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REVIEW

Nanomedicine-Enabled/Augmented Cell Autophagy to Mitigate and Boycott the Development and Progression of Atherosclerotic Plaque

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Abstract: Atherosclerosis (AS) is a chronic, inflammatory and systemic disease that seriously threatens human health and is the main factor leading to the morbidity and mortality of cardiovascular diseases. Autophagy has been regarded as an effective therapeutic strategy for AS, which can represent an important self-protecting intracellular system that can delivery and capture destroyed organelles and unnecessary proteins to lysosome for degradation. Thanks to the fast progress of nanotechnology, nanomedicine is widely used to enable, potentiate, and augment autophagy for promoting the AS-therapeutic efficacy and specificity. This review focuses on discussing the latest advances in this emerging field, with a particular emphasis on the nanomedicine-enabled/augmented autophagy approach for supporting the construction of next-generation nanomedicines to effectively trigger autophagy in the treatment of AS. Particularly, the biocompatibility and biosafety of engineering nanomedicine, the current challenges and futural prospects are also summarized in this comprehensive review, aiming to accelerate future clinical translation of this burgeoning field. It is highly anticipated that future clinical transformation of nanomedicine can be achieved by inducing autophagic activation based on bioactive nanomaterials.

Keywords: nanomedicine, autophagy, atherosclerosis, cardiovascular diseases, macrophages

Introduction

Cardiovascular and cerebrovascular diseases are rapidly spreading worldwide and have become a leading cause of morbidity and mortality globally.[1–3] Atherosclerosis, the primary reason for cardiovascular and cerebrovascular diseases, is a chronic, inflammatory and systemic disease, majorly influencing the medium or large-size arteries.[4–7] Smoke, hypertension, hyperlipidemia and diabetes are common risk factors of atherosclerosis occurrence, causing adverse consequences, including stroke, transient ischemic attack, coronary artery syndrome, renovascular hypertension or renal dysfunction, cold extremities or claudication, etc.[8–11] Therefore, early therapeutic intervention of atherosclerosis is urgent demand due to its current high incidence, morbidity and mortality rate, as well as the trend of younger age caused by changes in modern diet and exercise habits.

Autophagy is a complex intracellular mechanism that utilizes lysosomes to degrade intracellular substances and is closely associated with certain metabolic diseases, such as AS.[12,13] It is believed that autophagy is involved in decreasing the accumulation of foam cell in the early stages can inhibit plaque formation, while promoting cholesterol efflux can reduce inflammation and stabilize plaques in late stages of AS.[14,15] Thus, reasonable autophagy activation can efficiently reduce cardiovascular damage and pro-inflammatory leakage, thus, the regulation of autophagy may be a feasible modality for AS mitigation.[16–18] Despite the current autophagy-inducing drugs has achieved satisfactory progress in activating autophagy to mitigate and boycott the atherosclerotic deterioration, long-time drug treatments have usually

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contributed to severe adverse effects, including liver damage, gastrointestinal bleeding, arrhythmia, postoperative restenosis and bleeding complication.[19,20] As a result, it is necessary to explore an efficient and accurate approach to improve the efficiency of autophagic activation while decreasing their adverse reactions.

Advanced nanotechnology has effectively integrated contents among materials science, biology, physics, chemistry and other interdisciplinary fields, and is the product of combination of modern technology and science, which is used to explore the wonderful molecular world from a nanoscale perspective and has shone brightly in various fields.[21–26] With the fast progress of nanotechnology and the continuous increase of clinical demands, nanomedicine, a rising interdisciplinary field, has emerged and brought about profound paradigm shift.[27–31] During the past decades, various kinds of bioactive nanomaterials have been utilized in the treatment of malignant cancers, bacterial infections, cardiovascular diseases, and inflammatory diseases owing to the distinct advantages, including ultra-small size with specific surface area, diverse physical and chemical properties, favorable biocompatibility and biosafety, passive targeting accumulation of the enhanced permeability and retention (EPR) effect and abundant reaction sites for surface modification.[32–35] Hence, nanomedicine-enabled/promoted autophagy can not only compensate for limitations and defects of traditional therapeutic approach but also augment the therapeutic sensitivity and specificity for AS.

Intelligently designed and constructed bioactive nanomedicines can efficiently enhance the therapeutic outcome of atherosclerosis by inducing or augmenting the autophagy, which can result in exquisite concept for AS treatment in the future. A comprehensive summary and in-depth discussion of the very recent progress made in this emerging field were provided in this review. First, bioactive nanomaterials can directly trigger or boost autophagy for mitigating atherosclerotic plaques via photothermal therapy (PTT), photodynamic therapy (PDT), sonodynamic therapy (SDT), and ion-interference therapy (IIT). Second, autophagy activated by the intrinsic bioactivity of nanomaterials is also being paid more attention. Third, other approaches promoting autophagy and their underlying mechanism are also discussed in depth. Last but not the least, the important issues regarding the current challenges and future prospects of based nanomedicines will also be emphatically discussed for promoting their clinical translations in the future (Figure 1). The exact potential mechanism of autophagy enabled by bioactive nanomaterials as summarized in this review will widely extend the understanding of the association of autophagy with atherosclerotic plaque, which is expected to pave the avenues for personalized medicines in vulnerable plaque therapy.

Role of Autophagy in Atherosclerosis

Autophagy has been demonstrated to have a significant association with atherosclerosis, as evidenced by the expression patterns of autophagy-related genes (ARGs).[36] A lot of factors within atherosclerosis can effectively induce autophagy, such as reactive oxygen species (ROS), oxidized low-density lipoprotein (ox-LDL), and inflammatory factors.[37,38] Under conditions of mild cellular stress, mild adaptive autophagy of vascular cells can be stimulated to enhance cell survival by clearing damaged proteins and organelles, thereby shielding vascular tissues from the damage of inflammation and oxidative damage.[39] Accumulating research has indicated that the induction of autophagy can effectively reduce the area of atherosclerotic plaque and maintain the stability of plaque, characterized by decreased levels of lipid accumulation and pro-inflammatory macrophages, along with elevated contents of collagen, vascular smooth muscle cells (VSMCs) and anti-inflammatory macrophages within the plaques.[40] However, defective autophagy has also been observed during the development and deterioration of atherosclerosis, irrespective of the availability of above autophagy stimulators in plaques. For instance, expression of autophagy markers, such as LC3 and ATG13, is notably higher in aortic endothelial cells (ECs) with severe atherosclerosis compared to those without atherosclerosis.[41]

Intense inflammation and oxidative stress can trigger excessive cell autophagy, resulting in autophagy-dependent cell death, reduced collagen production, thinning of the fibrous cap, destabilization of plaque, and occurrence of acute coronary syndromes.[42,43] Hence, the control of excessive cell autophagy at an early phase is essential to avert arteriosclerosis and subsequent severe cardiovascular complications. Besides excessive autophagy, inadequate autophagy is common phenomena and plays a key role in atherosclerosis progression. In advanced lesions with substantial oxidative stress and inflammatory stimulation, insufficient autophagy fails to manage the excessive stress, ultimately leading to apoptosis.[44,45] Further investigation into the role of autophagy in atherosclerosis development revealed that ApoE$^{-/-}$

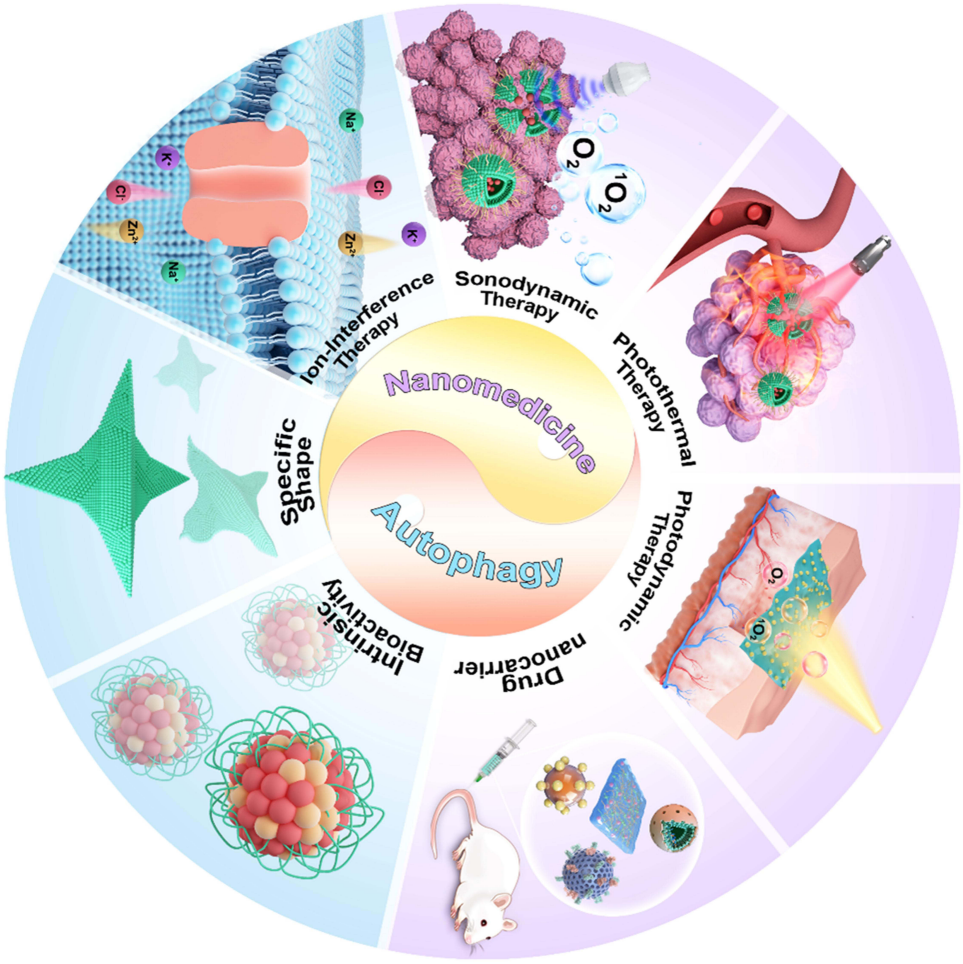

Figure 1 Summative scheme of nanomedicine-enabled/augmented autophagy to treat atherosclerosis.

mice with smooth muscle cell-specific deletion of Atg7 exhibited accelerated plaque progression following a 10-week high-fat diet. This was characterized by increased plaque cell death, thicker fibrous caps, enhanced inflammation, and elevated collagen content.[46] Furthermore, the inhibition of autophagy (3-MA, spautin-1, and bafilomycin A1) can effectively suppress the degradation of contractile proteins and inhibit the hyper proliferation and migration of SMC, thereby supporting the concept that autophagy could have an important part in the setting of restenosis.[47] The cytoprotective autophagic response can shift into a maladaptive response, which largely depends on the stage of plaque progression (Figure 2).[45] Hence, the dysfunction of autophagy in atherosclerosis aggravates vascular oxidative stress, inflammation, and plaque necrosis, indicating a mechanism-based strategy to effectively suppress atherosclerosis progression.

Application of Nanomedicine in Activating Autophagy

Autophagy Activated by Photothermal Therapy (PTT)

Photothermal therapy (PTT) shows promise as a minimally invasive approach with fewer undesirable side effects and high specificity for treating AS.[48–52] Promising results from the initial clinical trials (the ANOM-FIM trial; NCT01270139) demonstrated that plasmonic PTT significantly reduced coronary atherosclerotic plaque burden over the 12-month follow-up period, highlighting its potential in AS treatment.[53] However, only few research has focused on specifically restoring autophagy in atherosclerosis through PTT effect. Very recently, some significant reports on this hot-scientific topic have been published. For instance, the coupling of copper sulfide (CuS) nanoparticles to antibodies targeting TRPV1 (CuS-TRPV1) was devised and developed, which was employed to generate photothermal effects to

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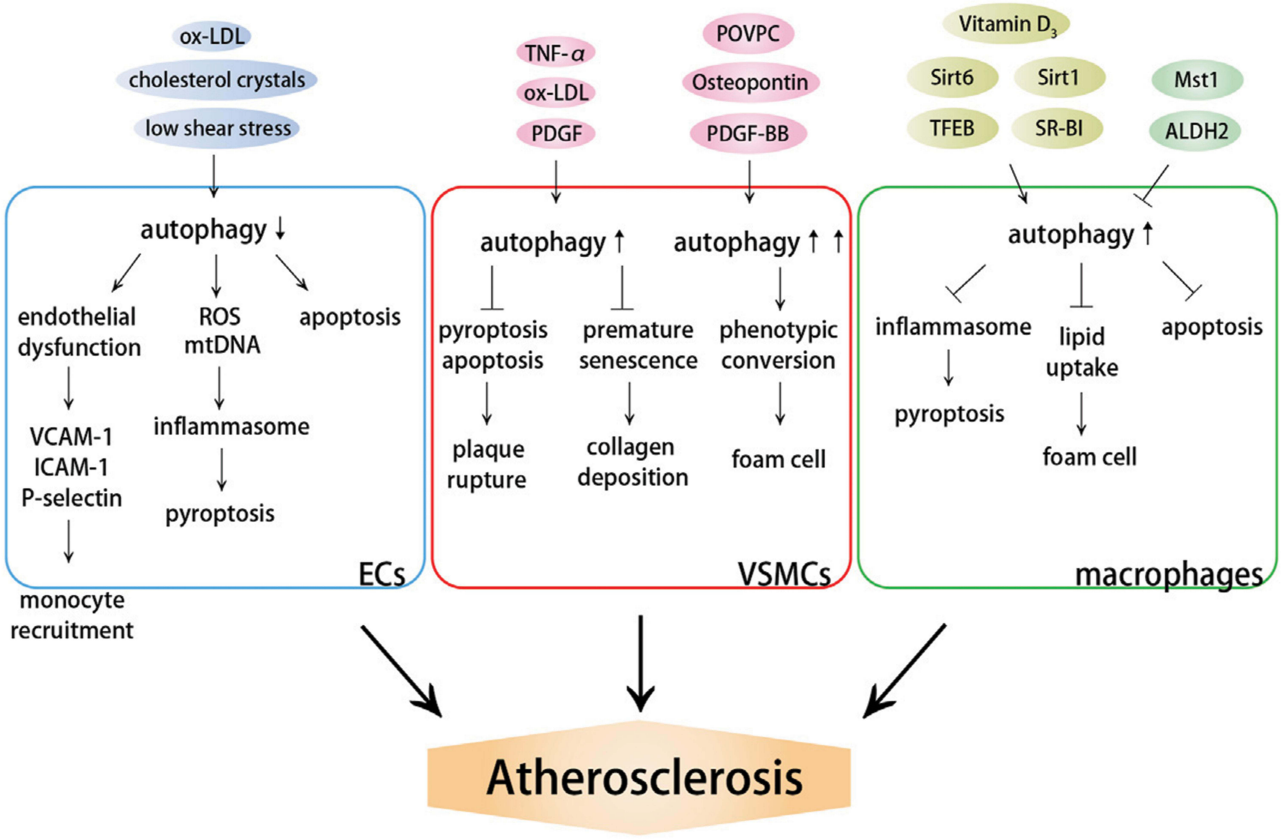

Figure 2 Role of autophagy in atherosclerosis. The dysfunction of autophagy induces endothelial dysfunction, inflammation, and cell death in ECs. The dysfunction of autophagy exacerbates plaque instability, collagen deposition and foam cells formation in VSMCs. Defective autophagy leads to intracellular lipid accumulation, macrophage foam cell formation, and induces cellular death in macrophages. Upward arrow indicates excessive autophagy, and downward arrow represents defective autophagy. Reproduced with permission.[45] Copyright 2022, Frontiers Media S.A.

activate autophagy and impede foam cell formation in VSMCs[54] (Figure 3a). The conjugation with TRPV1 monoclonal antibody endowed CuS-TRPV1 with specific binding to TRPV1 on the plasma membrane of VSMCs (Figure 3b), and meanwhile, photothermal agents, CuS nanomaterials, could absorb near-infrared (NIR) light to produce a local hyperthermia within oxLDL-stimulated VSMCs. After readily binding to TRPV1 on the membrane, the open of thermo-sensitive TRPV1 channels allowed calcium ions (Ca^{2+}) influx by means of low-power NIR irradiation for hyperthermia generation. The increased intracellular Ca^{2+} subsequently triggered autophagy activation, improved cholesterol efflux, attenuated lipid accumulation, and impeded foam cell formation within VSMCs and impeded foam cell formation in VSMCs stimulated by ox-LDL. oxLDL-injured autophagy was significantly rescued by CuS-TRPV1, which was also confirmed by several autophagy markers: autophagosome formation, up-regulated LC3II expression and downregulated LC3I expression after photoactivated effects (Figure 3c and d). Furthermore, as shown in in vivo experiments, Oil red O staining displayed a significant reduction in aortic root lesion areas and in en face prepared aortic arch lesion, indicating PTT treatment performed the best in targeted limiting atherosclerotic lesion progression in $ApoE^{-/-}$ mice compared to other groups (Figure 3e and f). In addition, Wang et al also developed a dextran sulfate modified hollow carbon nanospheres (HCN@DS), enabling autophagy activation and stimulating ABCA1-dependent cholesterol efflux by generating local hyperthermia upon laser excitation, thereby inhibiting the atherosclerosis progression[55] (Figure 4). According to bioactive nanomaterials-enabled photonic hyperthermia after NIR absorption, these results offered evidence for the activity of hyperthermia to autophagy activation and attracted wide interest in design other PTT-driven autophagic nanosystems in attenuating and boycotting AS progression. The significant progress in understanding the potential mechanism of cell autophagy triggered by the hyperthermia effect is useful to promote the strategy of optimization from the angle of treatment.

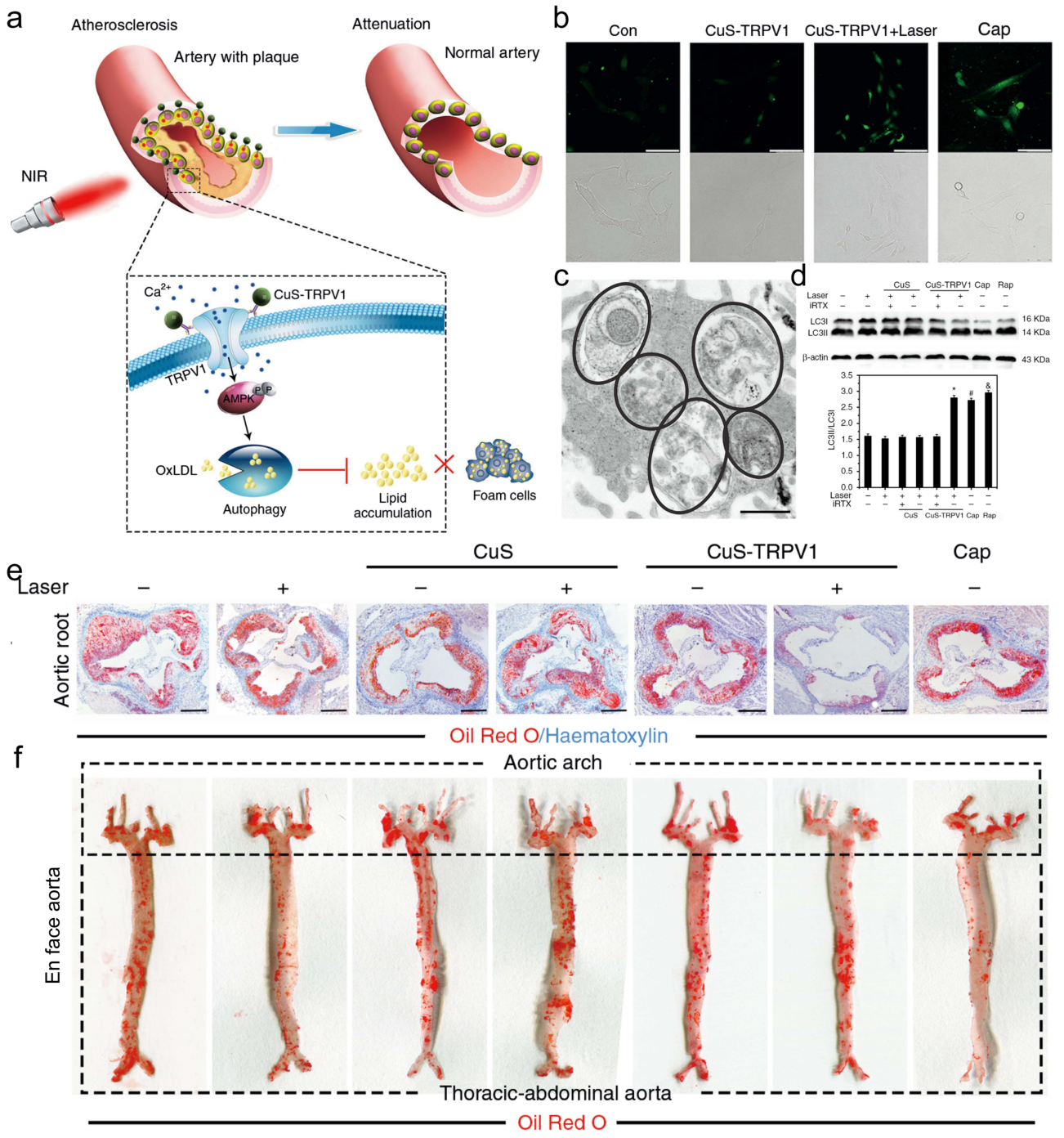

Figure 3 (**a**) Schematic diagram of CuS-TRPV1 switch for photothermal activation of TRPV1 signaling to resist the atherosclerosis. (**b**) Representative imaging flow cytometry pictures of VSMCs co-incubated with the fluorescein-conjugated CuS-TRPV1 or CuS nanoparticles for 2h. Scale bar = 50 μm. (**c**) Representative TEM picture of autophagosomes in VSMCs after 30 NIR irradiation cycles. Black circles were added to outline the double-membrane structures of autophagosomes. (**d**) In vitro Western blot analysis of LC3II/LC3I ratio in VSMCs after corresponding treatments. *indicating $P < 0.05$ for CuS-TRPV1 vs untreated group, #indicating $P < 0.05$ for Cap vs untreated group, and indicating $P < 0.05$ for Rap vs untreated group. (**e** and **f**) Representative pictures of ORO-stained aortic root sections and ORO-stained *en* face aortic preparation after different treatments. Reproduced with permission.[54] Copyright 2018, Springer Nature.

Autophagy Mediated by Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) is a clinically approved therapeutic strategy for specific malignant tumors and inflammatory diseases, which has been an alternative and supplementary approach to traditional radiotherapy and chemotherapy owing to their distinct advantages, including non-invasiveness, precise spatio-temporal controllability, and minimal side

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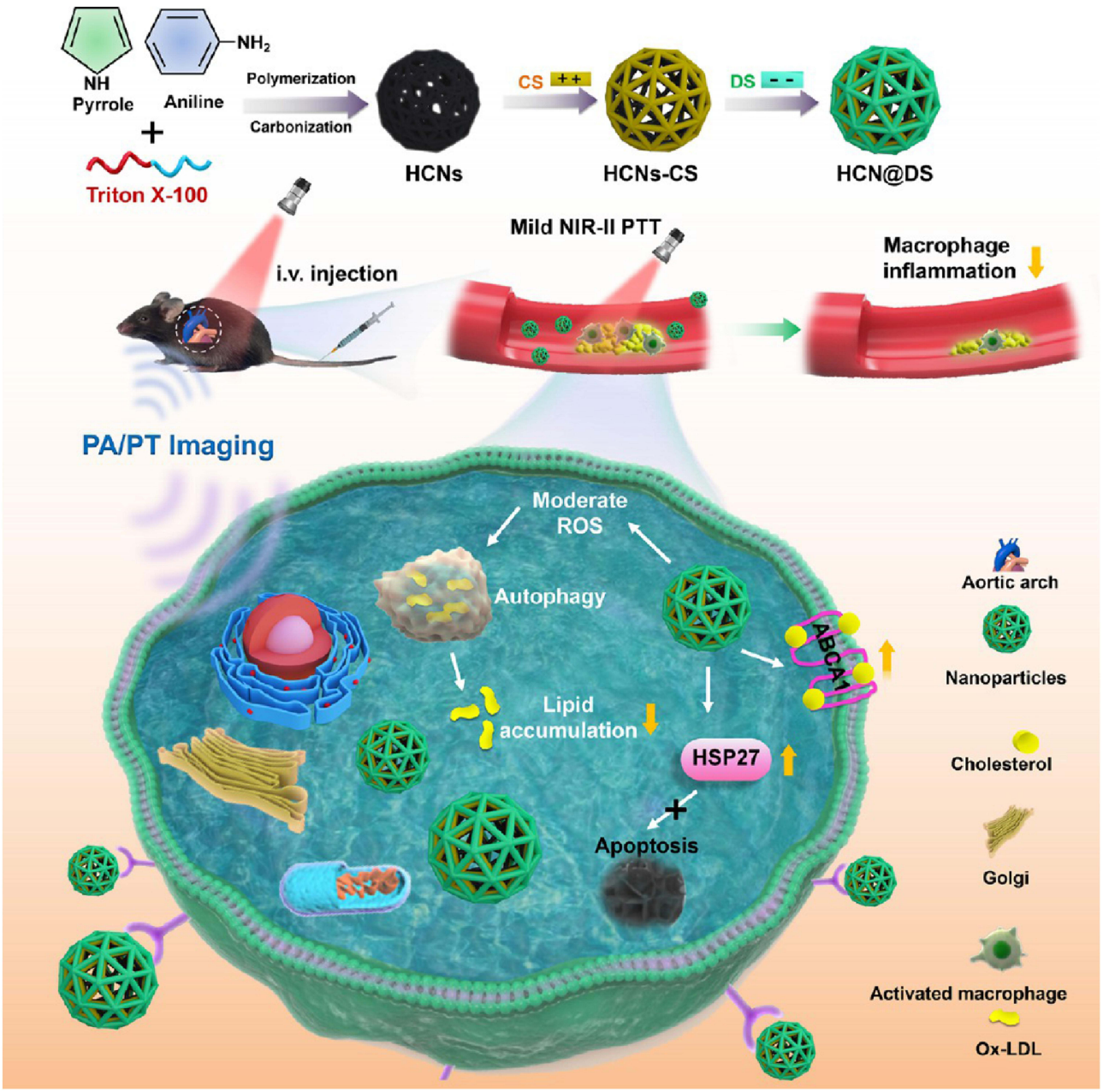

Figure 4 Schematic diagram of the HCN@DS preparation and the potential mechanisms of autophagic induction for atherosclerosis treatment. Upward yellow arrows indicate the increased expression of related protein levels. Downward yellow arrows indicate the decrease of the content of lipid accumulation or macrophage inflammation. Reproduced with permission.[55] Copyright 2024, American Chemical Society.

effects.[56–62] The underlying chemical mechanism of PDT involves the delivery of photosensitizers to the lesion areas, followed by excitation with the light of specific wavelength to produce cytotoxic ROS, thereby inducing the oxidative stress response.[63–65] Since ROS, as the major product of PDT, are early inducers of autophagy,[66] autophagy induced by PDT should also be worthy of our exploration. For instance, a UCNPs-Ce6 complex was constructed to induce autophagy activation via inhibiting PI3K pathways, degrade the lipids into free cholesterol, and benefit the cholesterol efflux[67] (Figure 5a). Intracellular ROS can be efficiently induced by UCNPs-Ce6 under laser irradiation (Figure 5b). In vitro experiments have found that PDT induced lipid deposition and cholesterol efflux via Oil red O staining and fluorometric assay (Figure 5c and d). Monodansylcadaverine (MDC) dye staining of autophagosomes demonstrated brighter green fluorescence of the MDC-positive cells in the PDT group than in the other groups and could be significantly attenuated

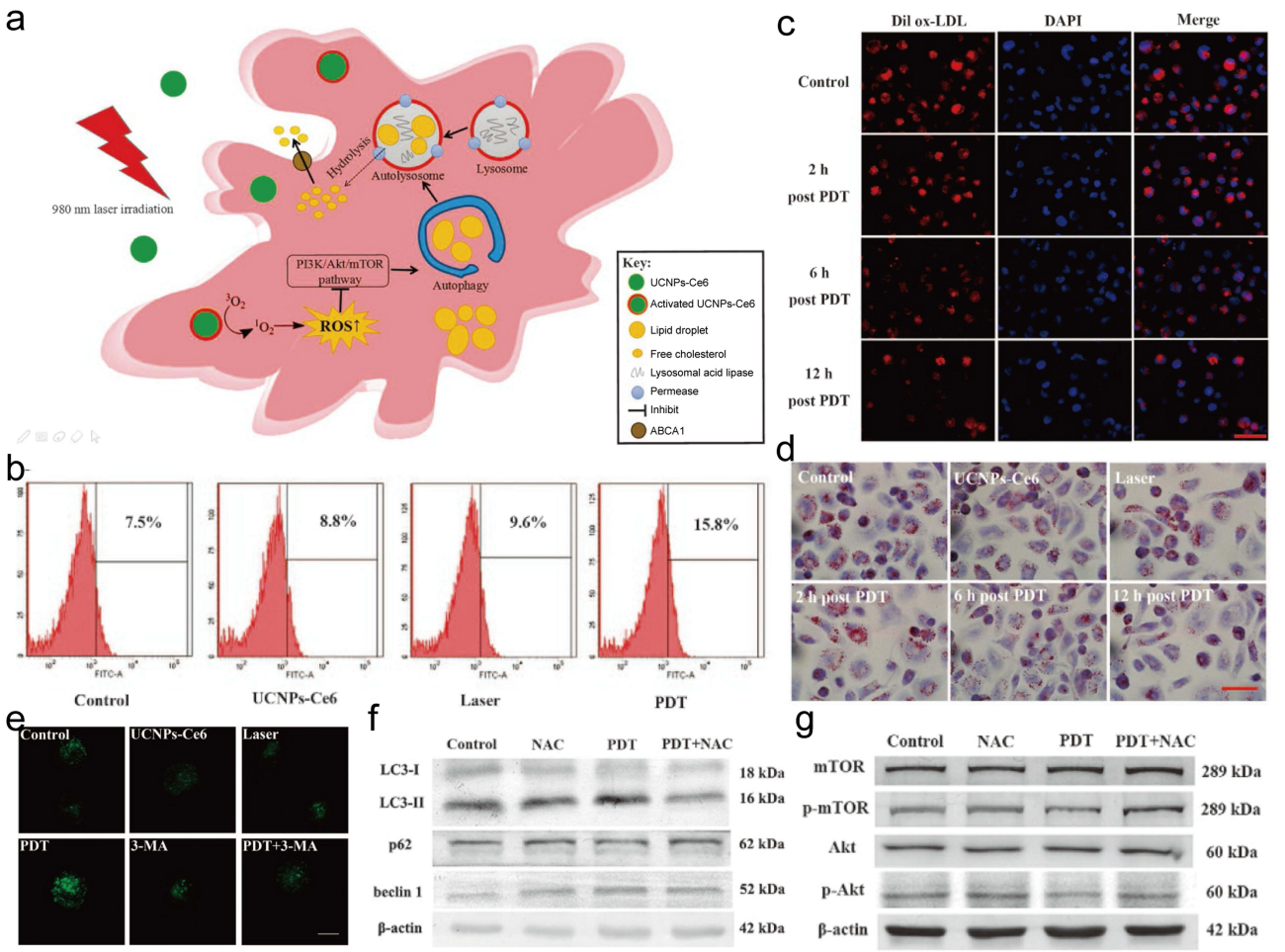

Figure 5 (**a**) Schematic illustration of UCNPs-Ce6-mediated PDT for autophagic induction. (**b**) Flow cytometry analysis of intracellular ROS generation after varied treatments. (**c**) Fluorescent images of Dil ox-LDL concentration. Scale bar = 50 μm. (**d**) ORO-stained images of intracellular lipid burden at the appointed times after PDT stimulation. Scale bar = 50 μm. (**e**) The MDC staining of AVOs after varied treatments. Scale bar = 5 μm. (**f** and **g**) Western blot analysis of autophagy-related proteins and PI3K/Akt/mTOR pathway-related proteins after various treatments. Reproduced with permission.[67] Copyright 2017, Springer Nature.

by autophagy inhibitor 3-methyladenine (3-MA), which indicated that PDT was responsible for autophagy induction in macrophage foam cells (Figure 5e). To further investigate the pivotal role of ROS produced by PDT in autophagy activation, ROS inhibitor, NAC, was found to significantly diminish the ROS production, reverse the effect of PDT on autophagy-related proteins and suppress the PI3K/Akt/mTOR pathway (Figure 5f and g). Thus, light-excited PDT can efficiently generate ROS and then initiate autophagy activation and cholesterol efflux to inhibit the progression of AS. These results have confirmed that PDT-accelerated autophagy features important advantages in AS suppression, which provides a great promise for broadening the PDT application in AS therapy.

Autophagy Driven by Gas Therapy

Gas therapy is an emerging therapeutic method based on specific gas molecules, such as hydrogen sulfide (H_2S), carbon monoxide (CO) and nitric oxide (NO), playing essential roles in various biological activities with the advantages of low toxicity, non-resistance, and synergy with other therapies.[68–72] Among these specifical gases, H_2S, the third critical biological molecule in the human body, can repair endothelial damage, regulate vasodilation, reconstruct the endothelial barrier, and decrease oxidative stress, but its synthesis is largely damaged during the atherosclerotic development.[73,74] To solve this tricky issue, one effective modality is directly introducing exogenous H_2S donor into the hepatocytes and AS lesion. For example, a H_2S donor incorporated into a thermal-sensitive polymer (UCST) was constructed to generate produce H_2S molecules to mediate hepatocyte autophagy, thereby contributing to reduce plasma triglyceride levels and

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suppress AS progression[75] (Figure 6). On the one hand, H_2S molecules can scavenge excessive ROS, increase anti-inflammatory cytokines, regulate macrophage polarization toward M2-like phenotype, and prevent foam cell formation, thereby performing protective effect to control and even reverse the AS progression.[76,77] On the other hand, the hepatocytes suffer from H_2S molecules deficiency, contributing to dyslipidemia and hepatic steatosis, thus accelerating the formation of foam cells and the deterioration of AS.[77] This H_2S gas can efficiently induce hepatocyte autophagy to improve the lipid metabolism and impede the plasma triglyceride levels to promote anti-atherosclerosis efficiency. This paradigm proves that H_2S gas is efficient as autophagic inducers for AS treatment, which creatively transforms the waste nanomedicine into the valuable asset to boost anti-atherosclerosis treatment.

Autophagy Enhanced by Ion Interference Therapy (IIT)

Bioactive ions released/produced from specific nanomaterials play an important role in various physiological processes, such as pH and osmotic pressure homeostasis, enzyme activity, signaling cascade activation, and biomolecule targeting activity.[78–80] Abnormal distribution or accumulation of these specific ions, regarded as ion-interference therapy (IIT), can influence normal physiological activities, which have been exploited against malignant cancers and inflammatory disease with high efficiency and non-drug resistance.[81–83] Among bioactive metal ions, zinc ions (Zn^{2+}), as an essential trace element for the human body, can promote lipid digestion by regulating cellular autophagy.[84,85] Inspired by this, a multifunctional nanomedicine was

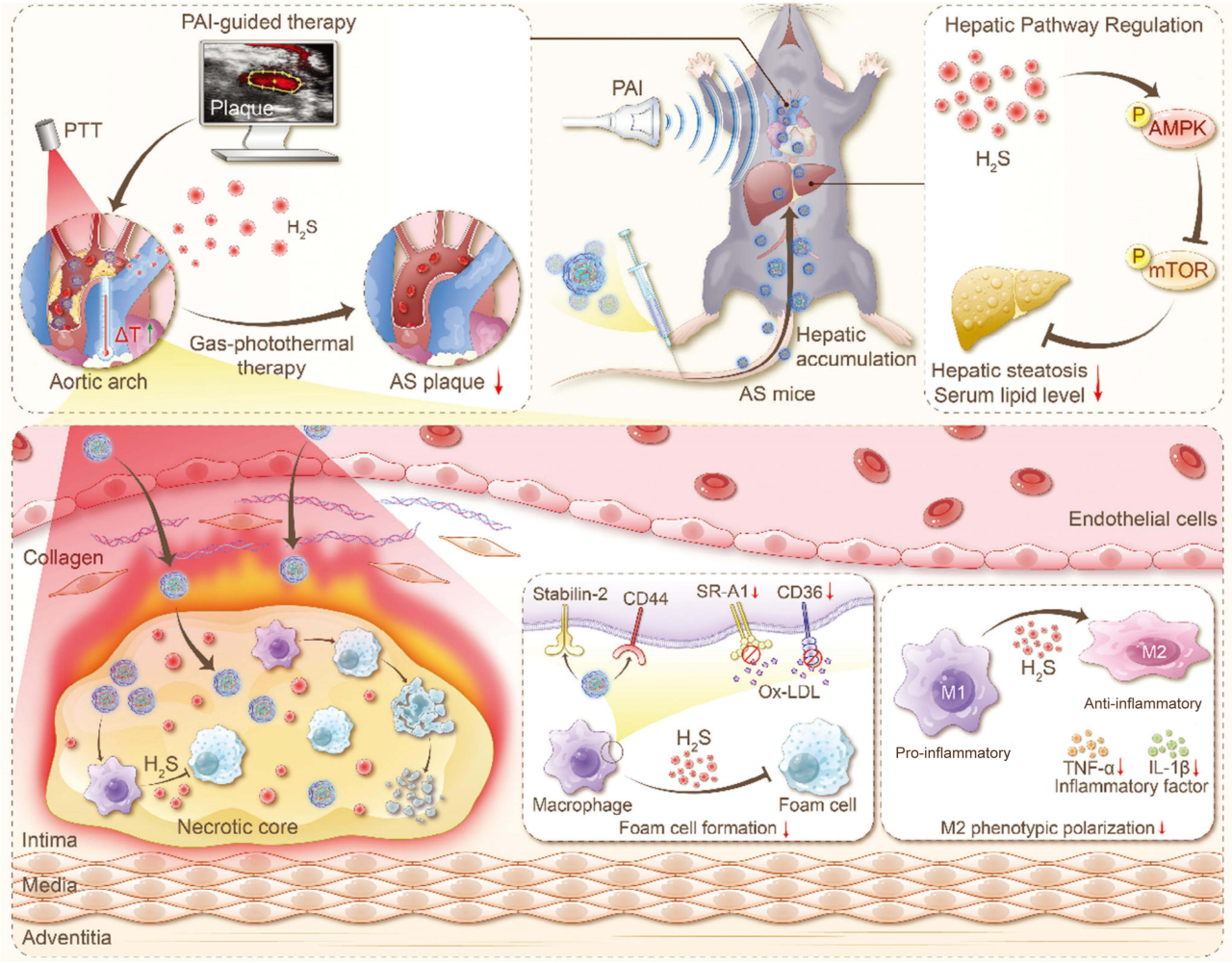

Figure 6 Schematic diagram of HPAAD-I NPs for photothermal synergized with H_2S gas therapy and underlying mechanism of autophagic activation induced by H_2S gas to attenuate AS progression. Green arrow indicates the increased temperature under laser irradiation. Red arrows indicate the inhibition of AS progression, decreased serum lipid level, foam cell formation and M2 phenotypic polarization, and reduced contents of SR-A1, CD36, TNF-α and IL-1β. Reproduced with permission.[75] Copyright 2025, Wiley-VCH.

constructed by PLGA nanoparticle as a template to realize the CpG encapsulation through coordination-driven self-assembly with Zn^{2+} and EGCG.[86] Upon cellular internalization, CEZP nanomedicine experienced intracellular disassembly triggered by within the plaque, releasing Zn^{2+} to improve lipid degradation by promoting macrophage autophagy[87](Figure 7a). Typical transmission electron microscopy (TEM) presented increased autophagosomes in both EZP and CEZP treatments (Figure 7b), and key autophagy-related proteins exhibited that Zn^{2+}-involved interventions (EZP and CEZP group) remarkably elevated the LC3β/α ratio while reducing p62 expression (Figure 7c–e), which suggested improved macrophage autophagy function was attributed to Zn^{2+} participation. This paradigm confirms that Zn^{2+}-based nanomodulators are effective as autophagic inducers for AS therapy through promoting intracellular lipid degradation, which offers distinct formulation design paradigms for IIT-augmented AS treatments.

Autophagy Initiated by Sonodynamic Therapy (SDT)

SDT refers to the transient ROS generated by acoustic sensitizers with the assistance of cavitation effect and sonoluminescence effect under US excitation.[88–91] Unlike PDT, SDT exerts superior anti-cancer and anti-inflammatory effects on the deep-seated

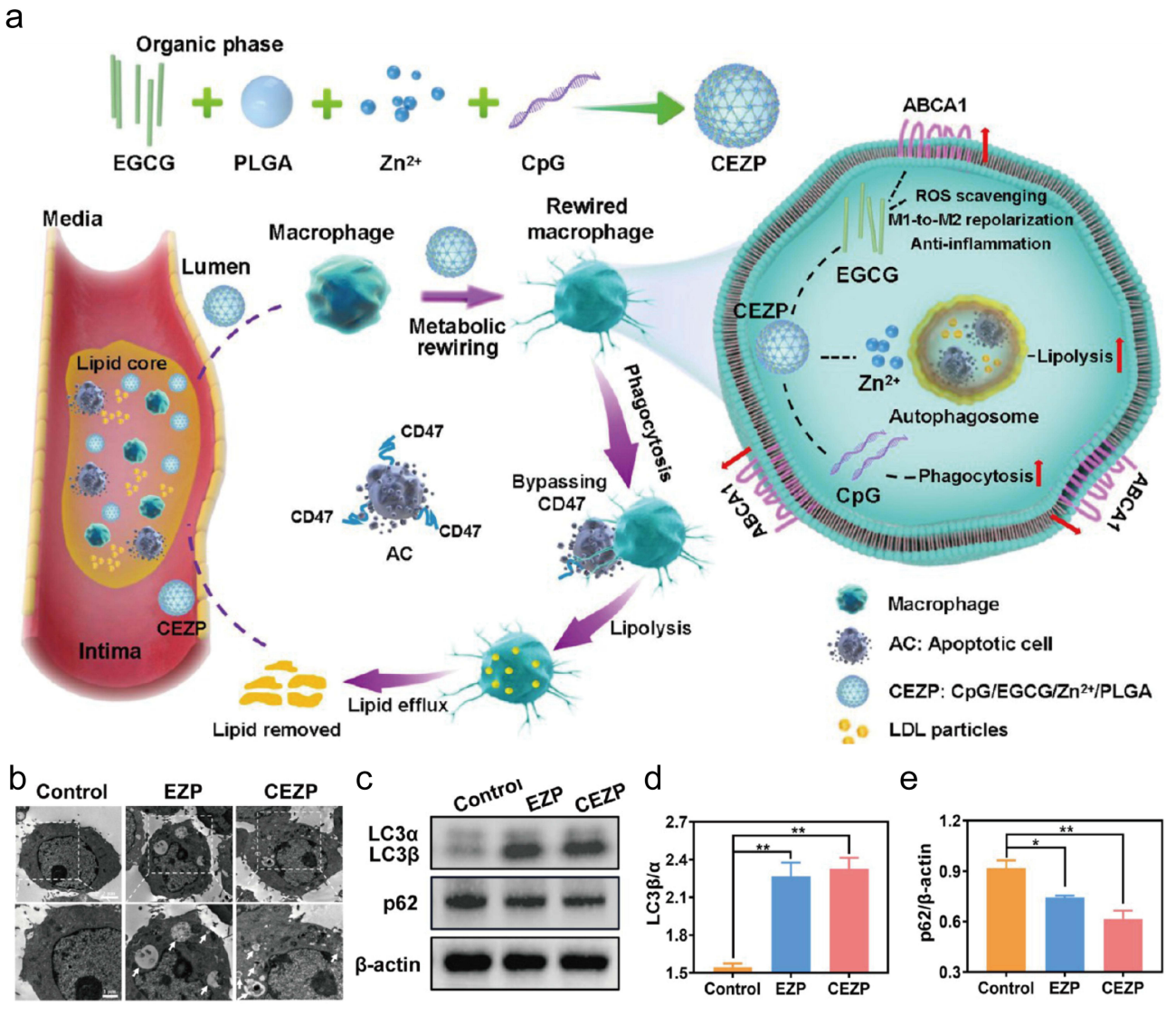

Figure 7 (**a**) Schematic illustration of CEZP synthesis and potential mechanism of autophagy triggered by Zn^{2+}-based nanomedicine. Red arrows indicate the increased expression of ABCA1 protein, promoted phagocytosis of phagocytes on apoptotic cells, and enhanced lipid degradation. (**b**) Bio-TEM images autophagosome observation after varied treatments. (**c–e**) Western blot analysis of LC3α, LC3β and p62 levels and corresponding semi-quantitative results after various treatments. *indicates $P < 0.05$, **indicates $P < 0.01$. Reproduced with permission.[86] Copyright 2025, American Chemical Society.

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diseases, being noninvasive, not expensive, and having a considerable deep penetration, providing a bright future in clinical AS treatment.[92–96] Wu et al has proposed that a rod-like Au-ZnO Schottky Junction nanomedicine could effectively alleviate the burden of subsistent foamy macrophages via ROS-initiated excessive autophagy and mitochondrial dysfunction, thereby promoting the apoptosis of foamy macrophages[97] (Figure 8a). As we all know, the cytoplasmic LC3-I is usually converted into LC3-II by a ubiquitination-like system. At the same time, the autophagy inhibitory protein 1 (P62), as an autophagy substrate, is also decomposed when autophagy occurs. The Western blotting analysis of LC3-II/LC3-I and P62 expressions in foam cells was conducted to find that the obviously autophagic activation in the SDT group was presented by the highest LC3-II /LC3-I ratio and the lowest P62 expression compared with other groups (Figure 8b). In addition, increased autophagosomes indicated the possibility of autophagic occurring in Au-ZnO Schottky Junction-based SDT (Figure 8c). The considerable foam cell removing in an apoptotic way could be attributed to the abundant autophagy and mitochondrial dysfunction in macrophages triggered by SDT from the piezocatalytic therapeutic performance (Figure 8d), which can not only effectively reduce the lipids

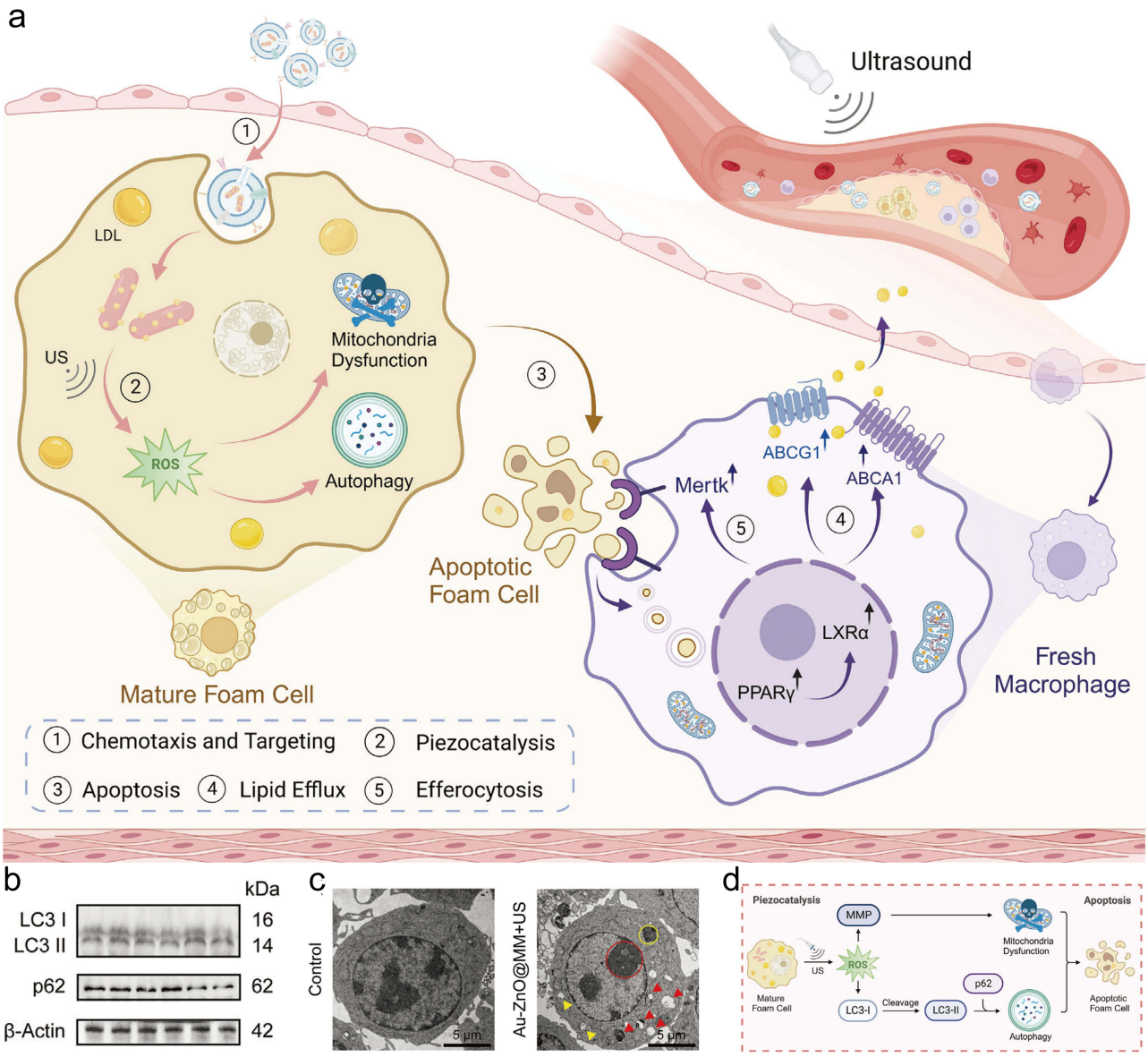

Figure 8 (**a**) Schematic diagram of fabrication process of biomimetic Au-ZnO@MM Schottky junction construction and its underlying mechanism of autophagic induction caused by SDT. Upward black arrows indicate the increased concentration of Mertk, ABCG1, ABCA1, PPARγ and LXRα. (**b**) Western blot analysis of LC3I, LC3II and p62 levels after various treatments. (**c**) Bio-TEM images of autophagosome observation after varied treatments. The apoptotic corpuscle, concentrated chromatin, autophagosomes, and vacuolated mitochondria were represented by yellow circle, red circle, red arrows, and yellow arrows, respectively. (**d**) Schematic diagram presenting the underlying mechanism of autophagic induction through SDT. Reproduced with permission.[97] Copyright 2024, Wiley-VCH.

and foamy macrophages burden but also provide a valuable avenue for suppressing plaque progression by SDT-inducing autophagic activity.

Autophagy Enabled/Augmented by Other Approaches

Autophagy Assisted by Targeting Nanocarriers

Although certain therapeutic drugs have been recognized to trigger autophagy induction for attenuating the AS progression, there are still critical issues in use of those autophagic molecules, such as quick clearance from body circulation, undesirable off-target effects, and inevitable adverse reactions. The passive/active targeting activities of bioactive nanocarriers can efficiently increase their cumulation in lesions by taking advantage of the endothelium permeability in the AS plaques and positive targeting different molecular receptors in the AS inflammatory microenvironment.[98] On this ground, Trehalose-releasing nanogels (TNG) were introduced to extend the circulatory time and increase the trehalose's bioavailability.[99] The incorporation of Acrylamide was helpful to hydrolyze the ester bond in 6-O-acryloyl-trehalose units, thereby enabling the continuous release of free trehalose from the nanogels network for autophagy activation in atherosclerotic lesions (Figure 9a). Owing to the excellent content of covalently bound trehalose (~58%), the

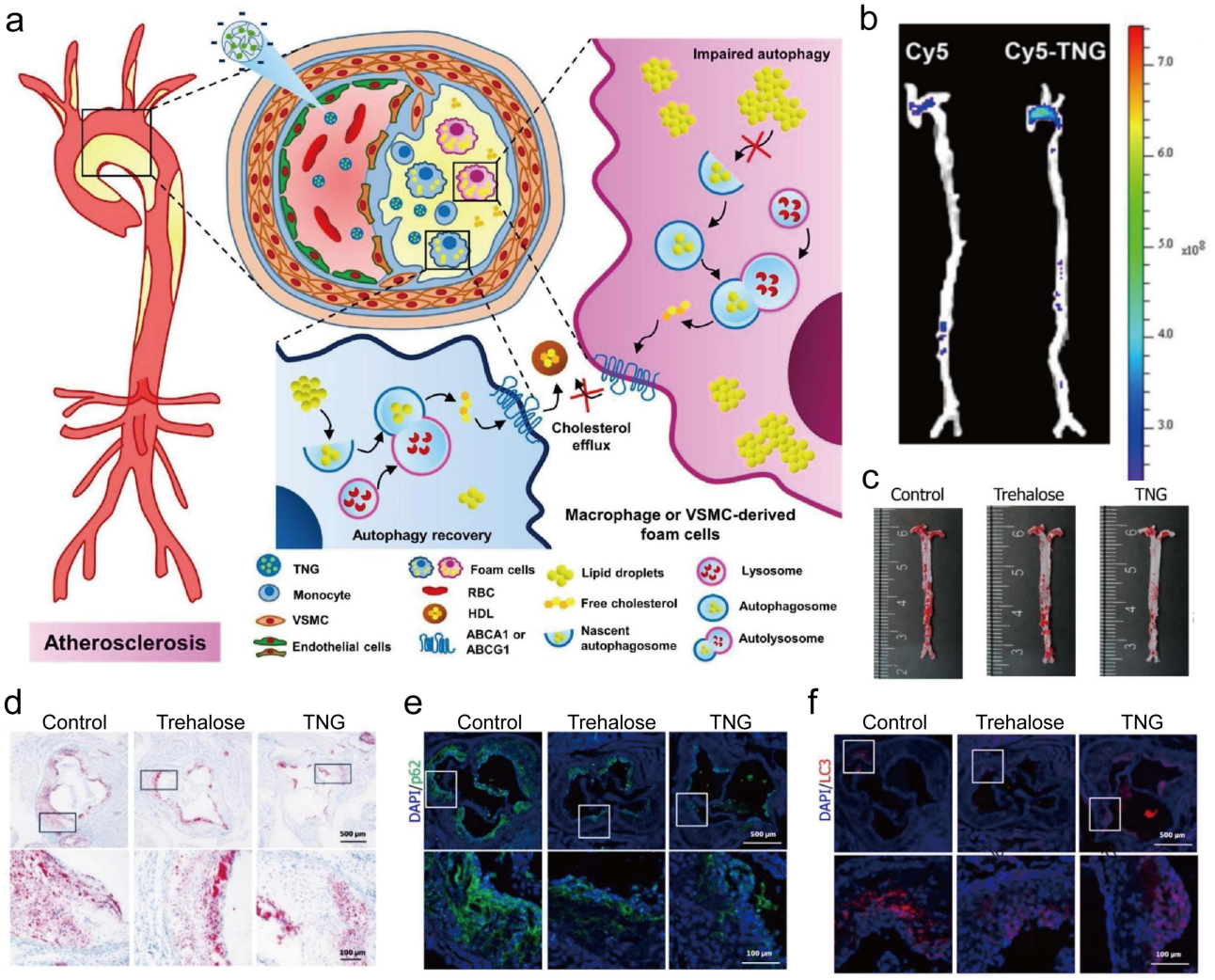

Figure 9 (**a**) Schematic diagram of trehalose-releasing nanogels (TNG) for AS management via autophagic activation. (**b**) The ex vivo fluorescence images of the aorta of ApoE$^{-/-}$ mice under different treatments (intravenous inject free Cy5 and Cy5-TNG). (**c**) Typical ORO-stained images of the isolated aorta of ApoE$^{-/-}$ mice after different treatments. (d) Representative ORO-stained images of aortic root sections ApoE $^{-/-}$ mice after different treatments. (**e** and **f**) Typical immunofluorescence images of p62 and LC3 expressions in atherosclerotic plaques of the aortic root sections in ApoE$^{-/-}$ mice after different treatments. Squares represent locally enlarged areas. Reproduced with permission.[99] Copyright 2023, Springer Nature.

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as-fabricated TNG system possesses satisfactory biostability in serum-enriched medium and has no hemolytic effect on red blood cells. As presented by fluorescent imaging, Cy5-TNG displayed a significant tendency to accumulate within the aortic plaques compared with free Cy5, with an average Region of Interest (ROI) about 1.6 times that of free Cy5 (Figure 9b). In in vivo experiments, TNG group showed a remarkable anti-atherosclerosis effect, and the total plaque area decreased by approximately 60% after one month of treatments (Figure 9c and d). Furthermore, immunofluorescent staining was performed on LC3 and p62expressions in the atherosclerotic plaque area to investigate the enhanced autophagy effect of TNG (Figure 9e and f). ApoE$^{-/-}$ mice treated with TNG showed a pronounced increase in LC3 levels and decrease in p62 levels than that of free trehalose group, which have confirmed that the synergistic effects of nanocarriers and trehalose could efficiently promote trehalose accumulation, stimulate autophagy activation, and decrease plaque areas on constricting AS deterioration.

Moreover, Atorvastatin-loaded graphene oxide quantum dots (GOQDs) encapsulated with hybrid cytomembrane can increase Atorvastatin accumulation in lesions and initiating autophagy stimulation in AS.[100] The multi-loaded self-assembled nanovesicle systems loaded with trehalose and the (HP-β-CD)/oridonin inclusion complex, which were used to synergistically drive the autophagosomes formation, suppress foam cell formation, and decrease inflammatory cytokines release.[101] Furthermore, the self-assembled LOX1-targeted siRNAs nanomicelles with bounding rapamycin/DNA are designed to stimulate macrophage autophagy in atherosclerosis[102](Figure 10). Taken together, targeting nanomaterials can exhibit enormously prospective applications for preserving the concentration of therapeutic elements within atherosclerotic plagues for activating the autophagy and improving therapeutic efficacy, providing a feasible solution to the low AS-accumulation issues.

Autophagy Enabled by Inherent Bioactivity

As we all know, a series of polypyridiniums compounds with inherent autophagy inducing activity was prepared by partial quaternization of poly(4-vinylpyridine) (PVP) using alkyl chains of different lengths, which can effectively

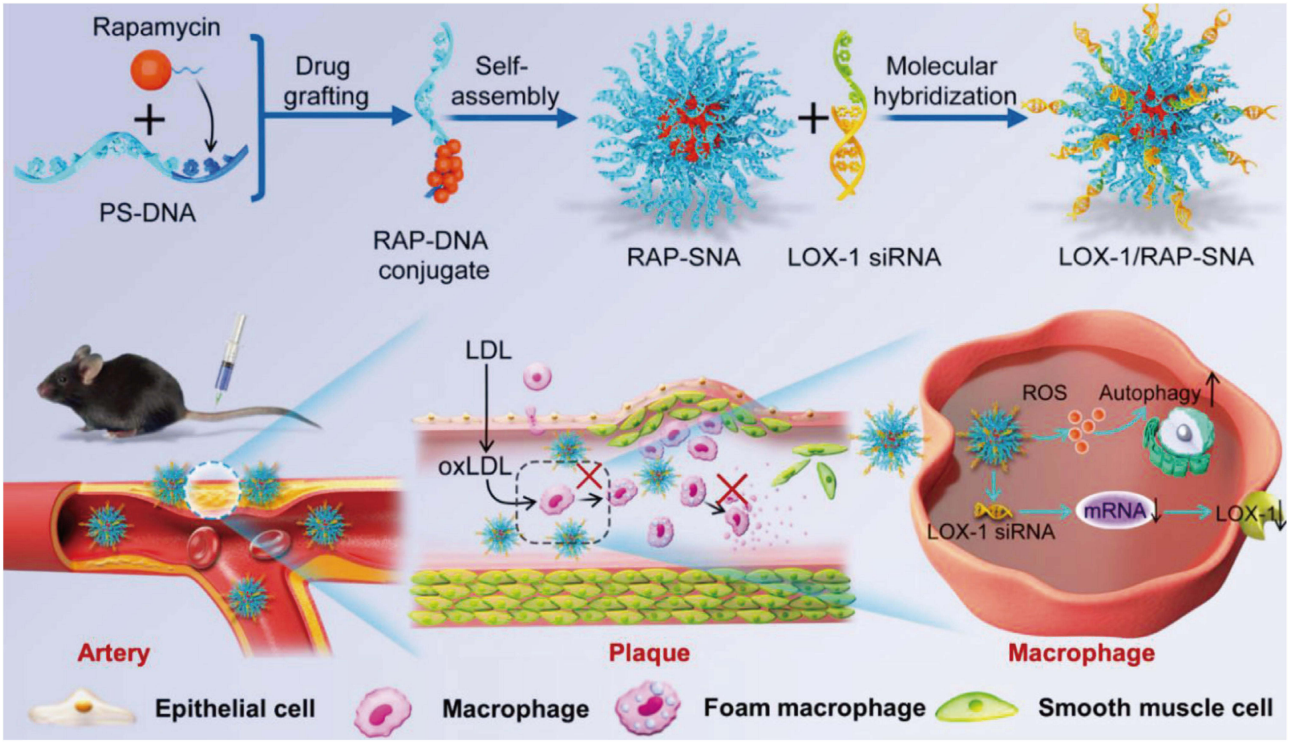

Figure 10 Schematic illustration of fabrication of RAP-grafted DNA conjugate and self-assemblies of RAP-loaded SNA and therapy performance in atherosclerosis via activating autophagy. Upward arrow suggests the induction of autophagy and downward arrows represent the decreased content of mRNA and LOX-1. Reproduced with permission.[102] Copyright 2022, Wiley-VCH.

connect with functional proteins through combined effects of hydrophobic interactions, ionic, cation-π and hydrogen bonding.[103] Thus, the polypyridiniums-based biostable complexes can be used to attenuate the AS progression according to their inherent autophagic activity. The lead polymer P5c was screened from the polypyridiniums library due to the inherent autophagy-inducing activity, considerable serum stability, and effective cargo proteins delivery. P5c can sufficiently activate macrophage autophagy and restrain foam cell formation in AS. Both superoxide dismutase (SOD) and catalase (CAT) encapsulated by P5c nanocomplexes can also down-regulate intracellular ROS, which provided a multifaceted therapeutic modality to combat AS, addressing both autophagy dysfunctions and over-production ROS within affected macrophages[104] (Figure 11a and b). Furthermore, the mCherry-GFP-LC3 assay was implemented to investigate the autophagy-inducing activity of P5c-based nanocomplexes.[105,106] When the autophagosomes are fused with lysosomes to form autolysosomes, the eGFP fluorescence can be partially quenched owing to acidification, while the mCherry fluorescence remains unchanged. Thus, cells treated with P5c are shown with red puncta dots, while yellow puncta dots are displayed in chloroquine (CQ), autophagy inhibitor,[107] treated cells, indicating effective autophagy induction in P5c-stimulated the cells (Figure 11c). In Western blot experiments, the transformation of cytosolic LC3-I to membrane-bound LC3-II and the degradation of p62 were often regarded as evidence of autophagic induction after P5c and P5c/S/C treatments (Figure 11d). This paradigm explores that polymer P5c screened from the polypyridiniums library are effective as autophagic inducers for AS treatment, which provides the distinct inspirations and strategies for inherent bioactivity of nanomedicine-based autophagic induction for AS attenuation.

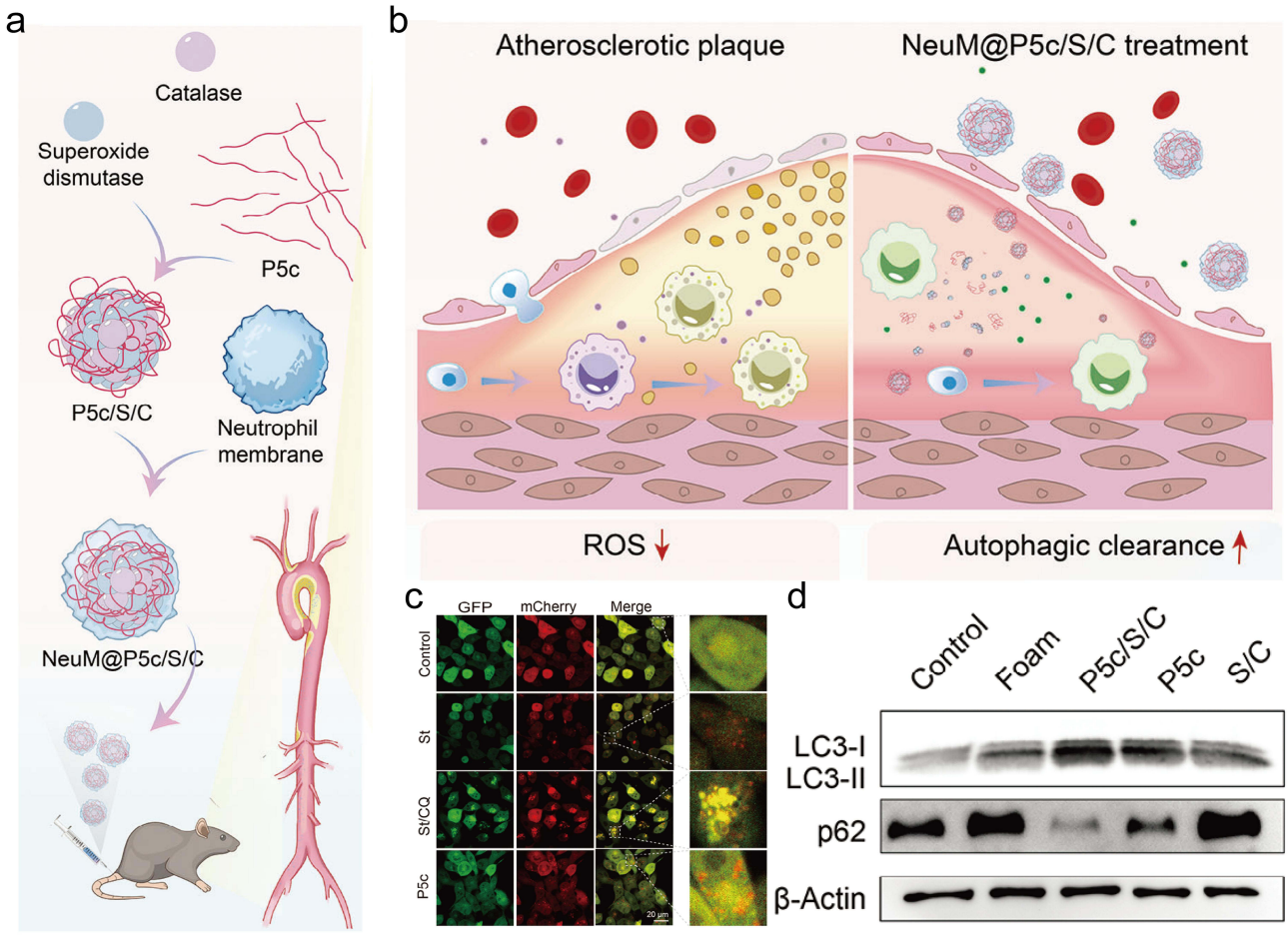

Figure 11 (**a** and **b**) Schematic diagram of neutrophil membrane-coated P5c/SOD/CAT nanoparticles (NeuM@P5c/S/C) synthesis and P5c with autophagy-inducing activity for AS management in ApoE$^{-/-}$ mice. Red upward and downward arrows represent the increased autophagic clearance and the decreased ROS concentration, respectively. (**c**) Typical CLSM images of RAW264.7 cells stained by mCherry-GFP-LC3 after different treatments. (**d**) The expression levels of LC3-I, LC-3II and p62 after different treatments. Reproduced with permission.[104] Copyright 2024, Wiley-VCH.

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Autophagy Promoted by Special Morphology

Up to now, accumulating evidence has reported there is a close mechanism relationship between morphology of nanomaterials and biological effects,[108–110] as well as autophagy activation.[111–113] For instance, specific gold nanoparticles were designed to modulate the autophagy response in a shape-dependent manner, in which nanosphere morphology could activate more autophagosome accumulation as compared with the morphology of nanorod.[112] In addition, spiky morphology can drive satisfactory pro-survival autophagy in a composition- and shape-dependent manner.[113,114] Rational design and tuning morphology of bioactive nanomaterials can perform great potential in modulating autophagy for atherosclerosis management. Inspired by this, a palladium−hydrogen (PdH) with specific morphology nanomedicine was designed to drive a powerful autophagic response within the atherosclerotic plaque (Figure 12a).[115] Bio-TEM images

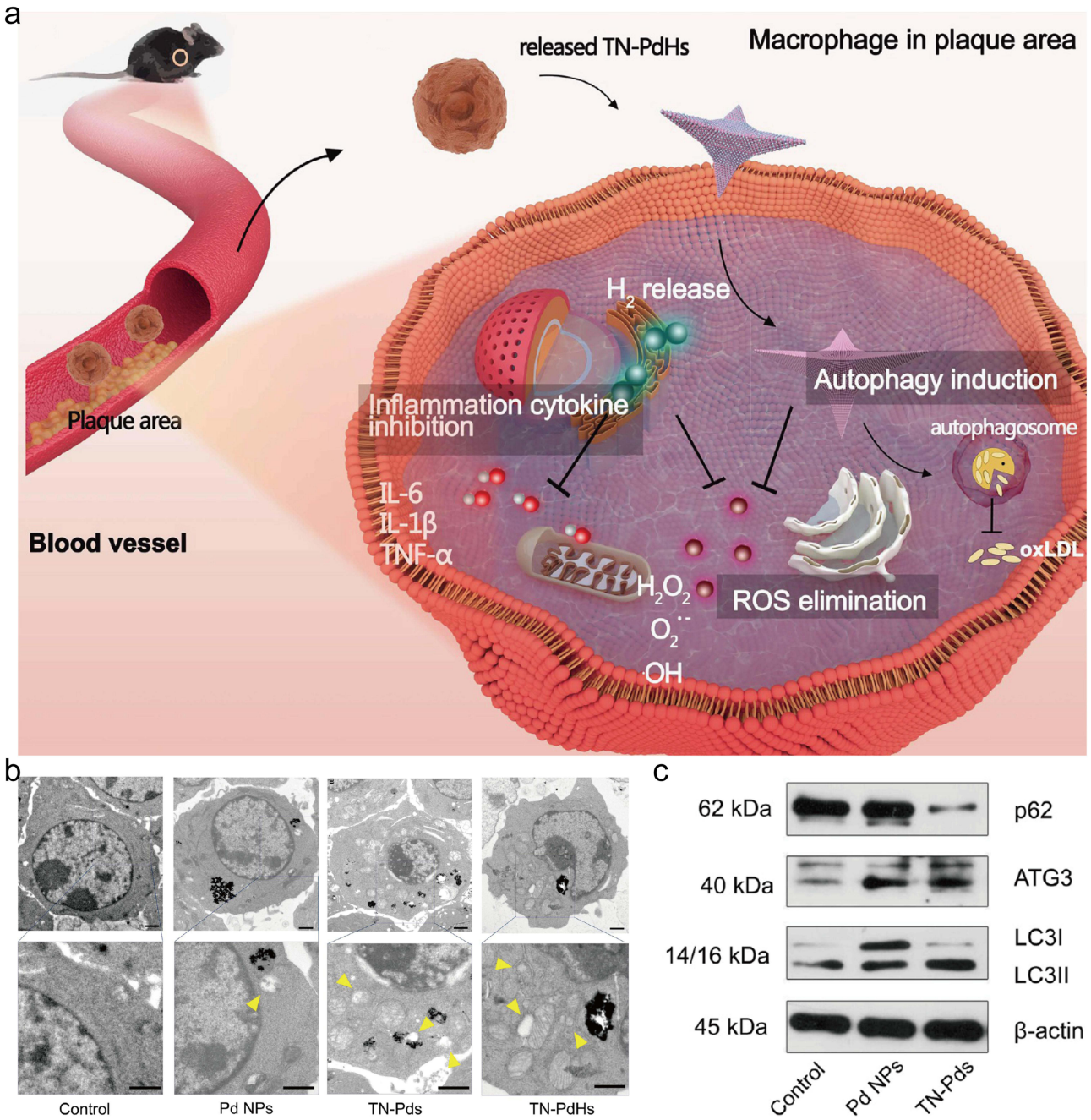

Figure 12 (**a**) Schematic diagram of autophagy activation for treating atherosclerosis as enabled by TN-PdH@Ms. (**b**) Bio-TEM images of macrophage cells after different treatments. Yellow arrows indicate autophagosome and autophagolysosome. Scale bar = 1.0 μm (**c**) The expression levels of LC3-I, LC-3II, ATG3 and p62 after different treatments. Reproduced with permission.[115] Copyright 2022, American Chemical Society.

were used to observe autophagic flux in macrophages after varied treatments. More autophagic vesicles can be found in TN-Pds and TN-PdHs groups, as compared to control group with few autophagic vacuoles, indicating the unique spiky morphology of TN-Pds nanomedicine could significantly facilitate autophagosomes formation to a large extent (Figure 12b). The upregulated LC3II expression and decreased p62 expression were recorded in TN-Pds group, much stronger than those in Pd NPs group and control group, which was similar to the bio-TEM results (Figure 12c). After targeting the plaque based on the chemotaxis towards macrophages, combinatorial engineering of nanomedicines with H_2 release under the NIR irradiation, ROS removed by PdH nanoenzyme activity, and strong autophagy activated by distinct spike-like structure can achieve the desirable therapeutic performance and considerable therapeutic effect on atherosclerosis management. This inspired paradigm provides a special paradigm for topology-related biological effects to perform therapeutic effect in the field of nanomedicine for atherosclerosis therapy.

Discussions

Recent development has uncovered that autophagy induction expands the traditional therapeutic concept and constructs the critical part in anti-atherosclerosis treatment. The rapid advances of nanobiotechnology improve the emergence of versatile effective therapeutic approaches for atherosclerosis management. Owing to the developed nanobiotechnology, the cooperated application with bioactive nanomaterials can effectively improve the therapeutic efficiency and meanwhile make up the recent autophagy-based therapeutic defects and limitations. In addition to the passive accumulation of enhanced permeability and retention (EPR) effect and the active targeting after surface targeted modification, their distinct biological activity and physicochemical nature of designed nanomaterials were able to accelerate AS-autophagic efficiency and specificity, contemporaneously decreasing cytotoxic destroy to normal tissues and organs. Although the fast progress of nanomedicine-enabled/promoted autophagy-based AS nanotherapies, several critical issues should be taken into consideration to strengthen the possible clinical transformation of their therapeutic modalities.

Design and Construction of Biocompatible Autophagic Nanomaterials

The occurrence of autophagy can not only attenuate the AS progress but also drive the autophagy in normal tissues/organs for a long time. Compared with conventional strategies of small molecule-initiating autophagy, advanced nanomedicine can create a reasonable chance to efficiently transport the optimal dose of autophagic inducers into atherosclerotic plaques. Despite several certain inorganic nanomaterials themselves are performed to be local sources for triggering autophagy via external energy fields, cytotoxic metal ions generated by their degradation may inevitably exert virulence on normal tissues/organs. Besides, some specific organic nanomaterials may also contribute to the ungratified enrichment in atherosclerotic plaques, which was resulted from the disadvantages of easy degradation and poor stability in the blood circulation. The following reach target is how to design and construct the bioactive nanomaterials with excellent physicochemical properties, such as size, shape, stiffness, surface charge and chemical composition for further increasing the autophagic efficiency while mitigating and relieving their side effects. The rapid and remarkable development and advancement in the fields of nanomedicine are highly expected to explore and provide more useful solutions for these important issues.

Surface Modification of Autophagic Nanomaterials

To realize the considerable therapeutic potency accompanied by negligible toxic effects, these fabricated autophagic nanomaterials should be surface modification for guaranteeing satisfactory AS enrichment. Usually, suitable surface modification of nanomaterials is of high importance for nanomedicine in the diagnosis and therapy. Appropriate surface engineering can ensure the long-term blood circulation and also escape the phagocytosis of reticuloendothelial system (RES). It is noted that surface-targeting modification can obtain the high-targeting enrichment of autophagic nanomaterials into inflammatory plagues, largely increasing the autophagic-therapeutic efficacy with minimal side effects of autophagy. Recent surface-modification approaches of designed autophagic nanomaterials have been much less investigated, which need to be devoted more attraction to future studies and research.

Biosafety/Biocompatibility of Autophagic Nanomaterials

The biocompatibility and biosafety of autophagic nanomaterials play a fundamental part in facilitating the clinical transformation. Currently, primary explorations have presented the fairly considerable biocompatibility and biosafety in vitro and in vivo experiments, however, the long-term toxicity and side effects of these specific bionanomaterials have not been thoroughly explored and discussed. It is noted that the vast majority of autophagic nanomaterials are constructed based on the inorganic nanoparticles, which has caused there is still a long way to go for their further clinical application. Hence, more detailed biosafety in vitro and in vivo evaluation of these autophagic nanoinducers should be carried out to provide credible evidence-based outcomes regarding the biocompatibility and biosafety issues.

Amplifying Nanomedical Applications of Autophagic Nanomaterials

The research of autophagy driven by specific nanoinducers has been widely investigated in anti-atherosclerosis therapy. It is highly expected that the modality to induce autophagy can be extended to other unexploited therapeutic fields. Apart from the autophagy-based synergistic nanotherapy, bioactive nanomaterials-inducing autophagic managements are anticipated to be completely fused with other therapeutic strategies to accelerate the therapeutic potency of autophagy-based anti-aheroclerosis therapy. It is unfortunate that there still lacks the real-time bioimaging approaches to visibly and feasibly manifest the induction of autophagy. Hence, some specific autophagic nano-inducer can also function as contrast agents observed by contrast-enhanced imaging patterns, which is expected to design and to establish the real-time imaging-guided autophagic anti-atherosclerosis therapy.

Conclusions

As one of the emerging and booming anti-atherosclerosis strategies and interdisciplinary exploration fields, nanomedicine-initiated/promoted autophagy can noticeably enhance anti-atherosclerosis therapeutic efficacy. Meanwhile, the field of bioactive nanomaterial-initiated autophagy in anti-atherosclerosis is still in the primary stage, thus more efforts of the related research should be put on benefiting personalized management in mitigating and boycotting atherosclerotic progress and development. It is firmly believed that anti-atherosclerosis approach based on nanomedicine-inducing autophagy will make great contributions to advancement of bioactive nanomaterials and achieving possible clinical-transformation to benefit more cardiovascular patients, as long as these present facing issues and critical challenges are fully addressed in the future.

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Disclosure

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