Vascular Repair by Grafting Based on Magnetic Nanoparticles

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Magnetic nanoparticles (MNPs) have attracted much attention in the past few decades because of their unique magnetic responsiveness. Especially in the diagnosis and treatment of diseases, they are mostly involved in non-invasive ways and have achieved good results. The magnetic responsiveness of MNPs is strictly controlled by the size, crystallinity, uniformity, and surface properties of the synthesized particles.

Keywords: magnetic nanoparticles ; vascular repair ; magnetic responsiveness

1. Magnetic Nanoparticles (MNPs) in Vascular Grafts

Vascular grafts (also called vascular scaffolds) have always been a clinically effective treatment strategy for large vascular defects caused by vascular disease or violent invasion [1][2][3], such as polyurethane (PU) [4], polyester (PET) [5], ePTFE [6] and so on. Although these vascular grafts, when used in larger-diameter vessels (>6 mm) show satisfactory long-term performance, they display inferior performance in small-diameter vessels (<6 mm), mainly because they are prone to intimal hyperplasia (IH) and thrombogenesis [7]. Given the above-mentioned unsatisfactory factors and the shortcomings of secondary operations caused by non-degradability, it has always been a goal to seek natural materials with better biocompatibility to construct vascular grafts. Unfortunately, the many properties of natural materials cannot meet the application requirements of vascular grafts, such as mechanical strength [8], elasticity [9], and degradation [10][11]. MNPs are believed to effectively improve the performance of vascular grafts and provide more applications in other areas (such as MRI [12] or nano-modification [13]). Ghorbani et al. [14] synthesized INOPs by co-precipitation technique and they were evenly distributed in PLGA-gelatin scaffolds. The results showed that the added MNPs had no special effect on the pore morphology but slightly reduced the pore size distribution. The MNPs containing the construct had enhanced mechanical strength, but the absorption capacity and biodegradation rate were reduced. The previous study [9] also proved that MNPs were evenly distributed in silk fibroin scaffolds by infiltration. The results showed that the obtained magnetic silk fibroin scaffolds significantly delayed the degradation rate and enhanced mechanical strength. Lekakou et al. [15] found that gelatin/elastin gels are nanocomposite scaffolds with flattened elastin nanodomains embedded in a gelatin matrix that mimic the structure of the arterial media. They studied gelatin/“hydroxyapatite” (HA) nanocomposite scaffolds, and “HA” was generated in situ in solution. When a magnetic field of 9.4 T was applied, the HA particles and gelatin microfibrils in the gelatin were oriented perpendicular to the direction of the magnetic field, which provided a basis for the preparation of arterial vascular layered scaffolds. Mertens et al. [16] prepared three ultra-small superparamagnetic iron oxide nanoparticles (USPIO), which were subsequently directly colonized in collagen scaffolds by chemical cross-linking and used indirectly as imaging graft scaffolds. Imaging can also be performed in the case of acellular implants to visualize the degradation of collagen scaffolds in vivo, which is beneficial for analyzing the in vivo degradation cycle and mechanism of rapidly degrading natural materials. Currently, MNP-added vascular grafts are mainly used to improve mechanical strength, mainly based on the high modulus, abundant functional groups. and uniform dispersion of MNPs [17].

2. MNPs Regulate Vascular-Related Cell Behavior and Factor Expression

Vascular injury repair is a highly organized engineering that mainly involves three stages, including inflammation, neointima, and remodeling [18]. For the initial acute inflammation stage, many macrophages will migrate to the injury site and secrete various inflammatory factors (such as TNF-α, IL-6, MCP-1) to clear the damaged cell debris and play a defensive role. When entering the late stage of inflammation and transitioning to the neointimal stage (active re-endothelialization stage), macrophages secrete various repair cytokines (such as bFGF, VEGF, and TGF-β) to regulate the microenvironment at the injury site. Thus, it regulates the behavior of various cells involved in re-endothelialization, including adhesion, migration, proliferation, phenotype, and homing [19][20]. However, regardless of the stage, various related cells and factors are involved, and favorable cell behavior and factor secretion can rapidly remodel blood vessels.

Numerous studies have proved that the unique magnetic properties of MNPs can regulate cell behavior and factor secretion, thereby promoting vascular remodeling [21]. MNPs regulate cell behavior and factor secretion in the following ways: (1) MNPs through the stimulation of labeled cells; (2) MNPs-labeled cells respond to magnetic fields; (3) MNPs bind to materials to affect adherent cell behavior and factors; (4) MNPs indirectly affect the behavior and factor secretion of target cells by affecting related pathway. Lshii et al. [22] assembled a magnetic cell sheet by combining Fe_3O_4 nanoparticles with mesenchymal stem cells (MSCs) and then transplanted them into the hind limbs of nude mice to evaluate the potential of angiogenesis. The results showed that the magnetic cell sheet group had more angiogenesis, increased vascular endothelial growth factor expression, and decreased apoptosis. Perea et al. [23] first labeled human smooth muscle cells (SMCs) and human umbilical vein endothelial cells (HUVECs) with MNPs and then used radial magnetic force to drive the cells to efficiently reach the lumen surface of tubular scaffolds, fixed the cells on the matrix surface, and adhered firmly, which effectively promoted the process of vascular endothelialization. To overcome irreversible damage to the endothelial cell layer caused by surgery in repairing blood vessels, resulting in impaired vascular function and restenosis, Vosen and his team [21] combined nanotechnology with gene and cell therapy for site-specific re-endothelialization and restoration of vascular function. The researchers overexpressed the vascular protection gene endothelial nitric oxide synthase (eNOS) in endothelial cells (ECs) using a complex of lentiviral vectors and MNPs. MNPs-loaded and eNOS-overexpressing cells are magnetic, and even under flow conditions, they can be positioned on the vessel wall in a radially symmetric manner by the magnetic field. The results demonstrated that the treated vessels showed enhanced eNOS expression and activity. Furthermore, the replacement of ECs with eNOS-overexpressing cells restored endothelial function in a mouse model of vascular injury. More interestingly, Mattix et al. [24] added MNPs to the cell spheres through the Janus method and then manipulated the cell sphere to fuse into a vascular tissue structure with a diameter of 5 mm through the magnetic force generated by the external magnetic field (EMF). For the binding of MNPs to materials, Filippi et al. [25] prepared novel magnetic nanocomposite hydrogels by incorporating MNPs into PEG-based hydrogels containing cells from the stromal vascular fraction (SVF) of human adipose tissue; the stimulation of an external static magnetic field (SMF) on the angiogenic properties of the constructs were investigated. The results showed that endothelial cells, pericytes, and perivascular genes were strongly activated, and the expressions of VEGF and CD31(+) were increased. After subcutaneous transplantation in mice, the magnetic drive structure showed denser, more mineralized, and faster-vascularized tissue. Gu et al. [26] studied iron oxide nanoparticles to regulate macrophage phenotype toward M1 polarization and down-regulate M2-related arginase 1 (Arg-1) by affecting the interferon regulatory factor 5 (IRF5) signaling pathway, in which iron-based MNPs are anti-cancer and inhibit tumor angiogenesis, providing new insights. However, MNPs have a concentration-dependent effect on the phenotypic polarization of macrophages. Many studies have shown that low-dose MNPs also can promote M2 polarization, but the related pathway mechanism is rarely studied [27][28]. The aforementioned favorable behaviors based on cell and factor secretion regulation by MNPs can effectively participate in vascular repair.

3. MNPs as Carriers for Targeted Drug Delivery

MNPs have unique advantages in the construction of drug delivery systems (magnetic drug delivery, MDD), such as inherent magnetic targeting, magnetocaloric drug release, and accessible surface modification, which can maximize drug delivery. By applying a permanent magnet near the target tissue, the accumulation of MNPs at the target site can be induced, reducing the drug's distribution in the whole body, thereby improving the therapeutic effect and reducing the toxic and side effects [29]. When using MNPs as drug delivery systems, the magnetic properties of nanoparticles are size-dependent, and magnetic nanoparticles with excellent performance can be obtained by adjusting the size. The charge and hydrophobic properties of MNPs affect their interactions with plasma proteins, the immune system, extracellular matrix, or non-targeted cells and determine their biological distribution. Hydrophobic MNPs readily adsorb plasma proteins, leading to recognition by the reticuloendothelial system and eventual clearance from the circulatory system under opsonization, resulting in a short circulating half-life. After modifying its surface with hydrophilic PEG and other molecules, its circulating half-life can be increased. Positively charged MNPs easily bind to non-targeted cells and undergo a nonspecific internalization process. Compared with negatively charged MNPs, positively charged MNPs generally exhibit higher cellular internalization effects [30][31]. In recent years, MDD systems have been widely developed to treat various diseases [32][33], including tumors, such as designing Fe_3O_4 nanoparticles-based targeted drug delivery systems to enhance cancer targeting to suppress tumors under static magnetic fields and laser irradiation growth, and the system proved effective for in situ transdermal drug delivery, magnetic fields, and synchronization of laser and biological targeting. Demonstrated in breast cancer models, this system is an effective alternative for the treatment of superficial cancers [34]; bone, for example, has developed an exosome derived from neutrophils modified by sub-5 nm ultra-small PBNP (uPB) engineering through click chemistry, which can target deep into cartilage, significantly improve the joint injury of CIA mice, and inhibit the overall severity of arthritis, showing considerable potential in the clinical diagnosis and treatment of arthritis [35]; in vascular structures, a developed nanoparticle (MMB-PLGA-PTX) can be used for in-stent restenosis (ISR) treatment that

is responsive to external magnetic fields and LIFU. The results showed that magnetic targeting increased the accumulation of MMP-PLGA-PTX 10-fold, while LIFU facilitated the penetration of the released PLGA-PTX into the arterial tissue, thereby increasing the retention time of the released PTX in the stented vascular tissue. Combined with efficacy, this strategy holds great promise for the precise delivery of antiproliferative drugs to stented vascular tissue for ISR therapy [36]; skin, such as heme-modified prussian blue nanoparticles (PBNP, an iron-based magnetic nanoparticle) forms a colloid with NO, which is locally dropped at the skin wound site in response to NIR light and releases NO in a targeted and controllable manner to enhance blood Microcirculation, thereby effectively enhancing angiogenesis and collagen deposition during skin wound healing [37] . In the treatment of vascular injury, the main focus is on treating the etiology [38]. For example, arterial occlusion caused by external force injury or cardiovascular disease can cause severe mortality [39] [40], so the rapid recanalization strategy can effectively reduce the risk of death. Intravenous injection of tissue plasminogen activator (tPA) at a fixed dose is the main method to dredge arterial occlusion [41][42]. Still, it will produce complications such as insufficient curative effect and bleeding. Therefore, magnetic drug targeting (MDT) is an effective therapeutic method, which uses an EMF to enhance the specific accumulation of drugs bound to MNPs in the diseased vascular system [43]. Ma et al. [44] first studied the possibility of local thrombolysis with MDT. MNPs combined with tPA (tPA equivalent is 0.2 mg/kg) were used in the rat embolism model. Herein, MNPs administered intravascularly moved and accumulated along the iliac artery affected by thrombus under the action of an external magnet, which resulted in effective targeted thrombolysis and was only less than 20% of the free tPA dose. Atherosclerosis (AS) is also a severe disease that can cause vascular damage [45][46]. Although many drugs can treat atherosclerosis [47][48][49], their systemic administration has serious disadvantages. In particular, the proportion of therapeutic dose reaching atherosclerotic lesions is small, resulting in poor therapeutic effect. Increasing the dose is often impossible in many cases because it can cause serious side effects and drug tolerance. Since the existing treatment strategies for AS are far from ideal, there is an urgent need for targeted therapy as an alternative strategy to exert better therapeutic effects. Cicha et al. [50] developed the combination of dexamethasone on MNPs, which magnetically targeted the balloon injury area in rabbits as well as advanced atherosclerotic plaques. Although the desired effect was not achieved, this may also be due to the selection of candidate drugs. In addition, myocardial infarction caused by coronary plaque rupture can also cause severe inflammation and even heart failure [51][52][53]. Zhang et al. [54] studied in a rat myocardial infarction model, using an in vitro epicardial magnet to accumulate MNPs that bind to the human VEGF gene encoded by an adenovirus vector in the ischemic area. Results showed that targeting MNPs resulted in higher VEGF gene expression in the affected area and better cardiac repair. Currently, the treatment of myocardial infarction with stem cell preparations promises to improve myocardial tissue recovery, but this is still limited due to poor accumulation and retention of therapeutic agents at target sites. Cheng et al. [55] used MNPs to enhance the targeted delivery of cardiac-derived stem cells (CDCs) in female rats with myocardial infarction. Then, a 1.3 T circular magnet was placed about 1 cm above the apex of the heart for 10 min, starting with an intramuscular injection of CDCs. During this process, the naked eye can see slight discoloration of adjacent tissues, suggesting that magnetic particle-labeled CDCs could prevent coronary washout. After 24 h, histology confirmed the retention of magnetic particle-labeled CDCs. Semi-quantitative fluorescence imaging showed that cells spread more in a subgroup of rats injected with non-magnetic or magnetically labeled CDCs without magnets than in rats that received labeled cells and additional magnetically targeted therapy to their lungs and spleen. Subsequently, the SRY gene that was decisively differentiated was analyzed by polymerase chain reaction (PCR). The results showed that CDCs implantation was three times higher in the myocardial tissue of rats in the magnetic target group. Therefore, it was concluded that magnetic targeting could effectively attenuate the flushing of magnetic-particle-labeled CDCs at the injection site and significantly increase short-term CDCs engraftment in just 10 min. As targeted carriers, MNPs can effectively participate in the treatment of vascular injury. More applications can also be used as magnetic resonance contrast agents for MRI, which can accurately evaluate vascular functional and structural parameters to diagnose and treat.

4. MNPs as Contrast Agents for Vascular Microenvironment Imaging

Magnetic Resonance Imaging (MRI) is one of the most effective diagnostic imaging tools in medicine, providing clinicians with a high spatial and temporal resolution of biological anatomy and metabolic/functional information in a non-invasive manner. Tissue necrosis, ischemia, and other malignant diseases are of great significance. Under the action of an EMF, different tissues and organs of the organism can generate different resonance signals to form MR images. The strength of the resonance signal is determined by the water content of each part of the body and the relaxation time of water protons. The contrast agent is an image-enhancing contrast agent that can change the body's relaxation rate of water protons, improve imaging contrast, and display lesions [56][57][58]. MNPs are considered to have promising applications in T2 MRI contrast agents, and especially iron-based MNPs exhibit longer half-lives than clinically used gadolinium-based contrast agents [59]. At present, a variety of iron-based MNPs have been developed as clinical MRI contrast agents for imaging various tissues. For example, the FDA approved Feridex to detect liver lesions, and Combidex has entered the phase III clinical trial stage for the imaging of lymph node metastasis [60]. In terms of vascular structures, in addition to participating

in vascular repair in the above ways, MNPs can also be used as vascular microenvironment imaging contrast agents to observe the dynamic changes of vascular graft contour, stenosis or occlusion, and other abnormalities through image visualization to evaluate the process and effect of repair [61]. Flores et al. [62] demonstrated the feasibility of MRI to assess the in vivo performance of tissue-engineered vascular grafts (TEVG) by labeling human aortic smooth muscle cells (HASMCs) with USPIO nanoparticles, which were then seeded into a TEVG and implanted in mice in vivo. The results showed that USPIO-labeled TEVG consistently had sharper boundaries and lowered T2 relaxation time values than unlabeled control scaffolds. In addition, MNPs labeled cells were also used to observe the behavior of related vascular cells by MRI. Perea et al. [63] Labeled HUVECs with clinically approved SPIO, then drove cells to the lumen of polytetrafluoroethylene (PTFE) tubular grafts through a particular electromagnet and then detected endothelial cells with a 1.5 T magnetic resonance scanner to evaluate vascular endothelialization.

5. Other Role of MNPs in Vascular Repair

MNPs are exposed to alternating EMF, which triggers particle movement and local heating, which produces a high-temperature effect that causes tissue damage in the area around the nanoparticles and have been applied to tumor treatment. The main mechanism of action is to raise the temperature above 42 °C through magnetic heating and lead to protein denaturation, which leads to cell death. At present, this method has also been an effective means to treat tumor vascular injury. Higher thermal stimulation based on physiological temperature can effectively kill intravascular tumor cells [64][65] and inhibit blood flow to promote the recovery of vascular function [66]. In recent years, studies have also found that MNPs also have biological effects, such as promoting the polarization of macrophages and producing ROS effects. These effects will also have a significant impact on the vascular repair. Zanganeh et al. [67] found that high concentrations of ferumoxytol can promote macrophage polarization to M1, thereby enhancing the regulation of cancer immunotherapy, including breast cancer, liver cancer, and lung cancer. However, some scholars pointed out that a low concentration of MNPs can also promote the growth of blood vessels [28]. There is no more evidence to prove whether it may regulate the polarization of macrophages at the injured site to M2 type to promote repair.

MNPs participate in vascular injury repair based on their unique physicochemical properties. However, no matter how it participates in vascular repair, MNPs will pass through the blood circulatory system, affecting the vascular wall's function, blood pressure, or hemodynamics. The most typical is that when INOPs are less than 7 nm, they will leak out of the vascular structures and be discharged by the kidney, while 200 nm–4 μM particles are easily phagocytized by macrophages of the mononuclear phagocytosis system (MPS). Therefore, the development of INOPs for vascular usually needs to be at 10–200 nm [68][69]. Secondly, it was known that the endothelial cell layer is the innermost layer of the vascular wall, which can maintain the hemostasis and smooth blood flow of vascular structures by releasing NO, heparin, plasmin, and other regulatory molecules [70][71]. The instability of INOPs sometimes leads to the release of iron ions, resulting in the dysfunction of most organelles in endothelial cells, such as lysosome, golgi apparatus, endoplasmic reticulum, and mitochondria, which in turn induces oxidative stress, inflammation, and gene mutation, and finally leads to the destruction of the endothelial cell layer, the impairment of vascular wall function, and thrombosis [72]. In addition, usually naked INOPs are prone to aggregate in complex saline solutions (such as blood), adversely affecting living tissue or occluding vascular structures. Stable anti-aggregation coatings, such as serum albumin, can greatly improve IONP dispersibility [73][74][75]. More importantly, studies have shown that the concentration of ions also significantly affects blood pressure and hemodynamics.

References

1. Zhuang, Y.; Zhang, C.; Cheng, M.; Huang, J.; Liu, Q.; Yuan, G.; Lin, K.; Yu, H. Challenges and strategies for in situ endothelialization and long-term lumen patency of vascular grafts. Bioact. Mater. 2021, 6, 1791–1809.
2. Liu, X.; Chen, B.; Li, Y.; Kong, Y.; Gao, M.; Zhang, L.Z.; Gu, N. Development of an electrospun polycaprolactone/silk scaffold for potential vascular tissue engineering applications. J. Bioact. Compat. Polym. 2021, 36, 59–76.
3. Fukunishi, T.; Ong, C.S.; Yesantharao, P.; Best, C.A.; Yi, T.; Zhang, H.; Mattson, G.; Boktor, J.; Nelson, K.; Shinoka, T.; et al. Different degradation rates of nanofiber vascular grafts in small and large animal models. J. Tissue Eng. Regen. Med. 2020, 14, 203–214.
4. Zheng, M.; Guo, J.; Li, Q.; Yang, J.; Han, Y.; Yang, H.; Yu, M.; Zhong, L.; Lu, D.; Li, L.; et al. Syntheses and characterization of anti-thrombotic and anti-oxidative Gastrodin-modified polyurethane for vascular tissue engineering. Bioact. Mater. 2021, 6, 404–419.

5. Tanaka, T.; Tanaka, R.; Ogawa, Y.; Takagi, Y.; Asakura, T. Development of Small-diameter Polyester Vascular Grafts Coated with Silk Fibroin Sponge. Organogenesis 2020, 16, 1–13.
6. Wang, C.; Zhang, Q.; Uchida, S.; Kodama, M. A new vascular prosthesis coated with polyamino-acid urethane copolymer (PAU) to enhance endothelialization. J. Biomed. Mater. Res. 2002, 62, 315–322.
7. Cai, Q.; Liao, W.; Xue, F.; Wang, X.; Zhou, W.; Li, Y.; Zeng, W. Selection of different endothelialization modes and different seed cells for tissue-engineered vascular graft. Bioact. Mater. 2021, 6, 2557–2568.
8. Teodorescu, M.; Bercea, M.; Morariu, S. Biomaterials of Poly(vinyl alcohol) and Natural Polymers. Polym. Rev. 2018, 58, 247–287.
9. Liu, X.; Sun, Y.; Chen, B.; Li, Y.; Zhu, P.; Wang, P.; Yan, S.; Li, Y.; Yang, F.; Gu, N. Novel magnetic silk fibroin scaffolds with delayed degradation for potential long-distance vascular repair. Bioact. Mater. 2022, 7, 126–143.
10. de Silva, R.; Vongsanga, K.; Wang, X.; Byrne, N. Development of a novel regenerated cellulose composite material. Carbohydr. Polym. 2015, 121, 382–387.
11. Zhang, L.; Liu, X.; Li, G.; Wang, P.; Yang, Y. Tailoring degradation rates of silk fibroin scaffolds for tissue engineering. J. Biomed. Mater. Res. Part A 2019, 107, 104–113.
12. Mertens, M.E.; Koch, S.; Schuster, P.; Wehner, J.; Wu, Z.; Gremse, F.; Schulz, V.; Rongen, L.; Wolf, F.; Frese, J.; et al. USPIO-labeled textile materials for non-invasive MR imaging of tissue-engineered vascular grafts. Biomaterials 2015, 39, 155–163.
13. Zhao, Q.; Shi, M.; Yin, C.; Zhao, Z.; Zhang, J.; Wang, J.; Shen, K.; Zhang, L.; Tang, H.; Xiao, Y.; et al. Dual-Wavelength Photosensitive Nano-in-Micro Scaffold Regulates Innate and Adaptive Immune Responses for Osteogenesis. Nano-Micro Lett. 2021, 13, 28.
14. Ghorbani, F.; Zamanian, A.; Shams, A.; Shamoosi, A.; Aidun, A. Fabrication and characterisation of super-paramagnetic responsive PLGA–gelatine–magnetite scaffolds with the unidirectional porous structure: A physicochemical, mechanical, and in vitro evaluation. IET Nanobiotechnol. 2019, 13, 860–867.
15. Lekakou, C.; Lamprou, D.; Vidyarthi, U.; Karopoulou, E.; Zhdan, P. Structural hierarchy of biomimetic materials for tissue engineered vascular and orthopedic grafts. J. Biomed. Mater. Res. Part B Appl. Biomater. 2008, 85B, 461–468.
16. Mertens, M.E.; Hermann, A.; Bühren, A.; Olde-Damink, L.; Möckel, D.; Gremse, F.; Ehling, J.L.A.; Kiessling, F.; Lammers, T. Iron Oxide-Labeled Collagen Scaffolds for Non-Invasive MR Imaging in Tissue Engineering. Adv. Funct. Mater. 2014, 24, 754–762.
17. Jaganathan, S.K.; Vellayappan, M.V.; Balaji, A.; Subramanian, A.; John, A.A.; Murugesan, S.; Supriyanto, E.; Yusof, M. Multifaceted prospects of nanocomposites for cardiovascular grafts and stents. Int. J. Nanomed. 2015, 10, 2785–2803.
18. Tu, Z.; Chen, M.; Wang, M.; Shao, Z.; Jiang, X.; Wang, K.; Yao, Z.; Yang, S.; Zhang, X.; Gao, W.; et al. Engineering Bioactive M2 Macrophage-Polarized Anti-Inflammatory, Antioxidant, and Antibacterial Scaffolds for Rapid Angiogenesis and Diabetic Wound Repair. Adv. Funct. Mater. 2021, 31, 2100924.
19. Witherel, C.E.; Sao, K.; Brisson, B.K.; Han, B.; Volk, S.W.; Petrie, R.J.; Han, L.; Spiller, K.L. Regulation of extracellular matrix assembly and structure by hybrid M1/M2 macrophages. Biomaterials 2021, 269, 120667.
20. Yan, W.; Li, T.; Yin, T.; Hou, Z.; Qu, K.; Wang, N.; Durkan, C.; Dong, L.; Qiu, J.; Gregersen, H.; et al. M2 macrophage-derived exosomes promote the c-KIT phenotype of vascular smooth muscle cells during vascular tissue repair after intravascular stent implantation. Theranostics 2020, 10, 10712–10728.
21. Vosen, S.; Rieck, S.; Heidsieck, A.; Mykhaylyk, O.; Zimmermann, K.; Bloch, W.; Eberbeck, D.; Plank, C.; Gleich, B.; Pfeifer, A.; et al. Vascular Repair by Circumferential Cell Therapy Using Magnetic Nanoparticles and Tailored Magnets. ACS Nano 2016, 10, 369–376.
22. Ishii, M.; Shibata, R.; Numaguchi, Y.; Kito, T.; Suzuki, H.; Shimizu, K.; Ito, A.; Honda, H.; Murohara, T. Enhanced Angiogenesis by Transplantation of Mesenchymal Stem Cell Sheet Created by a Novel Magnetic Tissue Engineering Method. Arterioscler. Thromb. Vasc. Biol. 2011, 31, 2210–2215.
23. Perea, H.; Aigner, J.; Hopfner, U.; Wintermantel, E. Direct Magnetic Tubular Cell Seeding: A Novel Approach for Vascular Tissue Engineering. Cells Tissues Organs 2006, 183, 156–165.
24. Mattix, B.M.; Olsen, T.R.; Casco, M.; Reese, L.; Poole, J.T.; Zhang, J.; Visconti, R.P.; Simionescu, A.; Simionescu, D.T.; Alexis, F. Janus magnetic cellular spheroids for vascular tissue engineering. Biomaterials 2014, 35, 949–960.
25. Filippi, M.; Dasen, B.; Guerrero, J.; Garello, F.; Isu, G.; Born, G.; Ehrbar, M.; Martin, I.; Scherberich, A. Magnetic nanocomposite hydrogels and static magnetic field stimulate the osteoblastic and vasculogenic profile of adipose-derived cells. Biomaterials 2019, 223, 119468.

26. Gu, Z.; Liu, T.; Tang, J.; Yang, Y.; Song, H.; Tuong, Z.K.; Fu, J.; Yu, C. Mechanism of Iron Oxide-Induced Macrophage Activation: The Impact of Composition and the Underlying Signaling Pathway. J. Am. Chem. Soc. 2019, 141, 6122–6126.
27. Wynn, T.A.; Vannella, K.M. Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity 2016, 44, 450–462.
28. Kargozar, S.; Baino, F.; Hamzehlou, S.; Hamblin, M.R.; Mozafari, M. Nanotechnology for angiogenesis: Opportunities and challenges. Chem. Soc. Rev. 2020, 49, 5008–5057.
29. Kang, T.; Li, F.; Baik, S.; Shao, W.; Ling, D.; Hyeon, T. Surface design of magnetic nanoparticles for stimuli-responsive cancer imaging and therapy. Biomaterials 2017, 136, 98–114.
30. Osaka, T.; Nakanishi, T.; Shanmugam, S.; Takahama, S.; Zhang, H. Effect of surface charge of magnetite nanoparticles on their internalization into breast cancer and umbilical vein endothelial cells. Colloids Surf. B Biointerfaces 2009, 71, 325–330.
31. Kenzaoui, B.H.; Vila, M.R.; Miquel, J.M.; Cengelli, F.; Juillerat-Jeanneret, L. Evaluation of uptake and transport of cationic and anionic ultrasmall iron oxide nanoparticles by human colon cells. Int. J. Nanomed. 2012, 7, 1275–1286.
32. Le, T.-A.; Zhang, X.; Hoshiar, A.K.; Yoon, J. Real-Time Two-Dimensional Magnetic Particle Imaging for Electromagnetic Navigation in Targeted Drug Delivery. Sensors 2017, 17, 2050.
33. Price, P.M.; Mahmoud, W.E.; Al-Ghamd, A.A.; Bronstein, L.M. Magnetic Drug Delivery: Where the Field Is Going. Front. Chem. 2018, 6, 619.
34. Zhang, L.K.; Du, S.; Wang, X.; Jiao, Y.; Yin, L.; Zhang, Y.; Guan, Y.-Q. Bacterial cellulose based composites enhanced transdermal drug targeting for breast cancer treatment. Chem. Eng. J. 2019, 370, 749–759.
35. Zhang, L.; Qin, Z.; Sun, H.; Chen, X.; Dong, J.; Shen, S.; Zheng, L.; Gu, N.; Jiang, Q. Nanoenzyme engineered neutrophil-derived exosomes attenuate joint injury in advanced rheumatoid arthritis via regulating inflammatory environment. Bioact. Mater. 2022, 18, 1–14.
36. Wang, S.; Guo, X.; Ren, L.; Wang, B.; Hou, L.; Zhou, H.; Gao, Q.; Gao, Y.; Wang, L. Targeting and deep-penetrating delivery strategy for stented coronary artery by magnetic guidance and ultrasound stimulation. Ultrason. Sonochem. 2020, 67, 105188.
37. Su, C.H.; Li, W.-P.; Tsao, L.-C.; Wang, L.-C.; Hsu, Y.-P.; Wang, W.-J.; Liao, M.-C.; Lee, C.-L.; Yeh, C.-S. Enhancing Microcirculation on Multitriggering Manner Facilitates Angiogenesis and Collagen Deposition on Wound Healing by Photoreleased NO from Hemin-Derivatized Colloids. ACS Nano 2019, 13, 4290–4301.
38. Chorny, M.; Fishbein, I.; Forbes, S.; Alferiev, I. Magnetic nanoparticles for targeted vascular delivery. IUBMB Life 2011, 63, 613–620.
39. de la Ossa, N.P.; Carrera, D.; Gorchs, M.; Querol, M.; Millán, M.; Gomis, M.; Dorado, L.; López-Cancio, E.; Hernández-Pérez, M.; Chicharro, V.; et al. Design and Validation of a Prehospital Stroke Scale to Predict Large Arterial Occlusion the Rapid Arterial Occlusion Evaluation Scale. Stroke 2014, 45, 87–91.
40. Loenneke, J.P.; Fahs, C.A.; Rossow, L.M.; Sherk, V.D.; Thiebaud, R.S.; Abe, T.; Bemben, D.A.; Bemben, M.G. Effects of cuff width on arterial occlusion: Implications for blood flow restricted exercise. Eur. J. Appl. Physiol. 2012, 112, 2903–2912.
41. Heiferman, D.M.; Li, D.D.; Pecoraro, N.C.; Smolenski, A.M.; Tsimpas, A.; Ashley, W.W. Intra-Arterial Alteplase Thrombolysis during Mechanical Thrombectomy for Acute Ischemic Stroke. J. Stroke Cerebrovasc. Dis. 2017, 26, 3004–3008.
42. Dalzotto, K.; Richards, P.; Boulter, T.D.; Kay, M.; Mititelu, M. Complications of Intra-Arterial tPA for Iatrogenic Branch Retinal Artery Occlusion: A Case Report through Multimodal Imaging and Literature Review. Medicina 2021, 57, 963.
43. Cicha, I.; Alexiou, C. Cardiovascular applications of magnetic particles. J. Magn. Magn. Mater. 2021, 518, 167428.
44. Ma, Y.-H.; Wu, S.-Y.; Wu, T.; Chang, Y.-J.; Hua, M.-Y.; Chen, J.-P. Magnetically targeted thrombolysis with recombinant tissue plasminogen activator bound to polyacrylic acid-coated nanoparticles. Biomaterials 2009, 30, 3343–3351.
45. Schachter, M. The pathogenesis of atherosclerosis. Int. J. Cardiol. 1997, 62, S3–S7.
46. Mannarino, E.; Pirro, M. Endothelial Injury and Repair: A Novel Theory for Atherosclerosis. Angiology 2008, 59, 69S–72S.
47. Luo, N.; Fang, J.; Wei, L.; Sahebkar, A.; Little, P.J.; Xu, S.; Luo, C.; Li, G. Emodin in atherosclerosis prevention: Pharmacological actions and therapeutic potential. Eur. J. Pharmacol. 2021, 890, 173617.
48. Song, L.; Zhang, J.; Lai, R.; Li, Q.; Ju, J.; Xu, H. Chinese Herbal Medicines and Active Metabolites: Potential Antioxidant Treatments for Atherosclerosis. Front. Pharmacol. 2021, 12, 675999.

49. Ji, C.; Yi, H.; Huang, J.; Zhang, W.; Zheng, M. Propofol alleviates inflammation and apoptosis in HCY-induced HUVECs by inhibiting endoplasmic reticulum stress. Mol. Med. Rep. 2021, 23, 333.

50. Cicha, I.; Matuszak, J.; Lutz, B.; Alexiou, C.; Lyer, S. Magnetic drug targeting to vascular injury regions and atherosclerotic lesions: In vivo pilot study. Eur. Heart J. 2018, 39, 801.

51. Carrillo-Jimenez, R.; Houser, S.L.; Jaffer, F.A. Culprit lesion atherothrombectomy during acute myocardial infarction—Extraction of an acute coronary plaque rupture. Circulation 2005, 112, E267.

52. Baghdasaryan, P.; Natarajan, B.; Nalbandian, M.; Varadarajan, P.; Pai, R.G. Myocardial Infarction with Nonobstructive Coronary Artery Disease-Definition, Etiopathogenesis, Diagnosis, and Management. Int. J. Angiol. 2021.

53. Wereski, R.; Kimenai, D.M.; Bularga, A.; Taggart, C.; Lowe, D.J.; Mills, N.L.; Chapman, A.R. Risk factors for type 1 and type 2 myocardial infarction. Eur. Heart J. 2021, 43, 127–135.

54. Zhang, Y.; Li, W.; Ou, L.; Wang, W.; Delyagina, E.; Lux, C.; Sorg, H.; Riehemann, K.; Steinhoff, G.; Ma, N. Targeted Delivery of Human VEGF Gene via Complexes of Magnetic Nanoparticle-Adenoviral Vectors Enhanced Cardiac Regeneration. PLoS ONE 2012, 7, e39490.

55. Cheng, K.; Li, T.-S.; Malliaras, K.; Davis, D.R.; Zhang, Y.; Marbán, E. Magnetic Targeting Enhances Engraftment and Functional Benefit of Iron-Labeled Cardiosphere-Derived Cells in Myocardial Infarction. Circ. Res. 2010, 106, 1570–1581.

56. Dadfar, S.M.; Roemhild, K.; Drude, N.I.; von Stillfried, S.; Knüchel, R.; Kiessling, F.; Lammers, T. Iron oxide nanoparticles: Diagnostic, therapeutic and theranostic applications. Adv. Drug Deliv. Rev. 2019, 138, 302–325.

57. Magro, M.; Baratella, D.; Bonaiuto, E.; de Almeida Roger, J.; Vianello, F. New Perspectives on Biomedical Applications of Iron Oxide Nanoparticles. Curr. Med. Chem. 2018, 25, 540–555.

58. Huang, Y.; Hsu, J.C.; Koo, H.; Cormode, D.P. Repurposing ferumoxytol: Diagnostic and therapeutic applications of an FDA-approved nanoparticle. Theranostics 2022, 12, 796–816.

59. Toth, G.B.; Varallyay, C.G.; Horvath, A.; Bashir, M.R.; Choyke, P.L.; Daldrup-Link, H.E.; Dosa, E.; Finn, J.P.; Gahramanov, S.; Harisinghani, M.; et al. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. Kidney Int. 2017, 92, 47–66.

60. Woo, K.; Lee, H.; Ahn, J.-P.; Park, Y. Sol–Gel Mediated Synthesis of Fe2O3 Nanorods. Adv. Mater. 2003, 15, 1761–1764.

61. Bremerich, J.; Bilecen, D.; Reimer, P. MR angiography with blood pool contrast agents MR angiography with blood pool contrast agents. Eur. Radiol. 2007, 17, 3017–3024.

62. Flores, D.; Yu, X. Innovative Tissue-Engineered and Synthetic Vascular Graft Models for the Treatment of PAD in Small-Diameter Arteries. Regen. Eng. Transl. Med. 2017, 3, 215–223.

63. Perea, H.; Aigner, J.; Heverhagen, J.T.; Hopfner, U.; Wintermantel, E. Vascular tissue engineering with magnetic nanoparticles: Seeing deeper. J. Tissue Eng. Regen. Med. 2007, 1, 318–321.

64. Senthilkumar, N.; Sharma, P.K.; Sood, N.; Bhalla, N. Designing magnetic nanoparticles for in vivo applications and understanding their fate inside human body. Coord. Chem. Rev. 2021, 445, 214082.

65. Lemine, O.M. Chapter 7—Magnetic Hyperthermia Therapy Using Hybrid Magnetic Nanostructures. In Hybrid Nanostructures for Cancer Theranostics; Ashok Bohara, R., Thorat, N., Eds.; Elsevier: Amsterdam, The Netherlands, 2019; pp. 125–138.

66. Wang, Q.; Deng, Z.S.; Liu, J. Theoretical evaluations of magnetic nanoparticle-enhanced heating on tumor embedded with large blood vessels during hyperthermia. J. Nanopart. Res. 2012, 14, 974.

67. Zanganeh, S.; Hutter, G.; Spitler, R.; Lenkov, O.; Mahmoudi, M.; Shaw, A.; Pajarinen, J.S.; Nejadnik, H.; Goodman, S.; Moseley, M.; et al. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat. Nanotechnol. 2016, 11, 986–994.

68. Zhao, J.; Gao, W.; Cai, X.; Xu, J.; Zou, D.; Li, Z.; Hu, B.; Zheng, Y. Nanozyme-mediated catalytic nanotherapy for inflammatory bowel disease. Theranostics 2019, 9, 2843–2855.

69. Zhao, J.; Cai, X.; Gao, W.; Zhang, L.; Zou, D.; Zheng, Y.; Li, Z.; Chen, H. Prussian Blue Nanozyme with Multienzyme Activity Reduces Colitis in Mice. ACS Appl. Mater. Interfaces 2018, 10, 26108–26117.

70. Otsuka, F.; Finn, A.V.; Yazdani, S.K.; Nakano, M.; Kolodgie, F.D.; Virmani, R. The importance of the endothelium in atherothrombosis and coronary stenting. Nat. Rev. Cardiol. 2012, 9, 439–453.

71. Jana, S. Endothelialization of cardiovascular devices. Acta Biomater. 2019, 99, 53–57.

72. Wang, Y.; Santos, A.; Evdokiou, A.; Losic, D. An overview of nanotoxicity and nanomedicine research: Principles, progress and implications for cancer therapy. J. Mater. Chem. B 2015, 3, 7153–7172.
73. Hajshafiei, P.; Fatahian, S.; Shahanipoor, K. In vivo toxicity assessment of bovine serum albumin and dimercaptosuccinic acid. coated Fe3O4 nanoparticles. Iran. J. Biotechnol. 2014, 12, e16858.
74. Khatiri, R.; Reyhani, A.; Mortazavi, S.Z.; Hossainalipour, M. Immobilization of serum albumin on the synthesized three layers core-shell structures of super-paramagnetic iron oxide nanoparticles. J. Ind. Eng. Chem. 2013, 19, 1642–1647.
75. Ramesh, R.; Ponnusamy, S.; Muthamizhchelvan, C. Synthesis, properties and heating characteristics of bovine serum albumin coated Fe3O4 magnetic fluid for magnetic fluid hyperthermia application. Sci. Adv. Mater. 2013, 5, 1250–1255.