Top Five Stories of the Cellular Landscape and Therapies of Atherosclerosis: Current Knowledge and Future Perspectives*

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[Abstract] Atherosclerosis (AS) is characterized by impairment and apoptosis of endothelial cells, continuous systemic and focal inflammation and dysfunction of vascular smooth muscle cells, which is documented as the traditional cellular paradigm. However, the mechanisms appear much more complicated than we thought since a bulk of studies on efferocytosis, transdifferentiation and novel cell death forms such as ferroptosis, pyroptosis, and extracellular trap were reported. Discovery of novel pathological cellular landscapes provides a large number of therapeutic targets. On the other side, the unsatisfactory therapeutic effects of current treatment with lipid-lowering drugs as the cornerstone also restricts the efforts to reduce global AS burden. Stem cell- or nanoparticle-based strategies spurred a lot of attention due to the attractive therapeutic effects and minimized adverse effects. Given the complexity of pathological changes of AS, attempts to develop an almighty medicine based on single mechanisms could be theoretically challenging. In this review, the top stories in the cellular landscapes during the initiation and progression of AS and the therapies were summarized in an integrated perspective to facilitate efforts to develop a multi-targets strategy and fill the gap between mechanism research and clinical translation. The future challenges and improvements were also discussed.
Key words: atherosclerosis; transdifferentiation; extracellular traps; efferocytosis; stem cell; nanoparticles

As a chronic inflammatory disease of the arterial wall, atherosclerosis (AS) is by far the most frequent underlying cause of atherosclerotic cardiovascular disease (ASCVD), carotid artery disease, and peripheral arterial disease. AS alone is rarely fatal; while thrombosis superimposed on a ruptured atherosclerotic plaque precipitates the life-threatening clinical events, accounting for 17.9 million deaths each year[1–3]. AS is characterized by dysfunction of endothelial cells (ECs), activated vascular smooth muscle cells (VSMCs) and a pro-inflammatory and pro-apoptotic niche due to evoked leukocytes[4–6]. Recently, plenty of studies demonstrated that the mechanisms appeared much more complicated than we thought. The recognition of roles of efferocytosis, transdifferentiation and novel cell death forms such as ferroptosis, pyroptosis, and extracellular trap (ET) provides a large number of therapeutic targets[7, 8].

In addition to limited understanding of mechanisms of AS development, the unsatisfactory therapeutic effects of current treatment serve as another factor that restricts the efforts to reduce global AS burden. Lipid-lowering drugs (e.g., statins) remain the cornerstone of the management of atherosclerotic disease[9]. Although stent implantation and bypass grafting are optional at acute or severe stage, both of them are invasive[10]. Therefore, it could be challenging to improve the prognosis in individuals with familial hypercholesteremia, statin intolerance or surgery contraindications[9]. And none of clinical medicine has been able to significantly recede plaques yet. Emerging evidence revealed that stem cells or nanomaterials could be promising strategies[11–13].

In this review, we summarized the advances in understanding of molecular and cellular mechanisms underlying the initiation and progression of AS and current therapeutic strategies of most interest in this field in an integrated way (fig. 1). An electronic search of PubMed, Web of Science, and Google Scholar along with major conference proceedings was conducted using the Medical Subject Heading and the key word search terms “atherosclerosis”,

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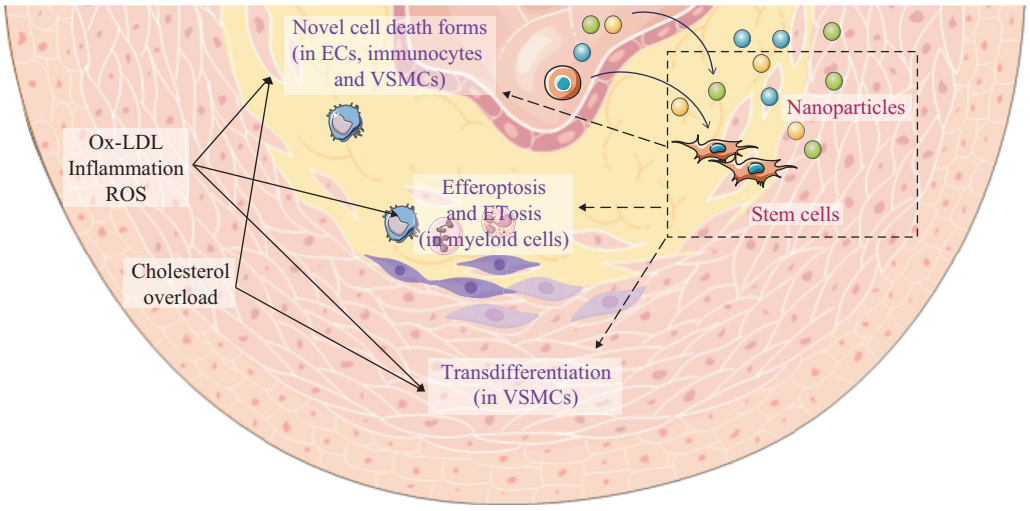

Fig. 1 Advances in the major cellular and biomolecular mechanisms and the key triggers they shared, as well as promising therapies ECs, endothelial cells; Ox-LDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells

"programmed cell death", "ferroptosis", "pyroptosis", "cuproptosis", "transdifferentiation", "extracellular traps", "efferocytosis", "stem cell", "nanoparticles" and combinations of two or more terms from inception through September 2023 with no language restriction. The future challenges and improvements that were required were also discussed. Previous reviews generally focused on a certain cell or molecular biological mechanism, and this fragmented perspective has limited the efforts to develop a multi-targets strategy and fill the gap between mechanism research and clinical translation.

1 TRADITIONAL PARADIGM OF THE MAJOR CELL PLAYERS AND THERAPIES IN AS

Elevated plasma cholesterol levels could be the unique one to be sufficient to drive the development of AS, the first of which is low-density lipoprotein (LDL)-cholesterol (LDL-C)[14]. Other atherogenic stimuli including male gender, hypertension, smoking, inflammatory markers and diabetes mellitus (DM) were considered critical accelerators[4]. ECs, leukocytes and VSMCs are the major players in the development of AS.

Dysfunctional ECs under atherogenic stimuli are the triggers of AS. AS lesions begin to develop under endothelium which is intact but activated and dysfunctional. Plasma molecules including lipoprotein particles extravasate through the leaky barriers into subendothelial space, leading to the modification and accumulation of atherogenic lipoproteins such as oxidated LDL (ox-LDL), which seems to be mediated by myeloperoxidase, arachidonate-15-lipoxygenase (ALOX15), and/or nitric oxide synthase (NOS)[4, 15]. Those activated ECs are also characterized by upregulated levels of adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), E-selection and P-selection, which lead to elevated recruitment of monocytes and T cells[9, 16–18]. In advanced lesions, de-endothelialized areas were observed.

The adhesion to impaired ECs and subsequent response to the chemokines enable transendothelial migration of the circulating leukocytes. Ox-LDL and CC-motif chemokine ligand 2/monocyte-chemoattractant protein-1 (CCL2/MCP-1) are recognized as the most important atherogenic chemoattractants[19]. Both ECs and VMSCs contributed to the elevation of MCP-1, which attracts monocytes and T lymphocytes potently[20]. The monocytes differentiate into macrophages within intima, internalize the atherogenic lipoproteins *via* scavenger receptors such as CD36 and SR-A until death[21]. Those cells that were initially recruited to clear cytotoxic components transform into foam cells and contribute to the formation of destabilizing lipid-rich core in the plaques. The focal leukocytes are also activated, generating proinflammatory factors [e.g., interleukin (IL)-1β, IL-6 and tumor necrosis factor α (TNF-α)], matrix-degrading proteolytic enzymes and more chemokines including MCP-1, leading to positive feedback of cell dysfunction and apoptosis, and continuous activation of local inflammation[6, 19]. Inadequate resolution of focal inflammation results in accumulation of necrotic lipid core mainly composed of necrotic macrophages and foam cells[22]. The matrix proteolytic enzymes [e.g., matrix metalloproteinases (MMP)] and tissue factors also possess destabilization, rupture and thrombogenic properties[23]. Additionally, although granulocytes and T lymphocytes are not necessary, several subsets of these cells such as neutrophils, T helper 1 (Th1) and regulatory T (Treg) cells could modulate the progression of AS; while some

subgroups (e.g., eosinophils) seem to be independent from the processes[24–26]. The persistence of the cellular response of ECs and immune cells underlies the occurrence and progression of AS.

In healthy vasculature, VSMCs are contractile and quiescent. VSMCs mediate an excessive and dominating fibroproliferative response under chronic atherogenic stimuli in the advanced stages of plaques[27]. Consequently, the lumen becomes narrow and the reduction of blood flow sets in. On the other hand, VSMCs and VSMC-derived collagen-rich extracellular matrix could be essential to stability of plaques and thus, protecting against rupture and thrombosis[28]. Plaque rupture generally occurs in the areas with the thinnest fibrotic cap and the most infiltrated by foam cells, which could be attributed to two concurrent mechanisms: gradual loss of VSMCs *via* apoptosis or senescence, and overactivated, infiltrating leukocytes[29].

The well-established, classic cellular pattern has provided insights to the occurrence and progression, and management approaches of AS. Achieving and maintaining a low cholesterol level is recognized as the cornerstone of AS management and thus has received the lion's share of current available treatment[30]. Those medicines include statin, fibric acid derivatives (fibrates), nicotinic acid (Niacin) and ezetimibe[31]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition using monoclonal antibodies or genetical methods is an emerging therapy for hypercholesterolemia[32]. Additionally, agents targeting glucose metabolism have been of great interest since insulin resistance, hyperglycemia and DM participate in almost every step of the AS development, including secondary lipidemia[33], subendothelial retention of atherogenic LPL[34], and evoked pro-inflammatory responses through activation of protein kinase C-beta and aldose reductase[35]. A bulk of anti-inflammation noncoding RNAs or drugs such as Canakinumab (IL-1β antibody) were also investigated[36, 37].

2 STORY ONE: REASSESSMENT OF NOVEL REGULATED CELL DEATH FORMS IN PLAQUES

The regulated cell death (RCD), which involves tightly structured signal cascades and molecular mechanisms, leads to ECs dysfunction, localized denudation, and subsequently, thrombus formation and the deposition of fibrous elements and lipids[38, 39]. Apoptosis was the first discovered and the most deeply described type of RCD[40]. However, novel RCD forms such as ferroptosis, pyroptosis and cuproptosis, and their effects on AS were recognized recently (fig, 2)[41–43], and the attention has also expanded from ECs to other cell types.

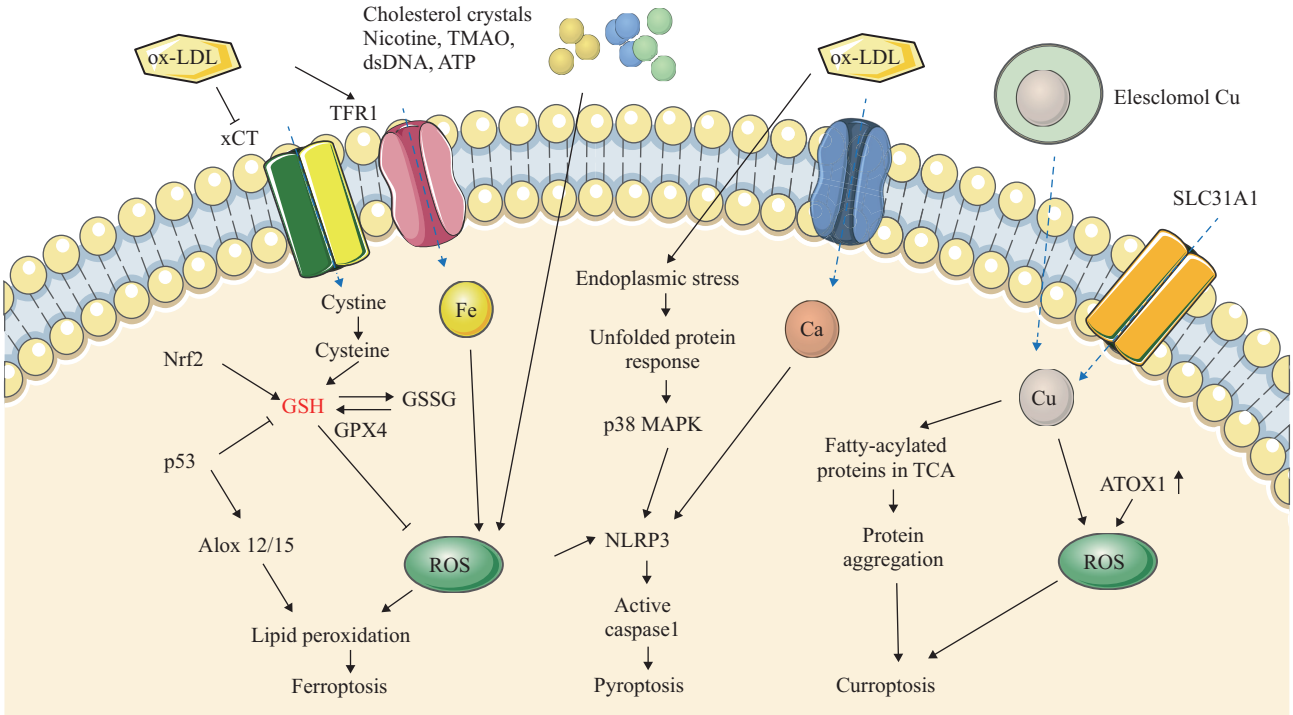

Fig. 2 Novel regulated cell death forms at a glance in AS

ATOX1, antioxidant 1; ATP, adenosine triphosphate; dsDNA, double-stranded DNA; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; MAPK, mitogen-activated protein kinases; NLRP3, NOD-, LRR- and pyrin domain-containing 3; Ox-LDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; SCL31A1, solute carrier family 31 member 1; SCL3A2, solute carrier family 3 member 2; SCL7A11, solute carrier family 7 member 11; TFR1, transferrin receptor 1; TMAO, trimethylamine N-oxide; xCT, X(c-) system

2.1 Ferroptosis

Ferroptosis is an RCS induced by the interaction of intracellular free iron with reactive oxygen species (ROS) *via* Fenton reaction, which leads to the depletion of plasma membrane polyunsaturated fatty acids (PUFAs) and impaired membrane integrity[44–46]. Ferroptosis is characterized by lipid peroxidation and iron retention, and regulated by complicated biological processes and molecular mechanisms such as glucolipid metabolism, redox homeostasis, iron handling and mitochondrial function[47–49]. Those are also main features of AS, making it not surprising that ferroptosis plays an essential, detrimental role in the development of AS.

The Cysteine/glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis, the GTP cyclohydrolase-1 (GCH1)/tetrahydrobiopterin (BH4)/dihydrofolate reductase (DHFR) system, and the NAD(P)H/ferroptosis suppressor protein 1 (FSP1)/CoQ10 system inhibit ferroptosis, while P53/glutaminase2 (GLS2) promotes ferroptosis[50–52]. GSH (the product of GPX4) and CoQ10 are critical anti-oxidative factors that prevent lipid peroxidation[53]. Guo *et al* indicated that overexpression of GPX4 in ApoE–/– mice also attenuated the upregulation of adhesion molecules and inhibited the development of AS[54]. GPX4 also suppressed lipoxygenase (LOX) and cyclooxygenase (COX), as well as AS-associated pro-inflammatory factors[55]. p53 inhibits synthesis of GSH and increases the hydrolysis of GSH by regulating the target genes such as glutaminase 2 (GLS2)[56]. Another target gene, spermidine/spermine N1-acetyltransferase 1 (SAT1), is an important global rate-limiting polyamine catabolic enzyme that increases the expression of ALOX15[57]. p53 could also activate arachidonate-12-lipoxygenase (ALOX12)[58]. ALOX12/15 promote trans-endothelial transport of ox-LDL and deposition of ox-LDL in the sub-endothelial space[59]. However, p53 seems to activate p21, which increases GSH and GPX4[60]; p53 also inhibits ferroptosis by blocking dipeptidyl-peptidase-4 (DPP4) activity in a transcription-independent manner[61]. Those recent observations have given rise to argument on the role of p53 in ferroptosis and AS. Nuclear factor erythroid 2-related factor 2 (NRF2), an important antioxidant and anti-inflammatory factor, is also one of the major pathways that regulate intracellular defense against ferroptosis, partly mediated by regulating iron handling and intermediate metabolism[62, 63]. In addition, NRF2 serves as an agonist of GPX4 and GSH synthesis proteins [to name a few, glutamate cysteine ligase, catalytic subunit (GCLC) and modifier subunit (GCLM) expression][64]. However, Ruotsalainen *et al* found that global NRF2 deficiency also reduced AS lesion size, which may be attributed to systemic effects on lipid metabolism[65]. NRF2 binds to the promoter of ATP-binding cassette B, member 6 (ABCB6) and regulates its expression level[66]. Murphy *et al* indicated that depletion of ABCB6 in bone marrow cells resulted in a significant increase in oxidative stress and platelet release, which promoted arterial deposition of chemokine ligand 5 (CCL5) and subsequently, AS development[67, 68]. Iron overload also promotes pro-inflammatory phenotype switch of macrophages, leading to instability of plaques *via* ROS/acetyl-p53 pathway[53, 69, 70]. It's interesting to note that ferroptosis could also occur in other cell types such as macrophages and VSMCs[71, 72]. Ferroptosis is considered another key mechanism linking DM to AS progression since long-term hyperglycemia could lead to increased intestine iron absorption and circulating iron levels, and impaired iron homeostasis[73, 74]. Elevated levels of glucose also increase mitochondrial ROS production and subsequently activate lipid peroxidation[75, 76].

Several drugs were applied in AS preclinical models based on the understanding of mechanisms of ferroptosis. For instance, ferrostatin 1 (Fer-1), an inhibitor of the iron accumulation and lipid peroxidation, reverses the expression of SLC7A11 and GPX4 in ECs in ApoE–/– mice, and attenuates the development of AS[77]. ROS is alleviated and cell viability is maintained in human umbilical vein endothelial cells (HUVECs) treated with ferroptosis inducer erastin[78]. Strikingly, Fer-1 alleviates iron overload, improves endogenous resistance to lipid peroxidation and prevents ferroptosis *via* E2-related factor 2/FSP1 axis rather than classic p53/SLC7A11/GPX4 pathway[79]. Similarly, another small molecular inhibitor, liproxstatin-1, can reverse lipid peroxidation and ferroptosis in macrophages, endothelial injury and progression of AS in a hyperlipidemic and hypererythroemic mice model[80]. Wang *et al* indicated that ferroptotic damage in ECS induced by exposure to PM2.5 could be partially rescued by Fer-1 and iron chelator deferoxamine mesylate[81]. There is accumulating evidence suggesting that ferroptosis is regulated by statins, thereby justifying an important lipid-independent pleiotropic action of statins including atorvastatin and simvastatin in atheroprotection[82, 83].

2.2 Pyroptosis

Pyroptosis is a novel cell death form that mainly occurs in macrophages[84]. Ox-LDL, cholesterol crystals and other risks [e.g., double-stranded DNA, lipopolysaccharide (LPS), extracellular ATP] evoke the assembly of inflammasome, a supramolecular complex including several types of NOD-like receptor protein 3 (NLRP3)[85]. NLRP3 recruits apoptosis-associated speck-like protein (ASC), which further converts pro-caspase-1 into caspase-1, followed by the cleavage of gasdermin D. One of the products, N-terminal gasdermin D, binds to cell membrane and boosts pore formation, leading to a release of bioactive IL-1β and

IL-18, and subsequent cell swelling and lytic death, which is known as pyroptosis[86]. Although pyroptosis contributes to prevention of microbial infections, excessive activation of pyroptosis contributes to AS development[87].

A bulk of investigations have discussed the mechanisms underlying the occurrence of pyroptosis and how pyroptosis contributes to AS. To name a few, ox-LDL-treated macrophages exhibit elevated endoplasmic reticulum (ER) stress [activating transcription factor (ATF) 4 and 6][88]. Unfolded protein response (UPR) induced by ER stress activates pro-IL-18 and pro-IL-1 by p38 mitogen-activated protein kinase (MAPK), which is an activator of pyroptosis[89, 90]. As mentioned above, ox-LDL is able to activate the Toll-like receptor 4 (TLR4) directly, increase nuclear factor κB (NF-κB) p65 phosphorylation and promote the transcription of pro-IL-1β and pro-caspase-1 in HUVECs[91, 92]. Ca^{2+} signal is required for NLRP3 inflammasome activation[93]. Ox-LDL also promotes Ca^{2+} influx by inducing the closure of inwardly rectifying K^+ channels and upregulating calcium-sensing receptor in monocyte/macrophages and VSMCs[94, 95]. Subsequent intracellular Ca^{2+} overloading results in mitochondrial disorders, ROS production and release and NLRP3 inflammasome assembly in ECs[96, 97]. NLRP3 inflammasome induces disrupted mitochondrial membrane potential (MMP) and ROS generation[98]. Afterwards, ROS could promote the cleavage of gasdermin D by stimulating cysteine oxidative modification, and induce the separation of thioredoxin-interacting protein (TXNIP) from thioredoxin (TRX) and combination with and further activation of NLRP3 according to a hepatologic study[98, 99]. Pyroptosis could be significantly evoked by hyperglycemia due to production of ROS and NLRP3 inflammasome assembly at least partly mediated by a series of non-coding RNA including miR-30d, miR-21-3p, miR-9 and lncRNA MDRL[100–102].

The massive release of pro-inflammatory cytokines (IL-1β and IL-18) leads to inflammation, plaque rupture and thrombosis[103]. An increased IL-1β level was observed among individuals with AS[104]. Those pro-inflammatory cytokines were reported to contribute to AS plaque progression *via* the upregulation of adhesion molecules on ECs and stimulation of VSMCs[104]. Inhibition of NLRP3 inflammasome with specific inhibitor MCC950 or INF39 abolishes ox-LDL-induced IL-1β maturation, LDH release and the development of AS[105, 106]. Anti-inflammatory therapy targeting IL-1β with canakinumab (150 mg every 3 months) significantly reduced ischemic events in patients being treated for secondary prevention, according to the CANTOS trial[36]. Pyroptosis was also identified as a target of traditional drugs and natural medicines such as statins[107, 108], melatonin[109], salidroside[110], resveratrol[92], sinapic acid[111] and dihydromyricetin[112]. However, it's noted that Z-VAD-fmk, an inhibitor of caspase-1, reduces AS plaque stability[113].

2.3 Cuproptosis

As another essential catalytic cofactor, copper (Cu) regulates a wide range of biologic processes such as mitochondrial respiration and energy metabolism[114]. In a recent report, excessive cellular copper ions could bind to fatty-acylated proteins in the tricarboxylic acid (TCA) cycle, leading to proteotoxic stress and subsequently, disturbed lipid metabolic homeostasis, oxidative stress, mitochondrial damage, and EC dysfunction, which is similar to ferroptosis[115–117]. Cellular levels of copper and antioxidant-1 (ATOX1), one of the major copper chaperone proteins increase in inflammatory lesions, including AS plaque[118, 119]. ATOX1 binds to tumor necrotic factor α (TNFα) receptor-associated factor 4 (TRAF4) and promotes ROS generation in a Cu-dependent way[120]. Tetrathiomolybdate (TTM), a compound that chelates copper with high specificity, could inhibit vascular inflammation and attenuate the development of AS, which is independent of oxidative stress and iron metabolism[121, 122].

However, research on the phenotype of cuproptosis, the effects of Cu homeostasis in AS and the regulatory mechanisms of the signaling cascade is still in its infancy; and several contrary observations have raised doubts about the role of cuproptosis in AS. For instance, Cu reduces the occurrence and alleviates the development of AS, which could be at least partly attributed to inhibited pro-inflammatory signals. Cu^{2+} coordination polymer inhibits the Notch pathway, an evolutionarily conserved cellular signaling pathway that mediates pro-inflammatory polarization of macrophages, and reduces inflammatory events in plaques[123, 124]. Li *et al* found that Cu^{2+} supplement enabled lower cholesterol and phospholipid levels, EC mortality in AS lesions and a minimized lesion size[125]. Increased copper intake reduced the risk of AS in young healthy women, indicating the effect of copper might be different in the early and advanced stages of AS[126]. However, Notch pathway was also shown to play a role in the establishment of anti-atherogenic and pro-survival niche, maintenance of EC integrity and prevention of activation and harmful transdifferention of medial VSMCs[127–129]. Given the aforementioned, more studies on the potential effects of cuproptosis and Cu supplement are required.

Conclusively, novel cell death forms have received extensive attention in the exploration of pathophysiologic mechanisms and potential therapeutic targets of AS. Many studies have asserted that cell death is crucial for AS development and a bulk of relevant small molecular inhibitors seemed to be beneficial. However, it remains inconclusive how much effects those death forms have since apoptosis is considered

the major form of programmed cell death[39]. And as asked by Dr. Green, how dispensable is something that is essential[130]? Additionally, the crosstalk of the death forms is also of great interest due to closely related pathways involved. Different programmed cell deaths share several same pathological processes, for instance, ROS production, mitochondrial dysfunction and inflammation[42]; and it's generally found that different forms of cell death occur simultaneously. For instance, the toxicity of copper oxide nanoparticles also activates the NLRP3 inflammasome and promotes levels of caspase-1 and IL-1β in macrophages in addition to cuproptosis[131].

3 STORY TWO: NOVEL FUNCTIONS OF FOCAL MYELOID CELLS

Myeloid cells, including granulocytes, monocytes and dendritic cells, are initially recognized as inflammatory cells. However, novel functions of those cell types have been reported, among which efferocytosis and extracellular traps are of the most interest[132, 133].

3.1 Efferocytosis

Roughly 200 billion cells die in the human body daily, and they are eliminated by phagocytes, including those with high phagocytic capacity (macrophages and dendritic cells) and those non-professional cells with lower phagocytic capacity (for instance, ECs and fibroblasts)[132]. Aside from the cell death forms mentioned above, AS lesions are characterized by a pro-apoptotic niche due to accumulation of intracellular lipid and cholesterol, high levels of inflammatory factors, angiotensin Ⅱ, ROS production and hypoxia[40, 134–136]. A quick phagocytic clearance and highly effective turnover of apoptotic cells, which is termed "efferocytosis", is essential for tissue homeostasis and restructuring, embryonic development and inflammation resolution[132, 137, 138]. Efferocytosis is considered a multistep process-the recognition and location phase, the eating phase and the digestion phase[132]. Phagocytes migrate towards the dying cells where the concentration of chemokines and other soluble signals (e.g., ATP and lysophosphatidylcholine) is higher[139, 140], and recognize the pro-phagocytic signals ("eat-me") exposed on the outer plasma membrane of dying or dead cells[141]. Well-established "eat-me" factors include externalized phosphatidylserine, annexin 1, ox-LDL, and modified ICAM-3[142–144]; conversely, CD47 and CD31 act as "don't-eat-me" signal by binding to signal regulatory protein α (Sirpα, CD172a) and CD300a and suppress the phagocytic function[145, 146]. The components of dead cells were mainly processed in a phagosome-dependent manner (canonical phagocytosis); additional pathway entails microtubule-associated protein 1A/1B light chain 3 (LC3)-related phagocytosis[147, 148].

Accumulating evidence indicated that defective removal of dead cells participated in the development of AS, mainly mediated by upregulation of "don't-eat-me" signals, downregulation and modification of "eat-me" signals. As described previously, pro-inflammatory niche in plaques suppressed the levels of active efferocytic molecules such as milk fat globule epidermal growth factor (EGF)-factor Ⅷ (MFG-E8) and MerTK[149, 150]. To be specific, TLRs stimulated by the inflammatory microenvironment suppress the MFG-E8-mediated clearance of apoptotic cells[150]. The expression of ADAM17 increases in AS lesions, which leads to an increased degradation of MerTK[151, 152]. Carriers of the risk allele at the chromosome 9p21 genome-wide association study (GWAS) locus have a significant decreased intraplaque expression of Calreticulin, another key "eat-me" ligand, according to studies investigating the heritable component of ASCVD[153, 154]. Besides, "don't-eat-me" signals CD47 and its receptor Sirpα are also upregulated in human AS arteries, resulting in secondary necrosis and further exacerbating lesion inflammation[155]. Ox-LDL also inhibits efferocytosis by competing with apoptotic bodies for scavenger receptors and masking oxidized "eat-me" ligands with ox-LDL-induced autoantibodies[156, 157]. Impaired removal of dying cells contributes to the size of necrotic core, reduction of luminal flow, and continuous stimulation of inflammation secondary to the release of previously-sequestered intracellular contents[158, 159]. Besides, efferocytosis was reported to prevent from the formation of foam cells, and promote reverse cholesterol transport pathways and the secretion of beneficial factors such as IL-10 and TGF-β, which could also explain the detrimental role of defective efferocytosis in the progression of AS[160–163].

It's interesting to note that impaired efferocytosis unequivocally contributes to the destabilization and rupture of plaques due to uncontrolled necrosis and subsequent necrotic core expansion, as demonstrated in several studies[164]. Plaques in mice expressing a cleavage-resistant form of MerTK had elevated efferocytosis and smaller necrotic cores[165]; while deficiency of MFG-E8 in hematopoietic cells increased necrotic core areas[166]. The role of miRNAs in impairment of efferocytosis has also been reported, for instance, miR-155 which downregulates B-cell leukemia/lymphoma 6 in advanced AS lesions[167]. DM leads to impairment of efferocytosis due to reduction of peroxisome proliferator-activated receptor γ (PPAR-γ) and activated receptor of advanced glycation endproducts (RAGE) pathways, which partly explains why hyperglycemia contributes to AS development[168, 169]. The roles that non-coding RNAs play in efferocytosis were preliminarily

demonstrated[170]. LncRNA MIAT, which positively modulates the expression of CD47 through sponging miR-149-5p, is markedly increased in serum of patients with vulnerable plaques and macrophages in advanced lesions[171].

Efferocytosis has been recognized as a promising diagnostic and therapeutic target. Antibody against CD47 and inhibitor of Sirpα such as Resolvin D1 reverses this defect in efferocytosis and the clearance of dead cells, and ameliorates the development of AS[172, 173]. Additionally, CD47 is considered directly downstream of TNF-α[174]. The expression of CD47 significantly decreased after treatment with antibodies against TNF-α (Infliximab or Etanercept)[172]. Despite comparable plaque burden between the IgG group (control) and the Etanercept group, the combination of anti-CD47 and anti-TNF-α antibodies displayed a mildly increased phagocytic index and alleviation of AS over the anti-CD47 treatment alone[172]. Activity of RhoA (a member of Rho GTPases family) seems to negatively affect basal engulfment in phagocytes[175]. Statins, the cornerstone of ASCVD, could enhance efferocytosis by inhibiting RhoA isoprenylation[175]; fasudil, another inhibitor of Rho-associated coiled-coil kinase (ROCK), the downstream of RhoA, also reduces plaque area, arterial intima-medial thickness (IMT) and maximal flow velocity[176]. In addition, single-walled carbon nanotubes (SWNTs) modified with an inhibitor of SH2 domain-containing phosphatase-1 (SHP-1), the downstream of Sirpα, allows increased phagocytosis and plaque regression as well as reduced expression of the inflammatory genes[177].

3.2 Extracellular Traps

Extracellular traps (ETs) are large web-like structures composed of decondensed DNA and neutrophil-derived nuclear, cytoplasmatic, and granular proteins[178]. The process of ET formation is also known as ETosis, which is initially used to describe a new form of neutrophil death, but ETs derived from macrophages, eosinophils, basophils, mast cells and dendritic cells have also been reported (table 1). There are 3 major pathways of ETosis: (1) "vital ETosis", which refers to a TLR2-dependent process that is stimulated by bacterium[179, 180]; (2) "suicidal ETosis", which refers to a TLR7-dependent process that is stimulated by activated platelets, antineutrophil cytoplasmic antibodies (ANCA) and cytokines such as TNF-α and IL-8 and characterized by activation of protein kinase C (PKC) and Raf-MEK-ERK pathway[181–183]; (3) caspase-dependent ETosis, which is induced by cytosolic LPS and characterized by caspase-11 activation and GSDMD cleavage[184].

In general, ETs are capable of ensnaring and killing pathogens; however, there is increasing interest in the role of ETs in AS nowadays[185, 186]. MMP9 and MMP2 in ETs directly induce ECs dysfunction[187]. Döring *et al* demonstrated that the released DNA and neutrophil-derived granule proteins (e.g., cathelicidin) stimulate a strong type I interferon (IFN-I) response by vascular plasmacytoid dendritic cells[188]. IFN-I affects plaque-residing macrophages, potentiates foam cells and further promotes extracellular trap formation[189]. Besides, experimental data also have attested that IFN-I induced production of CXC chemokines (CXCL) 9, CXCL10 and CXCL11, which mediate recruitment of leukocytes, activity of pro-apoptotic pathways and enhancement of the toxicity of ILs and B cell activating factor (BAFF), leading to impairment of ECs and endothelial progenitor cells (EPCs)[190]. Consistently, positive associations of NETs and their components with risks of AS severity and ASCVD indicate a detrimental role of NETs in AS. Findings by Borissoff *et al* revealed that double-stranded DNA, nucleosomes, and myeloperoxidase-DNA complexes serve as biomarkers predicting ASCVD, prothrombotic state, and adverse cardiac events[191]. Very few data are available on the effects of ETosis derived from other cell types, however, macrophage traps seem to dominate numerically in late (organizing) thrombosis[133]. According to a recent report, $CD68^+$ macrophage-like cells transdifferentiated from VSMCs in plaque also generate ETs as indicated by VSMCs-lineage tracing

Table 1 Innate extracellular traps

ET type	Stimuli	ET constituents
Neutrophil ETs (NETs)	Bacterium (LPS)[179, 180], GM-CSF, C5a[204], PMA, IL-8, activated platelets[182], ANCA[183], TNF-α[205], cytosolic LPS[184]	Nuclear DNA, mtDNA, histones, MPO, proteinase 3, Cathelicidin, Cathepsin G, α-defensins[206, 207]
Macrophage ETs (METs)	*H. influenzae*, *E. coli*, *C. albicans*[208, 209], PMA, LPS, hydrogen peroxide, cigarette[210]	Nuclear DNA, mtDNA, histones, MPO[211], MMP9/12[208], Citrullinate[210]
Mast cell ETs (MCETs)	*S. pyogenes*, *S. aureus*, *Streptococcus*, protozoa, fungi[212, 213], PMA, hydrogen peroxide[214, 215]	Nuclear DNA, mtDNA, histones, Cathelicidins, tryptase, β defensins, Piscidins, IL-17[133, 214–216]
Eosinophil ETs (EETs)	*E. coli*, IL-5, IFN-γ, LPS and C5a[217], IgG, IgA, PMA, GM-CSF(+PAF)[218]	mtDNA, MBP, ECP[217, 218]
Basophil ETs (BETs)	*E. coli*, *S. aureus*, IL-3[219]	Nuclear DNA, mtDNA, histones, ROS[219]
Dendritic cell ETs (DCETs)	*A. fumigatus*[220]	DNA, histones[220]

ECP: eosinophil cationic protein; GM-CSF: granulocyte-macrophage colony stimulating factor; IFN: interferon; IL: interleukin; LPS: lipopolysaccharide; MBP: myelin basic protein; MPO: myeloperoxidase; mtDNA: mitochondrial DNA; PAF: platelet activating factor; PMA: phorbol 12-myristate 13-acetate; ROS: reactive oxygen species

technology and single-cell RNA sequencing (scRNA-seq), which further regulates the direction of VSMC transdifferentiation *via* stimulator of interferon genes (STING)/suppressors of cytokine signaling molecules 1 (SOCS1) or TLR4 signaling pathways[192]. It's revealed that miR-146a is upregulated in serum of AS patients and macrophages-derived exosomes under exposure to ox-LDL; miR-146a promotes the generation of ROS and release of NETs by targeting superoxide dismutase 2 (SOD2), a radical scavenger and pivotal component of endogenous antioxidant defense barrier[193, 194]. Similarly, miR-505/Sirtuin 3 axis also induces NET formation in a ROS-dependent manner[195]. Therapeutic targeting of ETosis has been well explored in multiple diseases. In another elegant study, Apoe–/– mice lacking neutrophil-specific proteases neutrophil elastase (NE) and proteinase 3 (PR3; Apoe–/–Elane–/–Prtn3–/– mice) were utilized to assess the effects of NETosis in AS[196]. Genetic abrogation of NET formation diminishes plaque growth, at least partly mediated by suppressed IL-1β/Th17 response[196]. DNase I is the most commonly used enzyme to disrupt NETs after formation, which is well tolerated and readily poised for clinical translation[197, 198]. However, the benefit of DNase Ⅰ in the progression of AS remains unclear. Peptidyl arginase deiminases (PADs) are an essential series of enzyme to citrullinate histones and subsequently, induce chromatin decondensation and facilitate the expulsion of nuclear DNA[199]. PAD4 and PAD2 are largely associated with NETosis and macrophage ETosis (METosis), respectively. Knight *et al* reported that NETosis was significantly inhibited by cholarmidine, an irreversible inhibitor of PAD, in Apoe–/– mice, where the plaque size was reduced, and the carotid artery thrombosis was prevented[200]. Simvastatin was reported to reduce neutrophilic inflammation and NETosis by reducing PAD4 expression in mice with asthma or untreated thermal injury; however, the effects remain unclear in AS preclinical models and patients[201, 202]. Future studies should pay more attention to the differences among ETosis derived from different cell types. Besides, more efforts are required to develop a specific approach to target ETosis in lesions since ET is also required to reduce potential infection[203].

4 STORY THREE: THE UNDERESTIMATED CONTRIBUTION OF VSMCS TRANSFORMATION

Initially, the dysfunctional ECs and infiltrated immune cells are considered the primary features of AS plaques[5, 6, 221]. Despite VSMCs are a major cell type in plaques, the main effect of VSMCs is thought to be phenotypic conversion to proliferative synthetic cells and produce extracellular matrix (ECM)[221]. The ECM forms the fibrous cap and stabilize plaques, and as a result, VSMCs play a positive role during the development of AS[1]. As an initial step, dedifferentiation of VSMCs occurs under exposure to atherogenic factors. Those synthetic dedifferentiated VSMCs are characterized by calcification genes (e.g., osteopontin and osteocalcin), gap junction proteins (e.g., connexin 43), transcription factors (e.g., KLF4), and collagenase enzymes (e.g., collagenase Ⅳ)[222]. Although the precise molecular mechanisms underlying this event are still not well understood, Rho/Rho-associated coiled coil containing protein kinase (ROCK), a prominent regulator of cytoskeletal dynamics in VSMCs, is positioned to play a key role during VSMC dedifferentiation[222]. Rho/ROCK signaling can modulate the expression of a set of genes that maintain VSMC contractile status by promoting actin cytoskeleton polymerization and stimulating myocardin/serum response factor (SRF)-mediated gene transcription[223, 224]. However, accumulating evidence revealed that the role of VSMCs had been simplified and underestimated for a long period[1, 221]. For instance, VSMCs in AS lesions exhibit greater phenotypic plasticity than generally believed and multiple phenotypic switching of VSMC to other cell types has been reported in recent genetic lineage tracing studies.

4.1 Transdifferentiation of VSMCs to Foam Cells

Foam cells are the major cellular components of AS plaque where LDL is ingested, which participates in plaque development and rupture[225]. Although at first, macrophages are found to contribute to foam cells by uptaking lipid *via* acidified lysosomal synapse, VSMCs also transform into foam cells under exposure to lipid overload, ox-LDL, inflammation and oxidative stress in the intima and media in both mice and human, and the major source of foam cells seems to be transdifferentiated VSMCs[226–228]. Lipid excess is probably attributed to the reduced level of the ATP-binding cassette transporter A1 (ABCA1), a cholesterol exporter that binds free apolipoprotein A-I (ApoA-I) to the lipids[228]. The internalization and overloading of cholesterol, mainly mediated by LDL receptor-related protein 1 (LRP1), downregulates the expression of SMC-specific markers [α-smooth muscle actin (SMA), smooth muscle 22 α (SM22α), Calponin 1 (CNN1) and myosin heavy chain 11 (MYH11)] and upregulates macrophage-specific genes (CD68 and Galectin 3)[227–229]. Ox-LDL activates TLR4 thereby reducing NF-κB/acetyl coenzyme A acetyltransferase 1 (ACAT1), Src and Sirtuin1/3 pathways, which also promote the formation of foam cells[230, 231]. IL-1β increases LDL uptake and promotes the conversion to foam cells. On the contrary, IL-19 inhibits expression of LRP1 and ox-LDL uptake[232]. Macrophage migration inhibitory factor (MIF), a critical pro-

inflammatory mediator, inhibits the expression of p68 and SRF, which induces VSMC dedifferentiation[233]. A key regulator in this process is Kruppel-like factor 4 (KLF-4). Shankman *et al* developed mice with SMC-specific conditional KLF4-knockout and a marked reduction in lesion size and increase in plaque stability were observed[234]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) that depends on NOX activator 1 (NOXA1) plays an essential role in augmenting VSMC proliferation and migration and KLF4-mediated transition to macrophage-like cells, plaque inflammation, and expansion during AS[235]. The NOX and KLF4-dependent process is inhibited by SMC Drebrin, a F-actin-binding protein[236]. In a series of recent studies, patients with coronary diseases or type 2 DM have elevated levels of miR-320a, which is considered a key factor aggravating AS progression by promoting migration and proliferation of ox-LDL-stimulated VSMCs *via* targeting regulators of G protein signaling (RGS5)[237–239].

Dendritic cells, ECs and stem/progenitor cells are also sources of foam cells in AS lesions[240–242]. All foam cells have similar features, defective lipoprotein efflux and activated influx machinery[225]. However, it's important to investigate the differences between VSMC- converted foam cells and those from other sources and develop direct interventions to prevent phenotypic switching.

4.2 Transdifferentiation of VSMCs to Osteoblast- or Chondroblast-like Cells

Under some circumstances such as cholesterol excess and oxidant stress, VSMCs could express some markers of osteoblast cells rather than SMC-specific genes[243, 244]. KLF4 seems to participate in the osteochondrogenic transformation to generate $Lgals3^{+}$ osteogenic cells[245]. Ox-LDL induces the transformation by nuclear factor of activated T cells (NFAT) signal pathway, which could be inhibited by high-density lipoprotein cholesterol (HDL-C)[244, 246]. Chronic high glucose alone or combined with ox-LDL also induces expression levels of BMP2, alkaline phosphatase and secret phosphoprotein (SPP1) in VSMCs[247]. VSMCs that are exposed to high levels of phosphate and calcium or ROS have activated Wnt pathway and bone morphogenetic proteins (BMPs), at least partly mediated by upregulation of Runt-related transcription factor 2 (RUNX2) and msh homeobox 2 (MSX2) transcription factors[243, 248–250]. Badi *et al* indicated that the process of high phosphate-induced phenotype switching could be dampened by Sirtuin 1[251]. The expression of miR-34a, which targets Sirtuin 1, is associated with RUNX2 and induces vascular calcification. The osteogenic transformation and vascular calcification are inhibited by calcium and osteoprotegerin *via* insulin-like growth factor 1 receptor (IGF-1R)[252]. Kanno *et al* revealed that NO prevents differentiation of VSMCs into osteoblastic cells by inhibiting TGF-beta signaling in a cyclic guanosine phosphate (cGMP)-dependent manner[253]. In a rat model of chronic kidney disease, secreted Frizzled related protein 5 (SFRP5) was found to be negatively associated with VSMC transformation to osteoblast-like cells and vascular calcification by regulating RhoA/ROCK and c-Jun N-terminal kinase (JNK) pathways[254]. Vascular calcification could occur in the media, which also promotes arterial stiffness. It's suggested that a phenotypic transformation of VSMCs to chondrocytes rather than osteoblasts, is responsible for mid-layer calcification[249].

Lineage-tracing studies in mice show that 98% of all osteochondrogenic cells in AS lesions are VSMC-derived[255]. Those cells contribute to AS calcification, which is well-accepted synonymous with coronary AS plaque[256]. There has not been a consensus on whether calcification is benign or ominous. Some researchers believe that calcification has a reparative and stabilizing effect on the plaque[257, 258]. However, a greater fragility, increased stiffness and impaired EC function were also observed in calcified vessels[259–261]. Therefore, the dialectical idea that some forms of calcification [e.g., micro-calcified deposits (<50 μm)] may serve as a marker of inflammation and vulnerability of plaque whereas other forms [e.g., macrocalcification (>200 μm)] might identify stable lesions was increasingly recognized[262, 263]. As a result, more efforts on the opposites effects of osteochondrogenic transformation and vascular calcification are necessary for the development and clinical transition of novel therapeutics.

4.3 Other VMSC-derived Cells in AS Plaques

Using single-cell RNA sequencing, Wirka *et al* demonstrated the myofibroblast-like or fibromyocyte transformation of VSMCs in both mice and human[264]. Those myofibroblast-like VSMCs have decreased smoothelin level (a typical VSMC marker) as well as elevated expression levels of fibronectin 1, osteoprotegerin, collagen type 1a1, and an induction of fibroblast-specific pathways. TCF21, a casual cardiovascular disease gene, is essential to the transdifferentiation, and the knockout of TCF21 in VSMCs leads to reduced fibromyocytes in the protective fibrous cap of the lesions and increased risks of cardiovascular diseases[265]. In addition, contractile VSMCs cultured *in vitro* exhibit induced expression of EC markers, including CD31, von Willebrand factor, and VE-cadherin following laminar shear stress[266]. Hong *et al* developed an indirect approach to promote the transdifferention *in vitro* by reprogramming (using Yamanaka factors[267]) and regulation of Notch pathway[268]. It's important to note that the VSMC-derived ECs have not only typical endothelial markers expression, but also endothelial functions *in vitro*

and *in vivo*, implying that the EC subpopulation may also contribute to intraplaque neovascularisation and haemorrhage, which are associated with plaque rupture[268]. Lipid-containing VSMCs with elevated adipsin and lipogenesis gene expression levels were observed in human AS lesions[269]. However, exposure to adipocyte-conditioned medium leads to activation of pathways related to inflammation and fibrosis, but it remains unclear whether adipogenic transformation is induced[270]. Few studies reported the role and abundance of VSMCs-derived adipocytes in AS lesions. In response to environmental cues, the capability of medial VSMCs to convert to mesenchymal stem cell (MSC)-like cells has also been revealed and those MSC-like cells may further develop into adipocyte-like and osteoblast-like, and chondroblast-like cells[271]. However, robust evidence on the pluripotency of the VSMC-derived MSC-like cells is lacking.

Conclusively, VSMCs have been undervalued and mischaracterized for a long period, and accumulating studies emphasized the high plasticity of VSMCs, which offers the challenge to understand the full role of VSMCs in AS lesions and the opportunity to develop new drugs simultaneously[249]. However, the clinical transition of those studies is limited before several questions are addressed. Firstly, despite that altered expression levels of related specific genes were observed, direct evidence of those VSMC-derived cell subpopulations in human lesions is currently lacking. Secondly, unlike the intuitive role of ECs, the causal association between VSMC transdifferentiation and AS has not yet been fully elucidated. What's more, it's upset that few efficient and specific regulators that dampen the detrimental transformation and reverse the phenotype of VSMCs to protective cell types were discovered for further evaluation and potential transition due to inadequate current knowledge of the mechanisms of VSMC fate maps. Actin polymerization mediated by Rho/ROCK, the key pathway maintaining healthy phenotype, could also suppress the expression of VSMC contractile proteins, an integral step for VSMC dedifferentiation under induction of angiotensin II[224]. Interestingly, the contrary roles of miRNAs have been paid attention to recently. For instance, miR-21-3p/phosphatase and tensin homolog deleted on chromosome 10 (PTEN) axis promotes VSMC migration and proliferation and accelerates AS plaque development[27]. miR-143/145 are regarded as global regulators of VSMC phenotype switching. KLF2-expressing EC-derived exosomal miR-143/145 promotes atheroprotective transformation of VSMCs and reduces AS lesion formation in the aorta of ApoE–/– mice[272]. LncRNA CARMN, which was annotated as the host gene of the miR-143/145 cluster, was also reported to maintain the contractile phenotype of VSMCs and the loss of CARMN primes VSMCs towards an atherogenic phenotype[273]. However, the discordance of key regulators and the dynamic and complicated effects of hundreds of types of noncoding RNAs hinder a clear and definitive identification. Finally, several stimuli were applied to induce transdifferentiation in previous *in vitro* and *in vivo* studies; however, the real and combined effects in the pathogenesis of AS in human remain unexplored.

5 STORY FOUR: IMPROVEMENTS OF STEM CELL-BASED THERAPY

Currently blood lipid regulation is still the cornerstone of AS therapy in human. Although drugs such as statins could be efficient to lower blood lipid and/or cholesterol, potential adverse reactions and residual risks make them hard to be called a panacea. And it's generally considered that current medicine fails to reverse or eliminate plaques, leaving a large number of AS patients progressing to arterial stenosis or occlusion[31]. For those individuals with moderate- or severe artery stenosis, endarterectomy, endovascular stenting and other revascularization approaches are also commonly used; however, those interventions are limited due to invasiveness and the incidence of stent restenosis and thrombosis is pretty high[274]. Those limitations give rise to the development of novel therapies, such as stem cells and nanomedicine.

5.1 Current Knowledge of Stem Cell-based Therapy for AS

There are 3 major types of stem cells based on the origin: embryonal stem cells, induced pluripotent stem cells and adult stem cells (ASCs). ASCs include mesenchymal stem cells (MSCs) derived from bone marrow (BMSC), adipose tissue (AMSC) and umbilical cord (UCMSC), endothelial progenitor cells (EPCs), smooth muscle progenitor cells (SPCs) and hematopoietic stem cells (HSCs)[275]. Most of studies focused on stem cell transplantation therapy for AS utilized MSCs because the MSCs could be isolated easily and have unique properties of efficient self-renewing, releases of paracrine molecules, immune-tolerance, and multipotent differentiation potential[276, 277]. Although the beneficial effects on myocardial ischemia are convincing, only a few studies focused on the role in AS (table 2)[278–280].

The immunoregulation effects of MSCs have been extensively studied. Chronic systemic and local inflammation is one of the most pronounced features of AS. Decreased levels of serum C reactive protein (CRP), TNF-α and IL-6 as well as increased levels of IL-10 and TGF-β have been widely observed regardless of cell types and origins[281–285], which could be attributed to inhibition of pro-inflammatory cells and stimulation of anti-inflammatory cells according to a series of mechanistic studies. To be specific,

transplantation of BMSC dramatically decreased the levels of serum CCL2, IFN-γ and circulating monocytes, and promoted differentiation of T cells into Tregs rather than pro-inflammatory subpopulations (namely, Th1, Th2 and Th17)[286, 287]. Human gingival MSCs also alleviated AS in ApoE–/– mice by reducing the level of pro-inflammatory Ly-6Chigh monocytes; macrophage foam cell formation was also inhibited by modulating the expression of scavenger receptors (CD36, SR-A1, ABCA1)[288]. In an *in vitro* investigation, adipose tissue-derived MSCs exerted greater advantageous anti-inflammatory capabilities than BMSCs[289]. Inhibited inflammatory niche by MSCs could also stabilize and mend plaques to avoid rupture and superimposed thrombosis, which lead to acute coronary syndromes, strokes and sudden death. In a vulnerable atherosclerotic rabbit model, injection of allogeneic BMSCs downregulated NF-κB, MMP-1, -2, -9 and upregulated TNF-α stimulated gene/protein 6[285]. As a result, plaques from the MSC group had more stable morphological structure and a larger fibrous cap/lipid core ratio.

Whether transplanted stem cells can regulate blood lipids or directly repair the damaged ECs remains controversial. Cholesterol disorder is a critical factor of cardiovascular homeostasis and AS development. In a study where gingival MSCs were injected to ApoE–/– mice, the levels of serum LDL and TC as well as cholesterol accumulation in the plaque significantly decreased[288, 290]. Similarly, Frodermann *et al* also reported injection of BMSCs reduced serum cholesterol, mainly mediated by a reduced *de novo* hepatic lipogenesis[286]. High concentration of IL-10 and activation of Tregs have the capability of lowering serum cholesterol[291]. However, inconsistent findings were also observed[292, 293]. Besides, although a study reported that BMSCs injected from donor mice could engraft on recipient arteries in areas at risk for atherosclerotic injury to replace the senescent ECs, it's generally recognized that EPCs and SPCs, rather than transplanted stem cells, are major sources of regeneration and repair in AS lesions[294, 295]. However, a combined injection of BMSCs and platelet derived growth factor-BB (PDGF-BB)-loaded injectable hydrogel seems to exert an improved survival and EC differentiation of BMSCs and an accelerated wound healing by improving epithelialization and collagen deposition[296].

5.2 Problems and Future Directions of Stem Cells Transplantation

Firstly, it could be a priority to investigate how and where the injected MSCs play a role. Homing and migration of stem cells are dependent on ICAM-1/leukocyte function-associated antigen-1, VCAM-1/very late antigen (VLA)-4 and CXC Chemokine receptor 4 (CXCR4)/stromal cell-derived factor 1α (SDF-1α) axis. Although it's well documented that lesional inflammation upregulates ICAM-1, VCAM-1 and SDF-1α which could potentially promote the recruitment of stem cells[301–305], only one article has proven that stem cells can reach plaques yet[284].

Secondly, the wide range of tested cell injection strategies has been plagued by poor engraftment and survival of the transplanted cells due to pro-inflammatory and pro-apoptotic niche, which limits clinical translation. Besides, the therapeutic effects of natural, unmodified MSCs were far from satisfactory. With the development of enhancement strategies, pretreated or genetically modified MSCs provide a better choice. Although the efficacy of genetically modified stem cells has been verified in many other diseases, such as myocardial infarction and tumor, there are only a few studies on their role in vascular injury and AS[306]. The suppression of SMC proliferation was more pronounced when BMSCs were transfected with let-7a than unmodified BMSCs[307]. Tao *et al* genetically modified MSCs with high mobility group box 1 (HMGB1) and found that the infusion of engineered MSCs significantly alleviated vascular inflammation and promoted ECs regeneration by CXCR4/SDF-1 axis-mediated migration and multiple signaling pathway (p53 and MAPK)[308]. Combinatorial pretreatment with hypoxia and Tongxinluo, a traditional Chinese medicine, markedly enhanced the CXCR4 level of MSCs and promoted the retention in infarcted myocardium[279]; pretreatment with atorvastatin exerts similar benefits[309]. However, the therapeutic effects of both approaches remained unexplored in AS models.

Another obstacle of stem cell injection is potential embolism, carcinogenicity and immunogenicity, although no severe adverse effects were observed yet; in contrast, plenty of studies indicated the great biocompatibility, especially of the MSCs[310, 311]. However, with the development of bio-nanomedicine, it's increasingly recognized that extracellular vesicles (EVs) secreted by stem cells act as a major mediator of the benefits which could influence multiple aspects of AS progression. miR-233 in microvesicles (MVs) derived from BMSCs could bind directly to NLRP3 and inhibits pyroptosis and inflammation in plaques[312]. Mice treated with BMSC-MVs had a lower vulnerability index of plaques and intima-media thickness. Small EVs, also known as exosomes, that were derived from human umbilical cord MSCs and rich in miR-100-5p significantly reduced atherosclerotic plaque size and inflammation response in ApoE–/–mice *via* frizzled 5/Wnt/β-catenin pathway[313]. In another study, exosomal miR-21a-5p promoted polarization towards anti-inflammatory macrophages (M2) and reduced macrophage infiltration in lesions by targeting kruppel-like factor 6 (KLF6) or extracellular signal-regulated protein kinases 2 (ERK2)[314]. miR-145/Junction

adhesion molecule A (JAM-A) and miR-146a/Src pathways were also reported in AS models[315, 316]. Exosomes serve as a bulk of therapeutics, and could be an alternative choice of stem cell therapy.

Finally, a significant heterogeneity of the studies on stem cell transplantation for AS in terms of cells (type, origin and characteristics of donors), animal models (model methods, duration, concentration of cholesterol in diet), administration approach (injection method, dose and frequency) and evaluation parameters, is giving rise to a requirement of normalizing the protocols. It's worth mentioning that the difference between stem cells from female and male donors, young and older donors should be further identified and explained mechanistically since protective effects were only observed in mice receiving stem cells from young individuals or female individuals[295, 299]. Two models were theoretically recommended: ApoE–/– mice, for its widespread application, and high cholesterol-fed rabbit, for recapitulation of features of human AS[317]. In most reports, 5×10^5–5×10^6 cells were injected intravenously, weekly or biweekly (table 2). A comprehensive assessment of serum inflammatory indicators and major cellular biological processes in plaques mentioned above (growth and transdifferentiation of VMSCs, cell death of ECs and phenotype switching of inflammatory cells), as well as safety are necessary.

6 STORY FIVE: CLINICAL TRANSLATION OF NANOMEDICINE

Nanoparticles (NPs) are considered as another promising candidates for prevention, alleviation and regression of AS[318]. A multitude of NP types are currently under investigation, including lipid-based NPs, polymeric NPs, micelles, inorganic NPs, and exosomes. The application of those nanoscale particles improves the therapeutic effects and minimizes the adverse effects of traditional or novel therapies due to prolonged half-life period, attractive targeting capability and physical properties (table 3)[318].

Primary prevention refers to controlling risk factors of AS, one of which is hypertension[339]. Recent efforts revealed that encapsulation in poly-ε-caprolactone/Pluronic® F127 nanocarriers renders application of anandamide viable, which was once limited due to unfavorable physicochemical properties and psychoactive effects[322, 340]. Anandamide-loaded NPs could lower the blood pressure and LV hypertrophy in rats. Similarly, small hairpin RNA targeting angiotensinogen and Aliskiren were delivered efficiently by polymeric NPs and attenuated hypertension in rat models[319, 320]. Besides, poly lactic-co-glycolic acid (PLGA) NPs carrying propylene glycol alginate sodium sulfate, sirolimus or paclitaxel alleviated the detrimental effects of ischemia and glucose metabolic disorder[325, 326]. NPs may also help to make more drugs available and improve patient compliance which was limited by the requirement of frequent injection, by improving pharmacokinetic characteristics and providing a sustained drug release over a time course. In general, exendin-4 is injected subcutaneously; while exendin-4-loaded low molecular weight chitosan NPs enable a higher oral bioavailability and lower glucose in mice[327]. Another risk factor of AS is hyperglycemia. NPs have act as promising tools to develop orally administered insulin system, whose use was hampered by digestion by gastrointestinal enzymes, low absorption by the intestine, and protein modification by the acidic or basic environment in the last two decades[341, 342]. Metformin and glucagon-like peptide-1 (GLP-1) receptor agonists were also loaded into NPs, which have been summarized in a previous review[343].

Stimulated by the idea that targeting lesional macrophages in ApoE–/– mice lessens burden in plaque, Tom *et al* utilized HDL NPs, an atheroprotective bio-nanomaterial, to deliver an inhibitor of CD40/TNF receptor-associated factor 6 (TRAF6). Recruitment of leukocytes and activation of macrophages were suppressed[330]. Upon pathologic status, activated ECs express more adhesion molecules like selectins than normal, which may provide potential targets employed in atherosclerotic nanomedicine. In an elegant study, 5 adhesion molecules associated with recruitment of leukocyte into plaques were simultaneously inhibited by a siRNA-loaded poly(ethyleneimine) NPs and lesional inflammation waned in a post-MI ApoE–/– mouse model[333]. It's interesting to note that the activity of matrix-degrading plaque protease was reduced, which is an indicator of plaque stabilization. Ma *et al* developed a polyethylene glycol-polyethyleneimine (PEG/PEI)-based E-selectin-targeting multistage vector for delivery of miR-146a and miR-181b[329]. The plaques in ApoE–/– mice treated with the nanocarriers had a smaller size and a higher stabilization. Aside from these approaches, avoiding rupture and thrombosis could be another strategy once plaque forms. Nakashiro *et al* developed bioabsorbable, pioglitazone-incorporated PLGA NPs, and demonstrated its effects of inhibiting the activity of matrix metalloproteinases and cathepsins in the brachiocephalic arteries, as well as the expression of inflammatory cytokines[344]. NPs carrying siRNA targeting c-Jun N-terminal kinase (JNK2), which evokes macrophage uptake and internalization of ox-LDL and promotes the formation of resident foam cells by phosphorylating scavenger receptors, also restore endothelial barrier integrity and reduce thrombotic risk[332]. Conclusively, NPs enable delivery of therapeutic agents to target sites with high spatial and temporal resolution, thus increasing the

Table 2 Studies of effects of stem cell transplantation on AS

Animal model	Cell type	Delivery approach	Effects on			References
			Plaque size or pathology	Blood lipids	Others (including potential mechanisms)	
ApoE–/– mice (lethally irradiated)	BMSCs from WT mice	i.v. 5×10^6 cells	↓	↓	Secretion of ApoE	[297]
Ldlr–/– mice (lethally irradiated)	BMSCs from WT mice	i.v. 1×10^7 cells	ND	↓ (TC and LDL-C)	–	[298]
ApoE–/– mice	BMSCs or spleen cell-derived EPCs from ApoE–/– mice	i.v. 1×10^6 cells biweekly	↑ Larger lipid cores and thinner fibrous caps and a greater number of infiltrating CD3 cells in EPC treatment group	–	IL-10↓	[281]
ApoE–/– mice	BMSCs from WT and young ApoE–/– mice	i.v. 1×10^6 cells biweekly	↓(BMSC from young mice in particular)	ND	Replacement of senescent ECs; IL-6↓	[295]
ApoE–/– mice (male and female)	BMSC from WT mice (male and female)	i.v. 1×10^6 cells biweekly	↓(female to male) ND (others)	–	Vascular repair; gender difference in the hormonal and inflammatory response	[299]
ApoE–/– mice (splenectomized)	Lin-/Sca-1^+ or EPCs from WT mice	i.v. 5×10^5 cells	↓	–	Soluble vascular cell adhesion protein1, intercellular adhesion molecule1, E-Selectin; IL-6, ox-LDL and lipid peroxide↓	[282]
Ldlr–/– mice	BMSCs from WT mice	i.v. 5×10^5 cells every other day	↓ Reduced inflammatory infiltration	↓ (VLDL and TC)	*De novo* hepatic lipogenesis ↓ (due to downregulated Stearoyl-CoA desaturase-1 and lipoprotein lipase)	[286]
ApoE–/– mice	Human gingival MSCs	i.v. 2×10^6 cells weekly	↓ Reduced foam cell formation, lipid accumulation and activation of macrophages	↓ (TC and LDL)	SREBP-1c↓; PPARα and PGC-1α in the liver↑; M1 markers ↓ and M2 markers ↑	[288, 290]
ApoE–/– mice	Human amnion MSCs	i.v. 5×10^5 cells biweekly	↓ Reduced macrophage infiltration	↑ (HDL)	TNF-α↓, IL-10↑; phosphorylation of p65 and I-κB↓	[283]
ApoE–/– mice	Skin MSC from WT mice	i.v.	↓	–	TNF-α↓, IL-10↑; NF-κB signal↑	[284]
Rabbit model	Human umbilical cord MSCs	i.v. 6×10^6 cells biweekly	↓ Stabilization of plaque	–	Macrophage↓, CD36 and SRA1↑; Uptake of ox-LDL↓; IL-6 and TNF-α↓; IL-10 and TGF-β↑; Modulation of gut microbe (TMAO↓)	[300]
Rabbit model (with lipid nitrogen-induced vascular injury)	BMSCs from normal rabbits	i.v. 1×10^7 cells	More stable morphological structure and a larger fibrous cap/lipid core ratio	↓ (TC and LDL-C)	Hs-CRP, TNF-α, IL-6↓; IL-10↑; NF-κB and MMP↓; Apoptosis↓; TSG-6 mRNA↑	[285]

AS, atherosclerosis; BMSC, bone marrow-derived stem/stromal cells; ECs, endothelial cells; IL, interleukin; i.v., injected intravenously; LDL(-C), low density lipoprotein (cholesterol); MMP, matrix metalloproteinase; ND, no difference; NF-κB, nuclear factor κB; PGC-1α, peroxisome proliferator activator receptor-coactivator 1; PPARα, peroxisome proliferator-activated receptor α; SREBP-1c, sterol regulatory element binding transcription factor 1c; TC, total cholesterol; TMAO, trimethylamine-N-oxide; TSG-6, TNF-α stimulated gene/protein 6; VLDL, very low density lipoprotein; WT, wild type; ↑, upregulated; ↓, downregulated

Table 3 NPs-based prevention and treatment for AS

Animal model	NP type	Payload	Delivery Method	Therapeutic and preventive effects for AS		References
				Plaque/Vascular function	Others	
SHR	PLA	Aliskiren	Gavage		BP↓; aorta collagen↓; fibrosis of aortic tunica media↑; modulation of NOS	[319]
SHR	Biscarbamate-crosslinked Gal-PEG-PEI NPs	AGT shRNA	i.v.		BP↓; heart hypertrophy↓; myocardial ultrastructure ↑	[320]
SHR	Hyaluronic acid	Curcumin	Gavage		BP↓	[321]
SHR	PCL/Pluronic® F127	Anandamide	i.p.		IL-1, IL-6, TNF-α↓	[322]
Rats; streptozotocin induced DM	Trimethyl chitosan chloride NPs with a CKS peptide tag	Insulin	Gavage		Hypoglycemic effect↑	[323]
Rats; streptozotocin induced DM	Niosomes	Metformin	Gavage		Hypoglycemic effect↑	[324]
Rats; streptozotocin induced diabetic cardiomyopathy	PLGA	Propylene glycol alginate sodium sulfate	i.p.		Myocardial function and morphology↑; coronary microcirculation↑; plasminogen activator inhibitor-1 expression in cardiomyocytes↓; TNF-α, IL-1β, IL-6↓; NF-κB pathway↓; serum SOD and GSH↑	[325]
Mini-pigs; temporary carotid closure and balloon angioplasty	PLGA	Sirolimus or paclitaxel	Infused into the left common carotid segment	Vascular stenosis and expression of PCNA↓	Glycolysis and expression of HIF-1α in hypoxic ECs and SMCs↓	[326]
WT mice	Low molecular weight chitosan	Exendin-4	Gavage		A significantly enhanced hypoglycemic effect	[327]
Mice; 12-week high-fat diet	Leukosomes (liposome); fabricated with membrane proteins of macrophages	Rapamycin	Retro orbital injection	Plaque burden↓; proliferating macrophages in the aorta↓	MCP-1, IL-b1, MMP↓	[328]
ApoE–/– mice; 12-week western diet	PEG/PEI (loaded into an E-selectin-targeting multistage microparticles)	miR-146a, miR-181b	i.v.	Plaque size↓; Stabilization↑ (lesional collagen↑)	Lesional macrophages and chemokine expression in aorta↓	[329]
ApoE–/– mice; subcutaneous angiotensin Ⅱ-infusing minipumps or 11-week high-fat diet	PEGylated SWNTs	SHP1i	i.v.	Plaque burden↓; lesional phagocytosis↑; inflammatory genes in lesional macrophages↓		[177]
ApoE-/- mice	rHDL	TRAF-STOPs	i.v. twice a week for 6 weeks	Plaques↓; leukocyte recruitment↓; macrophages activation↓		[330]
Dogs; coronary bypass using the autoallergic saphenous vein	Albumin (linked to microbubbles)	t-PA plasmid	i.v.	Intimal thickness and proliferation of SMCs↓	Thrombotic rate↓; t-PA and D-dimer contents in blood↑	[331]
ApoE–/– mice; 14-week western diet	Amphipathic, cationic peptide	JNK siRNA	i.v.	Barrier permeability and disruption↓; foam cell formation, plaque necrotic area and macrophages↓	Thrombotic risk↓; NF-κB and STAT3 expression↓	[332]

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Animal model	NP type	Payload	Delivery method	Therapeutic and preventive effects for AS		References
				Plaque/Vascular function	Others	
ApoE−/− mice; high-cholesterol diet and I/R injury	PEI	ICAM1, ICAM2, VCAM1, Sel-E, Sel-P siRNAs	i.v. for 1, 2 or 3 week (s)	Neutrophil and monocyte recruitment into AS lesions↓	Matrix-degrading plaque protease activity↓	[333]
ApoE−/− Mice; 28-day high-fat diet	PLGA or liposome	Methotrexate	i.v. every third day		Intracellular lipids and ox-LDL↓; RANTES, IL-1β, TNFα↓; IL-1α↑	[334]
ApoE−/− Mice; 8-week high-fat and cholesterol diet	PEG and sebacic acid	D-PDMP	Gavage	AS plaque buildup, cholesterol ester crystal deposits, and fibrosis↓	FS↑ and cardiac hypertrophy↓;	[335]
Ox-LDL↓; changes of levels of genes associated with triglyceride metabolism	Lipid NPs	Methotrexate or paclitaxel	i.v. once a week for 6 weeks	Coronary stenosis, macrophages infiltration↓	Gene expression of TNFα, MCP1, IL-18, VCAM1, and MMP12↓; expression of IL-10 ↑	[336]
Rabbits; 8-week cholesterol diet	Lipid NPs	Methotrexate or paclitaxel	i.v.	Macroscopic atheroma plaque area↓	TNFα↓	[337]
Rabbits; 8-week cholesterol diet	Lipid NPs	Carmustine	i.v.	Lesion area↓	Macrophages, FOXP3, IL-1β, LDL-R↓	[338]

AGT, angiotensinogen; AS, atherosclerosis; BP, blood pressure; D-PDMP, D-Threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol; FOXP3, forkhead box P3; GSH, glutathione; ICAM, intercellular cell adhesion molecule; IL, interleukin; i.p., injected intraperitoneally; JNK, c-Jun N-terminal kinase; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; NOS, nitric oxide synthase activity; (ox-)LDL, (oxidized) low-density lipoprotein; PCL, poly-ε-caprolactone; PCNA, proliferating cell nuclear antigen; PEG, poly(ethylene glycol); PEI, polyethylenimine; PLGA, poly lactic-co-glycolic acid; RANTES, regulated upon activation normal T cell expressed and presumably secreted; rHDL, recombinant high-density lipoprotein; Sel, selectin; SEM, scanning electron microscope; SHP1i, SH2 domain-containing phosphatase-1 inhibitor; SHR, spontaneously hypertensive rats; SWNTs, single-walled carbon nanotubes; TNFα, tumor necrotic factor α; TRAF-STOPs, tumor necrosis factor receptor associated factor (TRAF) 6; t-PA, tissue-type plasminogen activator; VCAM, vascular cellular adhesion moledcule; vWF, von Willebrand factor

likelihood that they can be successfully translated to clinical settings[318].

Currently, the potential of NPs for AS prevention and treatment has not been fully realized and there is a huge gap between the research on NP and the in-depth, mechanistic investigations summarized above. For instance, it remains unexplored whether an NP system could regulate the fate of VSMCs directionally, or prevent ECs from ferroptosis, or inhibit "don't-eat-me" signals and promote efferoptosis. The major concerns of application of NPs are the biocompatibility. There are a few studies reporting NP-associated acute and chronic hazards in medicine applications, although some observations could be contentious. NP-associated toxicity is mainly mediated by oxidative stress injury, pro-inflammatory and pro-apoptotic effects secondary to production of ROS, phagocytic cell response and lack of anti-oxidants[345]. Potential off-target organs damage induced by NP accumulation should also be evaluated, especially for those NPs with poor degradability and slow clearance[346]. A general consensus is that toxicity of NPs depends on many parameters, comprising material composition, shape, size, surface charges and doses. For instance, organic NPs such as silica NPs could induce vascular ECs dysfunction and promote the release of procoagulant and pro-inflammatory factors *via* miR-451a/IL-6R/STAT pathway[347–349]. Exposure to gold (Au) NPs caused a potential nephrotoxicity[350]; cationic AuNPs seem to be more toxic than anionic AuNPs[351]. Nermar *et al* found that superparamagnetic iron oxide NPs led to cardiac oxidative stress and thrombosis[352]. Given the results, a recommendation for the development of NP-based AS therapy is comprehensive safety assessment. Exosomes and most of polymeric NPs are favored due to great biocompatibility[353]. Another well-recognized strategy is optimization of the physicochemical properties such as functionalization with nontoxic surface molecules[318]. What's more, novel mechanism-based NPs and advanced strategies in studies of tumor or ischemia models have not been introduced to AS models. These approaches include curroptosis-related NPs[354], ROS or inflammation responsive NPs[355, 356], and hybrid NPs[357].

7 CONCLUSIONS AND AN INTEGRATED PERSPECTIVE

In this comprehensive review, we listed 5 top research directions of AS based on the current popularity and prospect: (1) transdifferentiation of VSMCs; (2) novel cell death forms of ECs (and other cells); (3) novel functions of immunocytes, efferocytosis and ETosis; (4) stem cell-based therapy; (5) nanomedicine for AS. Present review provides a detailed update on those cellular and biomolecular mechanisms and therapies,

along with the future research directions and the points that require special attention. There is an urgent need on further studies on the biomolecular mechanisms and the roles in AS to improve the understanding of the stories since our knowledge is apparently not yet comprehensive. For instance, Liang *et al* identified phospholipid-modifying enzymes MBOAT1 and MBOAT2 as ferroptosis suppressors with a surveillance function independent of GPX4 in a recent study[358]. Yalcinkaya *et al* demonstrated that IL-1β derived from macrophages with cholesterol accumulation appeared to increase NETosis both by increasing neutrophil recruitment to plaques and by promoting neutrophil NLRP3 inflammasome activation, providing another evidence of the interaction between different pathogenic processes[359]. Those advances enable the likelihood to develop potential therapies. Given the fact that the majority of AS-related deaths occur following rupture of plaques and subsequent thrombogenesis, studies on the effects of the novel mechanisms reviewed in the current report on plaque stabilization is lacking.

Besides, it has been emphasized for a long time that single-target monotherapies have intrinsic limitations with respect to the maximum benefits; while given the complexity of cellular and biomolecular landscapes of AS and many other diseases, attempts to develop an almighty medicine based on single mechanisms could be theoretically challenging[360, 361]. Inspired by the idea, two or more antibiotics with multiple antimicrobial mechanism have been combined to lower risk of resistance development and improve outcomes in clinical practice[362]. AS actually shares a similar story with drug-resistant bacteria infection, thus next-generation strategies for AS are recommended here. Future efforts on this topic are also supposed to focus on either combined medication with multiple targets, or the key triggers those mechanisms share, including elevated production of ROS, evoked inflammatory response and internalization and interaction with ox-LDL (fig. 1), rather than merely preventing apoptosis or inhibiting transcription factors involved in the harmful transdifferentiation of VSMCs. Additionally, excess cellular cholesterol serves as a common inducer of cell death and transdifferentiation.

Optimized stem cell injection and multi-payload NPs serve as two promising all-in-one strategies. As living transplants, stem cells could secret a bulk of beneficial cytokines and exosomes that regulate numerous signals, including oxidative stress, inflammation and cholesterol disorders in AS and other CVD models (table 2)[278–280]. Nanocarriers loaded with multiple payloads targeting complementary signals are an alternative option with the advantages of short preparation duration, low cost, and high controllability. Sager *et al* have proved the feasibility in a marvelous study where 5 targets, all of which are critical adhesion molecules, were silenced concurrently by a siRNA/PEI NPs[333]. We hope this review could spur more efforts to develop an integrated strategy for AS prevention and regression.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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