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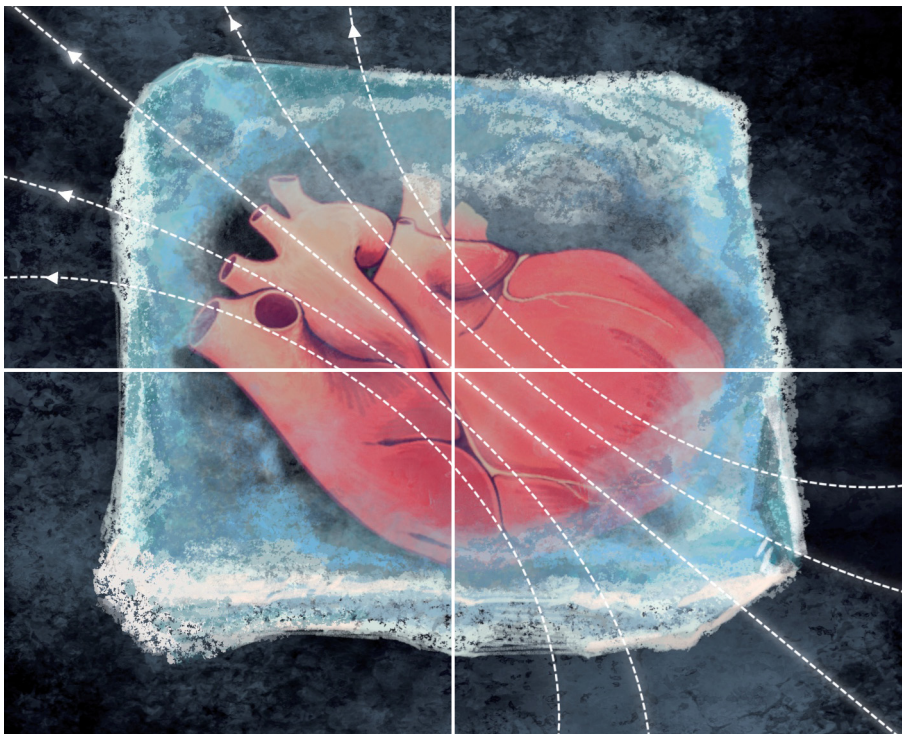

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Magnetic nanoparticles for nanowarming: seeking a fine balance between heating performance and biocompatibility

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Regenerative medicine has the potential to revolutionize healthcare by providing transplant options for patients suffering from tissue disease or organ failure. Cryopreservation offers a promising solution for long-term tissue and organ storage, but the challenge of rewarming cryopreserved biological samples without damaging them by fatal ice crystallization and thermal cracks remains. Nanowarming, a novel rewarming method that uses magnetic nanoparticles as heating agents, holds promise for addressing this challenge. However, the current designs of these nanoparticles need to be improved to balance their heating efficiency and biocompatibility. This paper discusses the need for designing magnetic nanoparticles that are both efficient and uniform in their heating while reducing their acute and chronic toxicity. By highlighting current challenges and potential solutions in achieving this balance, we envision that properly designed magnetic nanoparticles will enable efficient and safe nanowarming and address the critical issue of tissue and organ storage.

Introduction

Magnetism is a fascinating physical phenomenon with numerous practical applications. While many materials exhibit some magnetic properties (*i.e.*, diamagnetic, paramagnetic, ferromagnetic, antiferromagnetic, ferrimagnetic, and superparamagnetic), the term "magnetic materials" commonly refers to those attracted by an external magnetic field, such as Fe_3O_4. The magnetic dipole in these materials arises from the spin of unpaired electrons, which can be aligned along the direction of the external magnetic field, producing a net magnetic moment. The development of nanotechnology has brought magnetic nanomaterials to the forefront of diverse research fields, underscoring their growing significance. Due to their reduced size and increased surface-to-volume ratio, magnetic nanoparticles exhibit unique properties compared to their bulk counterparts.[1,2] The confinement of magnetic moment to a smaller space leads to stronger interactions between nanoparticles and an increased magnetic anisotropy.[3,4] Notably, when the domain size of a magnetic nanoparticle decreases to its critical size (typically around 20 nm), the nanoparticle transits to the superparamagnetic state, resulting in disordered magnetic moments due to thermal fluctuation and causing the nanoparticle to lose its magnetization in the absence of an external magnetic field.[5,6]

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Magnetic nanoparticles undergo directional movement when an external magnetic field is applied. For spherical nanoparticles, they move along the direction of the magnetic field gradient.[7] For anisotropic nanoparticles, their induced magnetic dipole tends to be parallel to the direction of the magnetic field, generating a magnetic torque that rotates the nanoparticles.[8] Under a high-frequency alternating magnetic field (AMF), induction heating occurs as the induced magnetic dipoles and nanoparticles undergo continuous re-orientation, resulting in energy dissipation. Two main mechanisms contribute to induction heating: hysteresis loss and relaxation loss. The former occurs due to the repeated reversal of magnetic domains in multi-domain materials and is proportional to the area of the hysteresis loop, while the latter occurs when magnetic moments (Néel relaxation) and nanoparticles (Brownian relaxation) rotate rapidly in response to a magnetic field, generating heat due to the energy barrier of magnetic moment re-orientation and frictional forces with the environment, respectively.[9,10]

Magnetic induction heating has been widely used in many fields, such as cancer therapy, drug delivery, and energy conversion.[11–14] One notable new application is using magnetic nanoparticles as a heating source for thawing cryopreserved biological tissues and organs. This technique is known as nanowarming, first developed by Bischof *et al.* in 2017.[15] Cryopreservation is a method of preserving biological samples at low temperatures for long-term storage, but rewarming frozen samples without causing damage can be challenging. Sufficiently fast cooling can avoid the formation of ice crystals

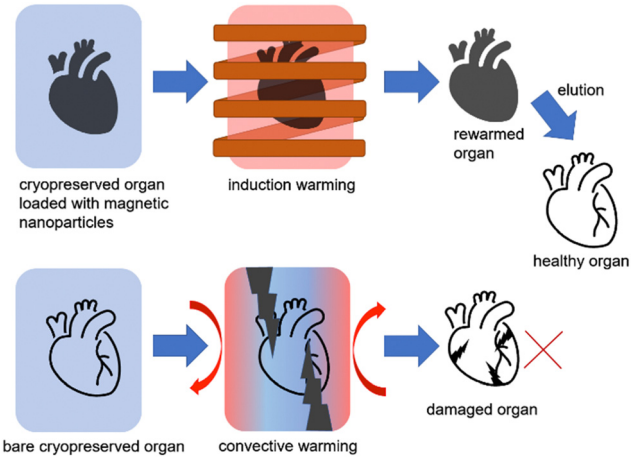

Fig. 1 Comparison of rewarming cryopreserved organs with the nanowarming technique using induction heating (top) and the conventional method using water bath convection (bottom).

during the freezing of liquid solvents by transforming it into the glass state through a process called vitrification.[16–18] Similarly, rapid rewarming is needed to prevent devitrification. Conventional thawing methods, such as water bath convection, may not be suitable for large-volume samples (>3 mL) due to limitations in heat transfer efficiency.[15] The slow heating generates ice crystals, while the uneven heating induces thermal-mechanical stress, which can cause fractures and cracks in biological tissues, leading to low post-thawing survival rates. In contrast, benefiting from the small sizes of magnetic nanoparticles and high tissue penetration of magnetic fields, the nanowarming technique enables rapid and uniform heating of biological samples (Fig. 1). Etheridge *et al.* first demonstrated the feasibility of using a high-frequency AMF for fast rewarming of small-volume CPAs, and simulated results showed the uniform heating of nanowarming agents in bulk vitrified biomaterials.[17] They proved that magnetic heating can rapidly and uniformly heat CPAs, achieving heating rates of up to 300 °C min^{-1}, and minimizing devitrification in cryopreserved biological samples during rewarming. Wang *et al.* studied the effect of magnetic heating of Fe_3O_4 nanoparticles on the cryopreservation of a 200 μL suspension of human umbilical cord matrix mesenchymal stem cells (hUCM-MSCs), and found that nanowarming significantly improved cell viability after rewarming.[25] Subsequently, Manuchehrabadi *et al.* successfully expanded the scale of nanowarming to an 80 mL system, testing a variety of different biological tissues and demonstrating that the viability of nanowarmed samples was considerably higher than that of samples heated using the conventional convection rewarming.[15] Chiu-Lam *et al.* synthesized polyethylene glycol (PEG)-coated superparamagnetic iron oxide nanoparticles that remained stable in CPA solutions and used them to rewarm vitrified rat hearts.[23] The nanowarming technique has been effectively applied to a range of biological systems, including porcine arteries, articular cartilage, heart valves and organs such as rat kidneys, livers, and hearts (Table 1). Moreover, Liu *et al.* showed that stem cells microencapsulated in hydrogels could be vitrified, nanowarmed, and recovered with high viability and preserved cellular function.[24] Encapsulating stem cells within hydrogels prevents direct physical contact with nanoparticles, thereby eliminating potential toxicity.

Although considerable progress has been made in developing efficient nanowarming protocols, only a few studies have been focused on designing nanoparticles.[19,30,31] Sufficient heating rates, necessary to prevent ice formation and devitrification during rewarming, can be achieved by tuning the composition and morphology of magnetic nanoparticles. However, the release of toxic metal ions and overheating can cause acute toxicity. Additionally, heating uniformity can be improved by distributing nanoparticles within avascular tissues, whereas effective nanoparticle clearance is crucial to prevent post-thawing accumulation and chronic toxicity. The challenge of identifying magnetic nanoparticles that can maximize heating rates while maintaining biocompatibility remains significant. Therefore, our discussion here focuses on the challenges and potential strategies for achieving the desired balance between heating performance (*i.e.*, heating rate and heating uniformity) and biocompatibility (*i.e.*, acute toxicity and chronic toxicity). We envision that this perspective will draw more research interest to this exciting and significant field and help guide researchers when designing magnetic materials for nanowarming.

Table 1 Summary of magnetic nanoparticles used for nanowarming

Nanowarming agent	Testbed	Heating rate (AMF conditions)	Ref.
Mesoporous silica-coated EMG308 Fe_3O_4 nanoparticles (msIONPs)	Porcine carotid arteries	90 °C min^{-1} (20 kA m^{-1}, 360 kHz)	15
	Porcine femoral arteries	130 °C min^{-1} (60 kA m^{-1}, 175 kHz)	15
Silica-coated EMG308 Fe_3O_4 nanoparticles (sIONPs)	Rat kidneys	130 °C min^{-1} (20 kA m^{-1}, 360 kHz)	19
	Rat kidneys	63.7 °C min^{-1} (63 kA m^{-1}, 180 kHz)	20
	Rat hearts	>60 °C min^{-1} (64 kA m^{-1}, 185 kHz)	21
	Rat livers	61 °C min^{-1} (63 kA m^{-1}, 185 kHz)	22
Superparamagnetic iron oxide nanoparticles (SPIONs)	Rat hearts	321 °C min^{-1} (42.5 kA m^{-1}, 278 kHz)	23
	Stem cells	100 °C min^{-1} (15 A, 375 kHz)	24,25
	Mouse preantral follicles	93 °C s^{-1} (magnetic and photothermal heating)	26
Fe_3O_4 nanoparticles (Dai-ichi High Frequency)	Induced pluripotent stem cell	95.2 °C min^{-1} (31.9 kA m^{-1}, 208 kHz)	27
	Pancreatic islets	123.9 °C min^{-1} (31.9 kA m^{-1}, 208 kHz)	28
Carboxylic acid-coated Fe_3O_4	Rat kidneys	87.5 °C min^{-1} (24.2 kA m^{-1}, 765.2 kHz)	29
$Co_{35}Fe_{65}$ nanowire	Human dermal fibroblast cells	1000 °C min^{-1} (20 kA m^{-1}, 360 kHz)	30
Phosphonate linked PEG-coated EMG308	Human dermal fibroblast cells	200 °C min^{-1} (20 kA m^{-1}, 360 kHz)	31

Balancing heating rate and acute toxicity

The critical cooling rate (CCR) and the critical warming rate (CWR) are the minimum rates required to suppress devitrification and ice formation, which depend on the composition and concentration of the CPA used.[32] VS55 is a commonly used CPA, consisting of 3.1 M dimethyl sulfoxide (DMSO), 2.2 M propylene glycol, and 3.1 M formamide (8.4 M in total), as well as salts and sugars as osmotic buffers. The CCR and CWR for VS55 are −2.5 and 50 °C min^{-1}, respectively.[33] Increasing the concentration of CPA can decrease the required CCR and CWR; however, a high concentration of CPA can also cause toxicity to biological samples, including osmotic shock and direct chemical toxicity.[33] Nevertheless, using a lower concentration of CPA increases both CCR and CWR.[33] While the heating rate can be regulated by the magnetic field conditions, such as frequency (f) and magnetic field intensity (H), $H \times f$ is suggested to remain below 5×10^9 A m^{-1} s^{-1} to avoid potential damage to tissues and organs caused by undesired eddy currents.[9,34] Therefore, enhancing the intrinsic heating efficiency of magnetic materials is crucial, as it can effectively reduce the need for high-concentration CPAs and increase the overall survival rate of cryopreserved samples.

The magnetic heating performance of nanoparticles can be tailored by adjusting their composition, shape, size, and assembly state.[35] The synthesis and basic heating performance of magnetic nanomaterials used in magnetic hyperthermia have been well reviewed.[9,11] However, it is important to note that although magnetic nanoparticles used for hyperthermia and nanowarming share similarities, their applications and requirements may lead to differences in their properties and heating performance. Two basic factors need to be considered when designing nanowarming agents: heating performance at low temperatures and acute toxicity (Fig. 2a). Low temperatures enhance the paramagnetism of magnetic particles due to the increased order of magnetic moments as the thermal energy is lower. On the other hand, Brownian relaxation and the associated heat generation are less efficient at low temperatures. Therefore, the magnetic heating performance at low and room temperatures is not necessarily the same. In addition, although doping Fe_3O_4 with metal ions such as Ni^{2+} or Mn^{2+} may improve its heating performance for hyperthermia applications, the potential toxicity of these dopants must be carefully evaluated, as their release could damage living cells.[36,37] One approach to mitigating this risk is by coating the surface of nanoparticles with a protective layer, which can encapsulate the nanoparticle and minimize the leakage of toxic components. However, the coated layer may act as an insulator and could potentially slow down the rewarming. Therefore, a delicate balance must be struck between improving heating efficiency and minimizing the risk of chemical toxicity.

In addition, the increase in heating rate is accompanied by the problem of local overheating, which leads to irreversible thermal damage to normal cells (Fig. 2a). The optimal temperature range for effective nanowarming is from its vitrified state at cryogenic temperature to just above the melting point (T_m) of the CPA, ensuring complete rewarming while minimizing the toxic effects of the CPA on tissues or organs. In practice, the induction heater can be switched off when the temperature exceeds T_m + 10 °C to achieve this balance.[20] While manual intervention is commonly used to stop the induction heater and prevent overheating, high-speed magnetic heating requires precise temperature monitoring and skilled operation. To address this issue, it is necessary to investigate magnetic materials with self-regulating heating properties, which can slow down their heating rate once the biological sample is thawed. Materials that undergo a ferromagnetic-to-paramagnetic transition at a temperature higher than their Curie temperature have emerged as promising candidates for self-regulating heating.[38,39] The Curie temperature of magnetic materials is positively related to the exchange interaction between metal ions, but reducing the exchange interaction also weakens the induction heating performance.[39] Therefore, finding biocompatible magnetic materials with both high magnetic heating performance and acceptably low Curie temperature at sub-zero temperatures remains a challenge that requires further investigation. In addition, other highly efficient self-regulating mechanisms must be explored to ensure the safety and efficacy of nanowarming for cryopreservation.

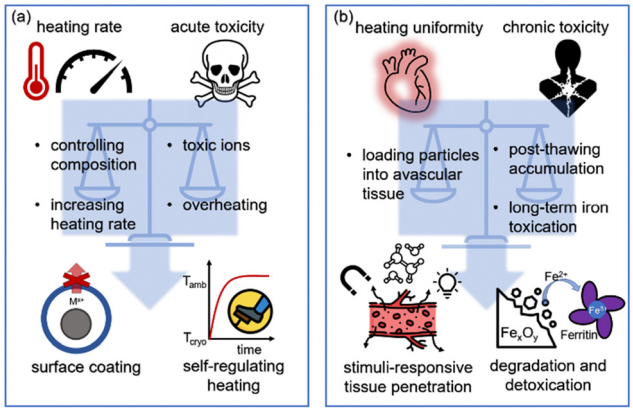

Fig. 2 Nanowarming requires achieving proper balances between the heating performance and biocompatibility of magnetic nanoparticles: (a) heating rate *versus* acute toxicity and (b) heating uniformity *versus* chronic toxicity. T_{amb} and T_{cryo} represent the ambient temperature and cryogenic temperature, respectively.

Balancing heating uniformity and chronic toxicity

Achieving heating uniformity is another critical issue in nanowarming since nonuniform heating can cause severe thermal mechanical damage to tissues and organs. Compared to other heating sources such as lasers, magnetic fields of hundreds of kilohertz can penetrate tissues and organs with negligible interference or attenuation, enabling efficient and uniform heating of magnetic nanoparticles in deep tissues.[16,40] Nanoparticles can be dispersed into CPAs and perfused into blood vessels to achieve a relatively even distribution in various regions of tissues or organs, thereby facilitating uniform heating. Maintaining nanoparticle stability in CPAs is crucial for preserving

their functionality and preventing aggregation throughout the cryopreservation and rewarming process. Aggregated nanoparticles could impede their penetration into microcapillaries, leading to nonuniform distribution within organs and nonuniform heating.[23] Additionally, aggregation may cause occlusion of blood vessels and hinder the full clearance of nanoparticles after rewarming, potentially resulting in detrimental effects on organ function. Common CPAs comprise a mixture of organic solvents and inorganic salts, which can cause aggregation of unmodified nanoparticles due to the high ionic strength. To address this issue, a steric layer can be applied to the nanoparticle surface to enhance the steric repulsion force and ensure nanoparticle stability in the CPA solution. Biocompatible polymer coatings, such as PEG, polyvinyl alcohol (PVA), or dextran, can improve nanoparticle stability in biological systems.[41,42] These polymer coatings create a hydration layer that prevents nanoparticle aggregation and reduces non-specific interactions with other molecules or cells. PEGylation, for example, has been widely used to improve the colloidal stability of magnetic nanoparticles in CPAs.[15,23] Alternatively, silica coating provides a robust and biocompatible shell around magnetic nanoparticles, enabling further functionalization with various chemical groups or biomolecules, and has been successfully utilized for rewarming several tissues and organs (Table 1). However, it is important to note that nanoparticles are predominantly distributed in the vascular space, which comprises less than 10% of the total volume of most tissues.[15] As a result, although perfusion can evenly distribute nanoparticles throughout the vascular region, it may not adequately load them in avascular regions.

Several strategies have been proposed to address the challenges of the nonuniform distribution of nanoparticles within tissues.[43] One approach involves surface modification of nanoparticles to enhance their binding and uptake by specific cell types within the tissue. For instance, ligand-mediated targeting of specific receptors on cell surfaces can promote internalization of the nanoparticles into the target cells, leading to their deeper penetration into the tissue.[44,45] However, this approach may require prolonged treatment time, potentially increasing the loading time of nanoparticles and the risk of aggregation-induced embolism. Another promising strategy involves the use of nanomotors that can autonomously move in response to different stimuli, such as chemical reagents, light, or magnetic field, to enhance tissue penetration (Fig. 2b).[46,47] For example, magnetic nanomotors can be actively manipulated to penetrate deep tissues with an external magnetic field.[48–50] Yet, it should be noted that for nanowarming applications, any movement of magnetic nanoparticles under a magnetic field must be carefully controlled to avoid irreversible mechanical damage to normal cells.[51,52] Although these strategies hold promise, it is crucial to conduct further *in vivo* investigations to establish their feasibility and safety.

Following the successful distribution of nanoparticles within tissues, their effective clearance from the body should be considered to prevent post-thawing accumulation in tissues that can cause chronic toxicity (Fig. 2b). Although nanoparticles in blood vessels can be eluted through perfusion, those getting stuck in avascular tissues are still difficult to remove. Generally, smaller nanoparticles are easier to remove by exocytosis.[53] In addition, nanoparticles with different surface modifications or coatings exhibit different removal rates. Nanoparticles with a positively charged surface can remain in cells for a longer time. In contrast, PEGylated nanoparticles can migrate within the cytoplasm as individual particles and exit the cell more quickly.[54] Another strategy for solving this problem is to induce the *in situ* degradation of nanoparticles after thawing. In this way, nanoparticles can spontaneously dissociate in the *in vivo* environment *via* mechanisms such as enzymatic degradation, dissolution, or oxidation.[55,56] The extent and efficiency of the *in situ* degradation may be affected by various factors, including particle size, surface charge, and chemical composition, and further optimization of the degradation process is necessary. Additionally, stimuli-responsive magnetic nanoparticles can be designed to dissolve and release their constituent ions into surrounding tissues in response to external stimuli such as changes in temperature or pH. However, prolonged exposure to reactive ions not efficiently excreted from the body may also lead to chronic toxicity.[56] As a potential solution to this issue, ferritin, a universal intracellular protein that stores iron ions, has been reported to participate in the degradation of iron oxide nanoparticles.[57] This finding suggests that ferritin may be applied as a detoxicating adjuvant of iron oxide nanoparticles. Again, advancing nanowarming technology requires a delicate balance between enhancing the biodistribution of heating agents through tissue penetration and minimizing their potential for chronic toxicity.

Conclusion and outlook

The utilization of magnetic nanoparticles in the process of nanowarming presents a promising alternative to conventional thawing methods for cryopreserved tissues and organs, offering rapid and uniform rewarming with reduced damage to the samples. Moving forward, future research endeavors in this area should be focused on improving the design of magnetic nanoparticles to enhance the heating efficiency while mitigating toxicity to biological samples. Current research in magnetic hyperthermia has made significant progress toward this goal, yet achieving optimal heating efficiency at cryogenic temperatures still needs further investigation. Additionally, the development of self-regulating magnetic materials could be a game-changer in this field, enabling the precise control of heating rates during nanowarming, which can reduce the risk of thermal damage to biological samples. Furthermore, careful consideration should be given to the design of post-thawing elution, degradation and subsequent detoxication of nanoparticles to prevent chronic toxicity. Achieving a judicious balance of the heating performance and biocompatibility of nanowarming agents provides an exciting opportunity to revolutionize cryopreservation and regenerative medicine. It is crucial to continue researching and developing in this area to fully realize the potential of the nanowarming technique.

Conflicts of interest

There are no conflicts to declare.

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