonucleic acid (DNA) epigenetic pattern, thus affecting various cellular functions.[69] Furthermore, AuNPs (3.3 nm in diameter) doped with chiral L- and D-glutathione (D-GSH) inhibit tissue damage caused by ROS and are crucial for developing a potential therapeutic agent for various diseases, including neurodegenerative diseases, such as Alzheimer's disease (AD).[70,71] For example, AuNPs with capped mesoporous silica decreased cell membrane disruption and inhibited ROS-mediated apoptosis in AD.[72] However, all of these effects caused by AuNPs depend on the specific pH environment; otherwise, the Haber-Weiss and Fenton reactions could be induced.[73] Interestingly, a study showed that the pro-oxidant effect in biological microenvironments is inhibited at different hydrogen potentials (pH) when gold nanoclusters are entrapped into amine-terminated dendrimers; however, CAT activity is maintained.[66] In contrast, at acidic pH, the pro-oxidant effect is observed to induce ROS and inhibit enzyme intrinsic activity,[66] suggesting that the appropriate application of AuNPs could allow them to act as pH-responsive nanoantioxidants to modulate oxidative stress-mediated damage in cells.

Role of AuNPs in Muscle Oxidative Stress and Inflammation

Although ROS-mediated molecular signaling contributes to structural and functional alterations in muscle, a small increase in local or systemic ROS alters this scenario and causes redox disturbances in the muscle. Indeed, skeletal muscle-like structures increase ROS levels owing to their contractile activities. Therefore, additional sources are required to balance this scenario, particularly when endogenous antioxidants have a lower buffering capacity for ROS. As previously mentioned, within specific physicochemical conditions, AuNPs can effectively neutralize ROS and contribute to muscle homeostasis. To date, various mechanisms have been proposed for AuNPs and oxidative stress. Notably, AuNPs with specific decorating molecules have been reported to influence inflammatory molecules to regulate ROS and vice versa. However, less attention has been directed toward using AuNPs in treating muscle-related disorders. Studies have shown that AuNPs improve muscle morphology during muscle injury. Here, we discuss some possible mechanisms. The regeneration phase after muscle injury requires ROS to activate specific redox signaling. For example, AuNPs activate ROS-mediated redox signaling, such as mitogen-activated protein kinase (MAPK) and factor nuclear kappa B (NF-κB), to induce a protective muscle response. AuNPs interact with cysteine (Cys-179) of kinase-beta (IKK-beta) to influence NF-κB, which could decrease the levels of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha) and Interleukin-1beta (IL-1beta), thereby regulating ROS formation at physiological concentrations (Figure 2). Moreover, excess ROS induces secondary damage in nearby and uninjured muscle fibers.

The interaction between AuNPs and Cys may depend on neutral hydrogen bonding or zwitterionic interactions, which facilitate the aggregation of AuNPs in the muscle to activate redox-sensitive signaling.[74] We reported that AuNPs with suitable decorating molecules, such as diclofenac and taurine, improved tissue repair in the later phase of the repair process by controlling ROS formation, as evidenced by an increased level of interleukin-4 (IL-4) and interleukin-10 (IL-10). A possible reason is that AuNPs with taurine or diclofenac increase myogenic differentiation and support tissue remodeling by regulating ROS in macrophage-1 (M1) and macrophage-2 (M2) cells. For example, our group showed that spherical AuNPs with taurine upregulate myogenic regulatory factor 5 (Myf-5), thereby reducing oxidative damage during muscle recovery.[47] Another study also showed that AuNPs and gold-silver nanoparticles (Au-AgNPs) increased the myogenic differentiation of C2C12 myoblasts by activating myogenic genes, such as MyoD protein (MYOD) and MyoG protein (MyoGenin), and promoting myotube formation by activating p38 MAPK.[75] However, these effects may be size-dependent. For example, AuNPs with a higher surface area can effectively support the intoxication of ROS when decorated with other doping molecules.

In contrast, electron donor or acceptor molecules of proteins such as GSH could decrease according to the gold surface area, thus allowing for higher ROS formation. These effects may be size-dependent in the absence of steric hindrance and lead to increased electron transfer-induced chemical reactions, which reduce the glutathione content in the cytosol.[51] In particular, spherical AuNPs (approximately 1.4 nm in diameter) could induce mitochondrial damage and cell death in various cell lines, suggesting that ROS-induced damage is linked to these approximate sizes.[76] Therefore,
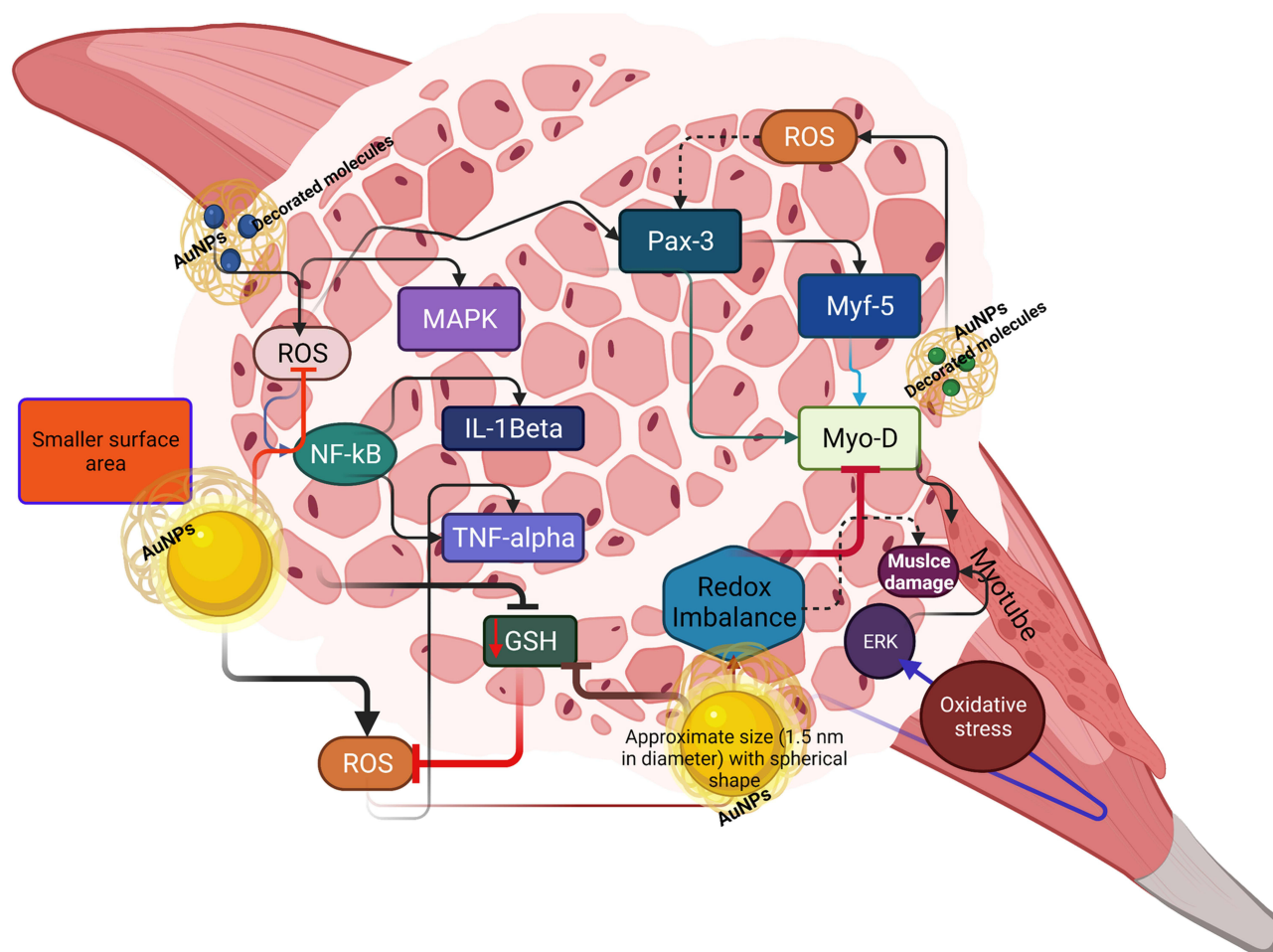
Figure 2 Schematic illustration explaining how AuNPs with decorating molecules influence redox homeostasis to improve muscle function. A smaller surface area with decorated molecules increases ROS formation and inhibits GSH (black inhibitory marks) and Myo-D (red inhibitory marks). However, AuNPs with selective ligands inhibit ROS formation and downregulate NF-kB and other inflammatory cytokines (TNF-alpha and IL-Beta), which activates Pax-3 and subsequently activates Myf-5 and Myo-D to induce myogenesis.

these sizes would produce significant damage, even in muscle. However, the doping of molecules with AuNPs can alter these effects. For example, AuNPs significantly upregulate myogenic differentiation and muscle degeneration. A recent study showed that AuNPs (5 nm in diameter) could selectively bind with the heparin-binding domain (HBD) of glycoproteins and are crucial for muscle repair because the HBD plays a major role in the retention of several growth factors, such as platelet-derived growth factors and vascular endothelial cell growth factors,[77,78] which may support muscle repair during muscle injury. Taken together, the selective size and shape of AuNPs with a larger surface area would effectively prevent ROS-induced damage in the muscle, which further supports muscle homeostasis in muscle injury. Table 2 summarizes some of the potentially toxic effects of AuNPs on living systems from in vitro and in vivo studies.

AuNPs in Muscle Regeneration and Inflammation

The injured muscle tissue regeneration process is dependent on an organized and sequential response mediated by cytokines and growth factors that are released by muscle fibers, and it involves macrophages, inflammatory cells, and connective tissue, including three distinct phases: degeneration, repair, and remodeling.[91,92] In this scenario, the regulation of the inflammatory response is crucial for the effectiveness of the repair mechanisms. However, when the release of inflammatory mediators is stimulated, adjacent tissues suffer secondary damage from excess leukocyte infiltration and consequent oxidative stress, which requires pharmacological intervention to restore or maintain an

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Table 2 Potential Toxicity of AuNPs on Living Systems from in vitro and in vivo Studies

AuNP Characteristics	Biomarkers	Experimental Model	Main AuNP Effects	Reference
AuNPs, 27 µg (spherical particles with a mean diameter of 25 nm).	Generation of mitochondrial superoxide; lipid peroxidation; protein carbonylation; SOD, GPX, and catalase activity; protein analysis by immunoblotting; and protein determination.	In vivo: Cross-sections of the gastrocnemius muscle.	Beneficial effects on muscle healing; reduced production of ROS and decreased expression of proinflammatory molecules.	Victor et al[79]
PEG-AuNPs, spherical, 5 kDa, with 4.5 ± 0.6 nm, with an Au mass concentration of 1 mg/mL and 1015 particles/mL.	Cell viability; change in ATP levels and mitochondrial membrane potential; modulation of signaling pathways mediated by PEG-AuNP; and susceptibility to apoptosis and production of cytokines.	In vitro: Skeletal muscle cells of the C2C12 lineage (myoblastoma cells).	Increased ATP levels and mitochondrial intracellular membrane potential; reduced p-AKT levels, and increased IFN-c and TGF-b1 levels.	Leite et al[80]
AuNPs, 10 nm.	Cell membrane permeation and nuclear localization of NanoScript-MRF; myogenic induction from stem cells; and quantification of muscle tissue-specific genes.	In vitro: Human cells	Activated genes that regulate myogenesis, differentiating adipose tissue-derived mesenchymal stem cells (ADMSCs) into muscle tissue.	Patel et al[81]
AuNPs, 25 nm.	Behavioral changes and creatine kinase levels, superoxide dismutase, and glutathione peroxidase activity; and levels of superoxide, nitrotyrosine, nitric, and oxidative damage markers.	In vivo: Gastrocnemius muscle of Wistar rats.	Reduced the inflammatory response, production of oxidants, and oxidative damage and improved the antioxidant defense system.	Zortéa et al[82]
AuNPs of medium diameter, with particles at 25 nm and 36 mg/L.	Measurement of mitochondrial superoxide generation, lipid peroxidation, protein carbonylation, SOD activity, GPx analysis, CAT activity, and protein determination.	In vivo experiment: Gastrocnemius muscle, Wistar rats (middle portion).	Decreased oxidative stress parameters and improved the antioxidant system response.	Silveira et al[83]
Spherical AuNPs and AuAgNPs, average diameters of 30 and 40 nm and concentrations of 40 mg/mL (in vivo) and 20 to 80 mg/mL (in vitro).	Cytotoxicity, myogenic differentiation, heavy chain protein (MHC) expression, Myod, MyoG, and troponin T1 expression levels, myofiber diameter, number of centronucleated myofibers, and capillary density	In vitro and in vivo: C2C12 myoblasts, anterior tibial muscle of female Sprague-Dawley rats.	Increased myogenic differentiation and myogenic genes related to the p38a MAPK signaling pathway and promoted skeletal muscle regeneration	Ge et al[75]
30, 60 and 100 nm AuNPs; 2 µg of IL-4/PA4.	M1 and M2 macrophages polarization; muscle regeneration; histological analysis	In vivo and in vitro: Female mice C57BL/6J, skeletal muscle of the tibialis anterior	Altered macrophage polarization and increased strength and speed of muscle contraction after ischemic muscle injury in vivo.	Raimondo and Mooney[15]

(*Continued*)

Table 2 (Continued).

AuNP Characteristics	Biomarkers	Experimental Model	Main AuNP Effects	Reference
AuNP rods (30 nm in diameter and 4500 nm in length) were added to a neutralized hydrogel (5% by weight) with a density of 500 μg/mL.	Histology; quantification of myogenic gene expression; and cell viability, orientation, and alignment.	In vitro and in vivo: C2C12 and H9C2 myoblast cells, temporal muscle of Sprague-Dawley rats	Improved the actin structural alignment and cell formation and obtained significantly higher myosin. Parallel O-GN-CS-E Group showed better implant results, which were completely transformed into mature muscle fibers with rare tissue fibrosis.	Kim et al[84]
AuNPs, 20 nm and 20 mg/kg.	Pro and anti-inflammatory mediators;	In vivo: Gastrocnemius of Wistar rats.	Reduced proinflammatory and oxidative stress parameters, preserved the morphology, and improved the locomotor response and pain symptoms.	Da Rocha et al[85]
AuNPs, 20 nm and 2.5, 7.0 and 21 mg/kg.	Production of oxidants, markers of oxidative damage, and activity of the antioxidant system;	In vivo: Gastrocnemius muscle MDX of mice	Reduced morphological changes and reduced inflammatory and oxidative stress markers.	Haupenthal et al[86]
AuNPs, 20 nm and 20 mg/L.	Intracellular determination of cytokines, ROS, and nitric oxide; levels of oxidative damage markers and antioxidant defenses; histological analysis; and analgesic effects.	In vivo: Gastrocnemius muscle of Wistar rats	Reduced pain, and inflammatory and oxidative stress response.	Haupenthal et al[87]
AuNPs, 20 nm and 20 mg/L.	Content of cytokines; intracellular determination of ROS, antioxidant defenses, and oxidative damage markers; and histological analysis.	In vivo: Cross-sections of the gastrocnemius muscle of Wistar rats	Reduced the inflammatory response, regulated the cellular redox state, and restored muscle integrity.	Haupenthal et al[2]
AuNPs, ~30 nm and ~50 nm.	Identification and quantification of cellular phenotypes.	In vitro, in vivo, and ex vivo: Monocytes derived from bone marrow; satellite cells; anterior tibialis muscle of C57BL/6J mice – MDX.	Increased the recruitment of T cells, the amount of T cells regs, and muscle fiber area. Improved muscle strength.	Raimondo and Mooney[88]
Tau-AuNPs, 100 μL.	Parameters of oxidative stress; DNA damage markers (frequency and damage index levels); and muscle differentiation protein.	In vivo: Quadriceps muscle of male Swiss mice.	- Reduced oxidative stress parameters. Upregulated the expression of myogenic regulatory proteins.	Thirupathi et al[89]
Polycaprolactone/gold (PCL/Au).	Parameters of the mesh structure and morphology; measuring the electrical resistivity of the meshes; assessing the cell viability, alignment, and morphology.	In vitro: BDIX mouse embryonic cardiac tissue cells.	- Mesh with aligned micro grooves obtained a better microenvironment for the formation and elongation of myotubes compared to mesh without micro grooves or random ones.	Zhang et al[90]

Abbreviations: DMSCs, differentiating adipose tissue-derived mesenchymal stem cells; ATP, adenosine triphosphate; AuNPs, gold nanoparticle; CAT, catalase; DNA, deoxyribonucleic acid; GPX, glutathione peroxidase; IFN-c, interferon c; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; MyoD, myogenic marker genes D; MyoG, myogenic marker genes G; p-AKT, protein kinase B; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF-b1, transforming growth factor beta 1; Tnnt1, troponin T1.

ideal cellular environment for muscle regeneration. In this sense, several recent studies have suggested the use of AuNPs for inflammatory and redox control in muscle injury models.[75,82,85]

Previous in vitro studies evaluated the effects of AuNPs on tissue regeneration mediators.[1–6] For example, Patel et al[81] showed that the application of 10 nm AuNPs to mesenchymal stem cells from human adipose tissue regulates muscle cell differentiation within 7 days via the expression of myogenic regulatory factors. In another study, Gê et al[75] showed that AuNP hydrogels with a mean diameter of 30 to 40 nm and concentration between 20 and 80 µg/mL caused increases in the myogenic differentiation of C2C12 myoblasts through the formation of myotubes and upregulation of the expression of myogenesis-inducing genes. Recently, Ko et al[93] applied 3 to 5 nm AuNPs to rat aortic vascular smooth muscle cells and revealed that the treatment increased the expression and phosphorylation of NFR2 mediated by a redox-related reaction and p38 MAPK activation.

A variety of in vivo studies on the use of AuNPs for muscle regeneration have been conducted in rats[5,8] and[9] and mice.[10,11,15] Most in vivo studies have used AuNPs at 10 to 30 nm, although variable sizes between 0.6 and 400 nm have been observed. The dosages used are also varied, with a predominance of 20 mg/kg.[85,86,94,95] Raimondo and Mooney[15] analyzed the effects of the injectable application of 30, 60 and 100 nm AuNPs conjugated to IL4 on the regeneration of the tibialis anterior muscle of C57BL/6J female mice after an ischemic injury model and revealed that the use of these nanoparticles favors the polarization of macrophages M1 to M2 and increases muscle regeneration, strength and contraction speed. AuNP rods at 30 nm (diameter) and 4500 nm (length) were added to hydrogel and applied to the temporal muscle of Sprague-Dawley rats, and the results showed better actin filament restructuring, greater myosin formation, and less fibrosis.[84] Effective results on gastrocnemius regeneration in Wistar Rats were also observed by Da Rocha et al[85] with the use of AuNPs with a size of 20 nm and concentration of 20 mg/kg, and these effects were associated with the microcurrent after a muscle injury. Moreover, the use of AuNPs restored the tissue histoarchitecture and promoted a reduction in proinflammatory and oxidative stress markers.

The effects of using AuNPs as an anti-inflammatory agent in regenerating muscle are due to the ability of AuNPs to permeate muscle tissue and interact with different molecules, which synergistically reduces the production of cellular oxidants (Figure 3). For example, Zortea et al[82] investigated the effect of ultrasound with AuNPs on inflammatory and oxidative stress parameters in an experimental model of muscle overuse. The anti-inflammatory action observed in this study was related to the ability of AuNPs to inhibit the expression of NF-kB, reduce the binding of inflammatory cytokines to their membrane receptors, and downregulate vascular endothelial growth factor (VEGF) expression, thereby reducing cellular infiltration. The authors also suggested that the antioxidant effects may be secondary to the anti-inflammatory action. A lower proinflammatory response results in lower production of oxidants, primarily from the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) complex. In addition, AuNPs cause an increase in the endogenous production of antioxidants. These effects may be related to the ability of AuNPs to interact with the thiol group of Kelch-like ECH-associated protein 1 (KEAP1), thus allowing for the translocation of nuclear factor erythroid 2-related factor 2 (NRF2) for subsequent transcription of antioxidant genes.[46,96]

Silveira et al[97] analyzed the effect of phonophoresis using ultrasound associated with AuNPs and dimethyl sulfoxide (DMSO) on oxidative stress parameters after trauma using a contusion model. The authors suggested that the benefits arising from the use of AuNPs may be related to the inhibition of nitric oxide synthase inducible (iNOS) production, suppression of ROS, and potential reduction in the production of CD68, which favored muscle tissue repair. In addition, AuNPs can increase myogenic differentiation by activating the p38 MAPK signaling pathway through the expression of myosin/MHC heavy chain proteins[75] or by targeting and activating regulatory genes of myogenesis, such as MyoD, myogenin, Myf5, and myogenic regulatory factor (Mrf).[81] When associated with anti-inflammatory cytokines, such as IL4, AuNPs can induce the polarization of M2 macrophages and promote the infiltration of immunosuppressive/proregenerative regulatory T cells (Tregs), thus favoring the muscle regeneration process.[15,81]
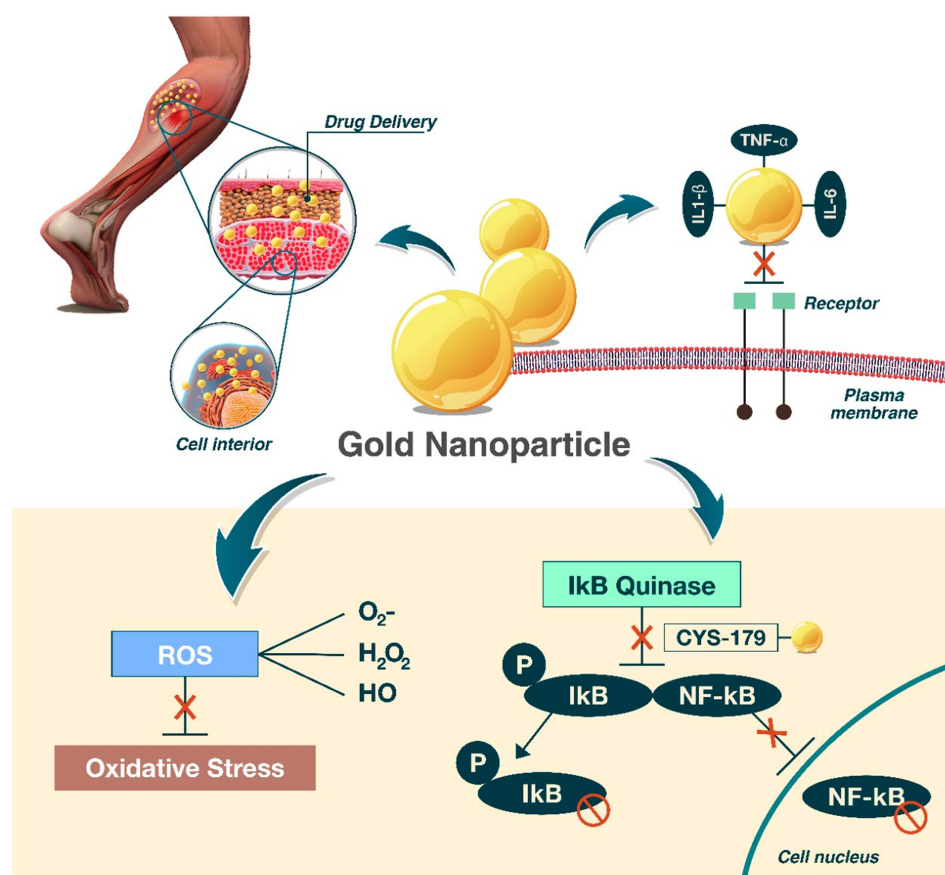
Figure 3 Gold nanoparticle effects on muscle injury: AuNPs promote anti-inflammatory and antioxidant effects and interact with different molecules, which synergistically reduce oxidative stress. The entry of AuNPs into the cellular environment inhibits circulating proinflammatory cytokines, and interactions with CYS-179 of IKK-B and subsequent inhibition of the NF-kB pathway and amplification of the inflammatory response impact the regulation of oxidative stress.

Conclusion and Perspectives

Although several in vitro studies and investigations in healthy and sick animals have reported the therapeutic efficacy of AuNPs based on different mechanisms underlying muscle regeneration, the extrapolation of these results to humans has not been performed. Future investigations are needed to better understand the safety and efficacy of AuNPs for different aspects of muscle physiology. Despite the research-based evidence presented here on the anti-inflammatory and antioxidant effects of AuNPs on muscle injury, treatment methods that apply these results and new applications have not yet been developed. Moreover, current data from different studies are fragmented from the experimental methods to the final conclusions, which has introduced confusion and uncertainty to the applicability of AuNPs. Although AuNPs may represent a therapeutic target of clinical relevance for living beings, their potential toxicity must be carefully and precisely studied. Several studies have reported that AuNPs are nontoxic, while others have shown dose- and route-dependent toxic effects. Moreover, the toxicity of AuNPs associated with ligands must be considered since certain cationic ligands seem to induce toxic effects in living organisms independent of AuNPs. Therefore, investigating the therapeutic use of AuNPs in muscle injury may be a promising approach, although it requires further preclinical and applied research, especially in terms of the formulation of new molecules and the association with ligands that transport these molecules to the target tissue and help tissue regeneration. Future challenges include evaluating the effects of AuNPs on the treatment of muscle injury in humans and determining the best shape, size, dose, and administration method based on the type, severity, and chronicity of the muscle injury.

Methodological Considerations About This Revision

This manuscript was written using data from several databases, including PubMed, Medline, Bireme, Web of Science, and Google Scholar, and a broad range of synonyms and related terms were applied, namely, AuNPs, inflammation,

oxidative stress, muscle-skeletal, and muscle damage. We included prospective cohort studies, cross-sectional studies, randomized clinical trials, experimental models, systematic revisions, and meta-analyses. For studies related to the effects of AuNPs on muscle, we considered the following eligibility criteria: (1) studies reporting human participants or animals (rats and mice); (2) search outputs that included only articles that were peer-reviewed and published in English language journals; and (3) papers that included parameters related to the effects of AuNPs on skeletal muscle. For each study, the study characteristics (authors, published year, and journal), specimens (human, rat, or mouse), study design (experimental design and groups), general aims, AuNP protocol (synthesis, type, size, dose, concentration), samples (tissue), biomarkers, and main outcomes were only extracted from studies related to the effects of AuNPs on skeletal muscle. The results of this search were organized in an electronic spreadsheet for further analysis.

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Author Contributions

All authors made a significant contribution to the work reported, such as in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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