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Anti-Inflammatory Strategies for Plaque Stabilization after Acute Coronary Syndromes

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Abstract Despite dramatic advances in standard of care, the risk of recurrent myocardial infarction early after an acute coronary syndrome (ACS) remains high. This period of elevated risk after a cardiovascular event is associated with an acute inflammatory response. While post-ACS inflammation correlates with the risk for recurrent events and is likely to play a causal role in this period, the precise pathophysiologic mechanisms have been unclear. Recent studies have proposed that the cardiac event itself activates the sympathetic nervous system to directly mobilize hematopoietic stem cells to differentiate into inflammatory monocytes, acutely infiltrate plaque, and lead to recurrent plaque rupture. Here, we summarize the existing and emerging evidence implicating post-ACS activation of systemic inflammation in the progression of atherosclerosis, and identify possible targets for therapeutic intervention. We highlight experimental therapies and ongoing clinical studies that will validate these targets.

Keywords Acute coronary syndrome · Vulnerable plaque · Inflammation · Therapeutics · Plaque stabilization

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Introduction

Cardiovascular (CV) disease, especially coronary artery disease (CAD) and acute coronary syndrome (ACS) (unstable angina or myocardial infarction [MI] with or without ST-segment elevation), continues to be the most common cause of mortality in the developed world. Despite advances in management, the rate of recurrence of an event, including ischemia and infarction remains at up to 54 % within 1 year [1, 2]. This elevated rate of re-infarction appears to decrease over time [3]. This suggests that ACS patients are uniquely vulnerable to recurrent events in the early post-ACS period, perhaps driven by unique pathophysiology and amenable to specifically tailored therapies.

It is not clearly understood how an ACS event elevates risk for recurrent events. Many of the earliest events are likely to be due to thrombotic complications at the culprit lesion and complications of the myocardial infarction itself, including arrhythmic death, periprocedural infarctions, and death due to cardiogenic shock and pump failure. However, coronary imaging studies in post-ACS patients strongly suggests that many recurrent events are attributable to nonculprit coronary lesions. The PROSPECT study studied the natural history of coronary plaque using VH-IVUS, although it was limited by a low incidence of both vulnerable plaque and hard clinical endpoints (86 % of MACE were due to unstable or progressive angina) [4•]. Clinical events in PROSPECT were equally attributable to culprit and non-culprit lesions, and more than half of the nonculprit lesions leading to events had vulnerable features (thin cap fibroatheromas) [4•, 5]. Other studies using OCT (optical coherence tomography) have further support that ACS patients often present with multiple inflamed nonculprit vulnerable lesions [6–8]. This has led to the concept that ACS activates

a pan-vascular process ("pan-coronaritis") resulting in a higher prevalence of vulnerable plaque and subsequent recurrent ischemic events.

The systemic inflammatory response after ACS has been well described, and may play a role in recurrent events after ACS. Both circulating inflammatory markers, such as IL-6 and hsCRP, as well as circulating inflammatory cells, including leukocytes and inflammatory monocytes, are elevated acutely after an ACS event in a temporal pattern that corresponds to elevated event rates and is predictive of recurrent events [9].

The hypothesized pleiotropic effects of statins may point to a role for modulating inflammation to prevent post-ACS recurrent events [10, 11].The benefits of statin therapy in a stable CAD setting may be related to low-density lipoprotein (LDL) lowering and inflammation reduction independently; in both plaque regression studies [12] and clinical outcomes studies [13], the on-treatment reduction in C-reactive protein (CRP) correlates with benefit independently of the change in LDL cholesterol. Specifically in ACS patients, the use of high-dose statins reduce the risk of recurrent events as early as 30 days post-ACS, along with a corresponding decrease in inflammatory biomarkers. [14, 15]. Despite the use of statins, there remains a significant residual risk of destabilization of plaque in the post-MI state and potential for modifying this risk using therapies with more potent and/or plaque targeted anti-inflammatory effects.

In this review, we present an overview of the pathophysiology of the post-MI state leading to the vulnerable plaque, including recent concepts, and also discuss potential targets for intervention and therapeutics (Fig. 1).

Increase Hematopoietic Stem Cell (HSC) Production and Monocytosis Following ACS

Acute coronary syndrome (ACS) involves an acute yet transient increase in the inflammatory state, as manifested through activation of both innate as well as adaptive immunity. Despite the overwhelming evidence for immune cell activation following ACS, the molecular and cellular mechanisms that drive the initiation and progression of these processes are still under investigation.

It is speculated that the combination of stress, pain and tissue damage associated with the trauma of ACS are the initial drivers of immune cell response [16, 17•]. These seminal events are orchestrated by multiple organs and mediators and are likely to provide infarct healing through the removal of dead cells, angiogenesis, and extracellular matrix turnover in the acute infarct (Reviewed in Nahrendorf [18]). Monocytes were shown to play a major role in these processes, and significant peripheral monocytosis was seen in patients within 24 hours after acute myocardial infarction (AMI) [18, 19]. The monocyte response post ACS is biphasic, with a first wave of CD16-CD14+ 'inflammatory' monocytes that responsible for removal of dead cells followed by CD16+ CD14dim 'reparative' monocytes that promote resolution of inflammation and tissue repair, suggesting the involvement of distinct monocyte subsets at different stages of infarction to promote infarct healing [20]. Similar subpopulations of monocytes were shown to be involved in AMI models in rodents, where the 'inflammatory' and 'reparative' monocytes correspond to Ly-6C^{hi} and Ly-6^{low} [21].

Fine-tuning of the proper monocyte response is critical for the healing process, and insufficient or exuberant responses compromise infarct repair and can drive left ventricular remodeling in ACS patients and AMI mouse models [19, 22•]. Furthermore, increased peripheral monocytosis is directly correlated with non-recovery of left ventricular function in ACS patients and is associated with increased risk of heart failure [23]. Whether monocytosis following primary ACS can also contribute to the destabilization of non-culprit lesions, thereby increasing the risk for a reoccurring infarction, is still unanswered. It is well established that circulating monocyte can migrate into blood vessels guided by activated or damaged endothelium, thereby increasing the inflammatory load of existing vascular lesions (Reviewed in [24]). Growing evidences suggests that an exaggerated monocyte response correlates with cardiovascular risk. Classical CD14++CD16- and intermediate CD14++ CD16+ monocytes independently predicted cardiovascular events [25•] were associated with coronary plaque vulnerability in patients with stable angina pectoris [26•], and strongly correlate with reduced fibrous cap thickness, as measured by intravascular optical coherence tomography (OCT) in patients with unstable angina [27•].

Mechanisms Associated with Monocytosis Following ACS

An ACS event triggers the proliferation and mobilization of progenitor cells from the bone marrow, including endothelial progenitor cell (EPC) and hematopoietic progenitor cells (HPCs) [28•, 29]. Patients with ACS demonstrate a six-fold increase in circulating CD34+ progenitor cells, including both EPC and HPC, which peak at admission and gradually return to baseline within 2 months [30]. Studies in preclinical models have shown that the mobilization of progenitor cells requires the action of chemokine receptors and their cognate ligands (reviewed in [31]). Specifically, the CCR2

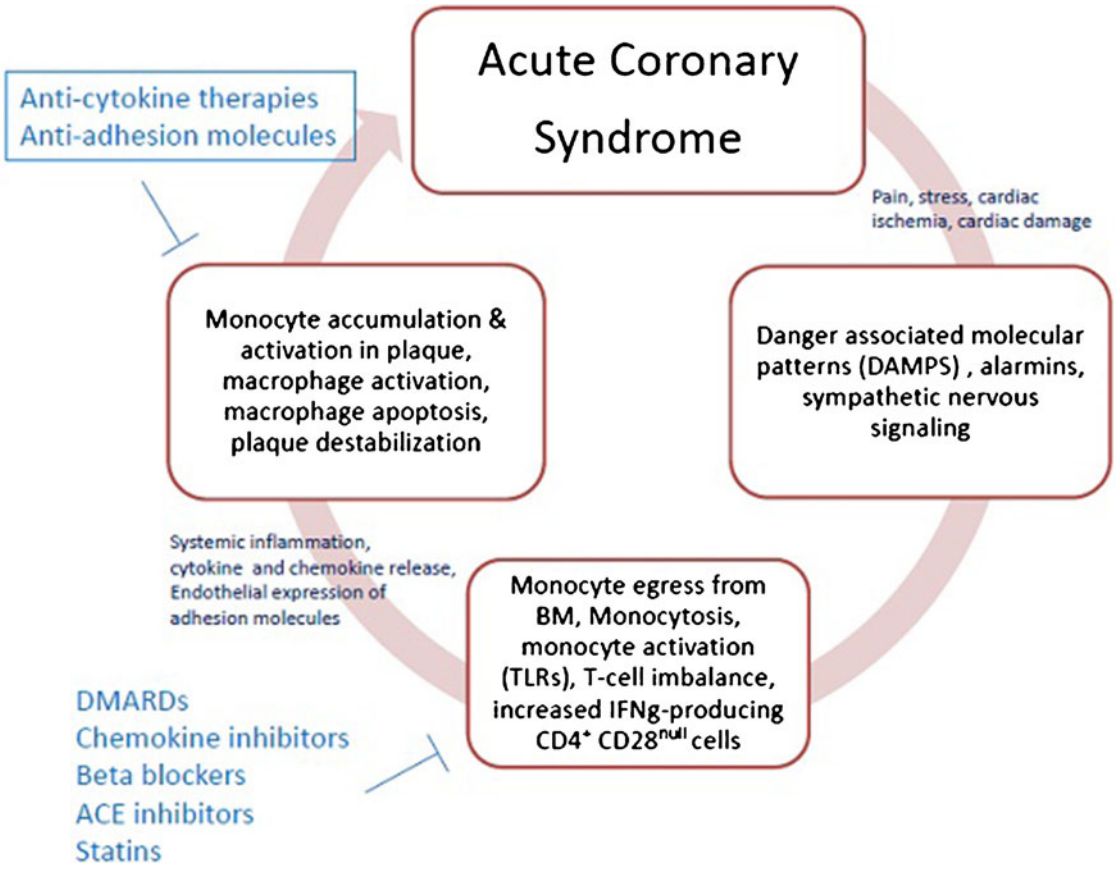

Fig. 1 Mechanisms promoting plaque destabilization following acute coronary syndrome (ACS)

ligands monocyte chemotactic protein-1 and 3 (MCP1, MCP3) are best described as essential for monocyte emigration from the bone marrow during infection and inflammation [32]. Whilst the mechanisms are unknown, one hypothesis suggests that dead cells and damaged extracellular matrix within the infarcted tissue release mediators that can be sensed by different cell and organs, including the bone marrow (reviewed in Liaudet and Rosenblatt-Velin [33] and in Swirski and Nahrendorf [34]). These endogenous signals, termed 'danger associated molecular patterns' (DAMPS) or 'alarmins', can activate toll-like receptors, especially TLR4 and TLR2, and can be sensed in immune as well as stromal cells [35••]. In the bone marrow, mesenchymal stem cells and their progeny can release MCP1 in response to circulating TLR4 ligands, thus providing an activating migratory signal for bone marrow monocyte progenitors.

Another compelling hypothesis suggests that signals from the sympathetic nervous system, following the pain and stress associated with ACS, can trigger the egress of cells from the bone marrow. Innervating neurons can alter the adrenergic tone within the bone marrow through the release of norepinephrine, which in turn disrupts osteoblast-derived retention signals such as CXCL12 (SDF1a) [36]. In support of this hypothesis, administration of B2-adrenergic receptor agonists or a Beta3 blocker in mice effectively enhanced or blocked HSC mobilization from the bone marrow, respectively [36, 37••]. The activation of the stem cell niche within the bone marrow in an ACS model was shown to be mediated by Wnt signaling, suggesting another potential link between catecholamines and progenitor cell response [28•].

In addition to the bone marrow response, the splenic red pulp retains a reservoir of undifferentiated monocytes that can be mobilized and migrate to the injured myocardium [38]. The migration of monocytes from the spleen is mediated by Angiotensin II and in a mouse model of exaggerated infarct inflammation, ACE inhibition reduced the levels of spleen-derived monocytes in the circulation and improved infarct healing [39]. Conversely, it was shown that the spleen is essential to the infarct healing process by providing a continuous supply of cells to the site of myocardial injury, and splenectomy after coronary ligation led to impaired wound healing and heart failure [22•]. These studies highlight once more the physiological challenge in achieving a balanced immune response leading to an efficient healing process without exacerbation of the inflammatory process. There is no clinical evidence that a similar extramedullary monopoiesis

mechanism exists in humans; however, a study that included 745 ex-servicemen who had splenectomy for trauma during the 1939-45 war reported an increased rate of ischemic heart disease, suggesting a potential a cardio-protecting role for the spleen [40].

Potential therapies to reduce post-ACS monocytosis could target HPC release from the bone marrow or monocyte release from the spleen. Chemokine antagonists (e.g. MCP-1 decoy, anti-CSF antibodies) and B3 antagonists could target HPC mobilization from bone marrow, although potentially at the cost of impaired infarct healing. In a study conducted in patients with high CV risk and elevated CRP, it was demonstrated that administration of anti-CCR2 mAb significantly attenuated inflammation, as measured by CRP [41•]. As described above, ACE inhibition or ARB (angiotensin receptor blocker) therapy may decrease splenic monocyte release, and multiple animal studies have shown plaque stabilization with these drug classes [42, 43]. Although CV outcomes studies with ACE inhibitors show reduction in CV death and reinfarction post-MI, this is mainly in patients with STEMI and systolic dysfunction, and thus seems to be due more to beneficial effects on myocardial rather than plaque remodeling. A small human study has shown a beneficial effect of these therapies on plaque stabilization; however, ACE inhibition has failed to demonstrate plaque regression in randomized clinical trials [12, 44]. Since the current standard of care mainly targets the Beta adrenergic receptors I and II isoform, it would be of value to assess the specific impact of beta III inhibitors on risk of ACS recurrence [45].

Activation of Monocytes Following ACS

The activation of TLRs and the subsequent NFkB signaling can be elicited by a variety of endogenous signals derived from the injured myocardium (Reviewed in Liaudet and Rosenblatt-Velin [33]). These stimuli include HMGB-1, Heat Shock Proteins, myosin, hyaluronic acid, fibrinogen, fibronectin EDA and nucleic acids, as well as myeloid signals such as neutrophil-derived proteins MRP8 and MRP14 [46], (Reviewed in Liaudet and Rosenblatt-Velin 2013 [33]). All monocytic subtypes can respond to TLR ligands; however, CD14++ monocytes respond well to TLR4 and TLR2 stimuli, while CD14dim monocytes sense TLR7 and TLR8 ligands (reviewed in Liaudet and Rosenblatt-Velin 2013 [33]). Expression of TLR4 in myeloid cells is elevated in patients with ACS compared with angina patients or healthy subjects [47•, 48, 49]. TLR4 upregulation peaks within 24 hours after AMI and declines by Day 14 [50]. TLR4 expression correlated with cytokine response (IL-6, TNFa) derived from innate immune cells [50]. Interestingly, mononuclear cells from UA patients with recurrent ischemia showed enhanced production of IL-6 in response to LPS 6 months post-ACS [51].

Another potent activator of monocytes is the cytokine IL1b. It was reported that the Nlrp3 inflammasome is activated in response to cardiomyocyte necrosis and can trigger the release of IL-1b, which in turn exacerbates the inflammatory state [52]. In vivo studies further show that activation of the inflammasome in cardiac fibroblasts plays an important role in inflammatory responses and subsequent injury after myocardial ischemia reperfusion, and the activation is partly mediated by potassium efflux and ROS production [53]. Interestingly, the activation of TLR4 and IL1R in monocytes through the intracellular TIR (toll/IL-1 receptor) domain results in prominent production and release of multiple cytokines and chemokines that regulate both innate and adaptive immunity (TIR reference, Reviewed in Tedgui and Mallat [54]). In addition, a reduction in anti-inflammatory cytokines was recorded in ACS patients, reflecting the imbalance in systemic cytokine response following an ACS [55].

Potential therapies that could modulate post-ACS monocyte activation are currently in development. These include an anti-TLR antibody in preclinical development (Opsona OPN-305), the TLR2/4 antagonist VBL-201 [56] and anti-IL1b (Novartis, Canakinumab, [57]), currently in a large cardiovascular outcomes study.

Involvement of T cells in ACS

Unstable plaques show marked increase in T cell infiltration [58] accompanied by a dramatic increase in plaque IFNγ, but not IL-4, suggesting an imbalance between Th1/Th2 T cell subsets. Similarly, circulating Th1 cells undergo dramatic expansion within 6-hours post ACS) [48, 49] Importantly, Th1-derived IFNγ as well as CD40 ligand are potent stimuli of plaque-resident macrophages, and act synergistically to induce the expression of multiple proinflammatory genes, as well as plaque destabilizing metalloproteinases [59]. An additional subset of IFNγ-producing Th1 cells that can release IL-17 has been implicated in ACS [60•]. A sharp increase in these Th17/Th1 was observed in ACS. Interestingly, a concomitant decrease in the number of anti-inflammatory Treg cells, the related transcription factor (Foxp3+), and plasma TGF-β1 was observed in ACS patients [60•, 61]. These changes highlight the imbalance in T cell response following ACS, and suggest the potential involvement of pro-inflammatory T cells in the development of atherosclerotic plaque instability.

Typically, T cells require costimulation of both an HLA/antigen complex, as well as an additional APC stimulus to transform into effector cells. From the many different

proteins with described costimulatory activity, the best defined and perhaps most significant receptor/ligand complex is B7/CD28. Recently, a unique subpopulation of T cells that lack CD28 was shown to be involved in ACS [62]. CD4+ CD28null cells undergo considerable expansion during unstable angina compared to patients with stable angina [62]. These cells have a distinctive T cell phenotype and have gained cytolytic activity through expression of perforin and granzymeB, which can damage vascular endothelial cells [63] and release large amounts of IFNγ [62], a potent stimulus of macrophages. In addition, it was shown that CD4+ CD28null cells derived from ACS patients express a killer immunoglobulin-like receptor (KIR) variant that induces cytotoxic activity of these cells independent of the T cell receptor [64]. The combination of such features makes CD4+CD28null cells highly aggressive with the potential to destabilize vascular lesions. Indeed, it was established that the level of this unique T cell subtype is correlated with high reoccurrence of acute coronary events [65]. Interestingly, CD4+CD28null cells isolated from ACS patients' express high levels of the costimulatory receptors OX40 and 4-1BB of the Tumor necrosis factor (TNF) super family [66]. Blocking of these costimulatory signals reduced IFNγ secretion and perforin release, thereby offering a potential path for inhibiting the harmful impact of these cells in the pathophysiology of atherosclerosis.

No therapies specifically targeting T cells for post-ACS risk are in clinical practice; however, a large cardiovascular outcomes study of the effects of methotrexate may inform on this hypothesis [67]. Strategies to inhibit T cell Th1 production and promote Treg function, such as FK506, and anti-CD3 antibody are potential approaches to reduce atherosclerosis [68].

Mechanisms of Plaque Destabilization and Potential Targets for Therapeutics

Coronary plaques generally manifest clinically by creating a flow-limiting stenosis or by resulting in thrombi that can block the blood flow at the event site, or distally due to an embolic event. Paradoxically, the thrombotic events do not occur preferentially at the most significantly narrowed lesions, but at sites with plaques that are structurally vulnerable to rupture. Inflammatory cells are implicated in the destabilization of these plaques and in subsequently hastening the thinning and weakening of the fibrous cap.

There are several mechanisms by which the activated immune cells can affect plaque structure. The role of macrophages in the initiation and propagation of plaque progression and destabilization and the contribution of inflammatory cytokines and MMPs is well studied in non-clinical models and reviewed elsewhere [69]. In this section, we highlight the current trends that will direct our thinking about future therapies.

Macrophages within the atherosclerotic lesion morph into foam cells through the continuous ingestion of modified lipoprotein particles such as oxidized LDL. Although reported to be intimately involved in plaque initiation and progression, foam cells were shown to suppress rather than activate inflammatory gene expression [70]. However, this seemingly protective behavior of macrophages can often go astray as the intracellular accumulation of lipids and cholesterol induce cytotoxic effects and can lead to cell death and the formation of a destabilized lipid core [71]. One of the mechanisms that facilitates macrophage cell death is the blocking of macrophage egress out of the lesion through the secretion of Netrin-1, a neuroimmune guiding molecule [72]. Hence, the combination of inefficient macrophage exit and lipid-driven cell death within the vascular lesion is a major driver for lesion development and plaque vulnerability.

It is widely recognized that the hallmarks of apoptotic cell death, whether chromatin condensation, annexin-V staining or morphological characteristic, are associated with the maturation of atherosclerotic plaque. The appearance of apoptotic debris, including evidence of macrophage apoptosis, accumulates when the phagocytic machinery is impaired. Apoptosis is abundant in human atherosclerotic lesions, and is associated with inflammatory and engulfing cells (T cells and macrophages) [73]. This process often leads to the appearance of necrotic tissue in mature plaques and likely reflects the complex pathology or secondary necrosis following apoptotic cell death. Numerous pro-inflammatory stimuli, including cytokines (TNFa, IL-6) reactive oxidants, oxidized-LDL and free cholesterol are evident in advanced plaque and, whilst undoubtedly contribute to the evolving pathology, their casual role in vulnerability to rupture remain uncertain. Clinical antioxidant therapies, for example, have not translated into clinical success [74]. Non-clinical approaches to assess the contribution of macrophage apoptosis to the progression of atherosclerotic plaque use bone marrow transplantation from animals with selective deletion in established apoptotic pathways. For example, transfer of bone marrow cells from p53-/- mice to syngeneic LDLr-/- mice: supported a protective role for p53 in slowing down atherosclerosis development and, interestingly, promoting remodeling of the lesion from a vulnerable to a stable-looking phenotype [75]. Similar observations were seen for bone marrow from Bax-/- mice into LDL receptor deficient mice; this reduced the degree of apoptosis and promoted development of atherosclerosis [76]. Whilst these studies indicate that apoptosis plays a critical self-defense mechanism in limiting atherosclerosis progression,

further experimental studies using pharmacological inhibitors are required to confirm these conclusions. Despite the limitation of non-clinical studies, most converge on the notion that phagocytic clearance of apoptotic cells is important to slow the evolution of the lesion and stabilize vulnerable plaques. The process of phagocytosis and egress appears highly efficient, and interruption can rapidly lead to accumulation of cell debris and promotion of the inflammatory milieu [77]. Indeed, the "rate of apoptosis" as well as serological markers of apoptosis can be considered reflective of vulnerability. It is therefore tempting to speculate that impediment of this process, either due to a loss of apoptotic signalling that "tags" the cell for phagocytic removal or the loss of phagocytic activity can lead to enhanced plaque rupture. Pro-thrombic factors (including tissue factor) released from post-apoptotic macrophages or increased secretion of matrix degrading proteases can cause atheroma development, and thereby contribute to plaque vulnerability. Free cholesterol and cholesterol crystals are found in large amounts in the macrophages of advanced lesions, and are thought to contribute to macrophage cell death by induced ER stress [78]. Whilst the detailed mechanistic response for induction of apoptosis and limited efferocytosis of the macrophage and other inflammatory cells of advanced plaque remains to be fully elucidated, therapeutic strategies aimed at preventing macrophage apoptosis or maintaining their phagocytic function and egress should clearly be evaluated.

Autophagy

Autophagy is a process of “self-clearance” and refers to a well-conserved process to turn over organelles and proteins in order to maintain normal cellular homeostasis. The processes of autophagy, efflux and efferocytosis are fundamental to the stability of the lesion. It becomes activated by environmental stress, and in atherosclerotic plaques, the inflammation, reactive oxygen species, hypoxia, oxidized lipoproteins and endoplasmic reticulum stress can all act as inducers of autophagy [79].

Autophagy, once activated can have a dual role—it promotes smooth muscle cell (SMC) and endothelial cell (EC) survival when exposed to oxidative stress by removing intracellular debris. There is also recent evidence that autophagy plays a critical role in regulating the cholesterol efflux from macrophage foam cells via lysosomal acid lipase [80].

However, excessive stimulation of autophagy can cause autophagic death [79]. Loss of SMC in plaque can result in destabilization of plaque, due to reduced synthesis of collagen and thinning of the fibrous cap. Endothelial cell death can weaken the structure of the plaque, and may also promote thrombotic events.

Experimental Therapies Targeting Plaque Inflammation

Blocking inflammatory monocyte infiltration into nonculprit lesions is an attractive target to reduce post-ACS reinfarction (Table 1). Therapies currently in clinical development that may address this mechanism include anti-P-selectin (Phase II, Roche), PA-508 (MCP-1 decoy, preclinical, ProtAffin), and Serp-1 (Viron, Ph II, Circ cardiovascular interventions [81]). Intracellular signalling inhibitors, such as p38 MAPK GSK-856553 (losmapimod), may reduce macrophage activation in plaque. GSK 2586881, a recombinant human angiotensin converting enzyme-2 is in Phase I development with ACS as a potential indication, and may promote plaque stabilization by cleaving angiotensin II into atheroprotective peptides [82].

Although ApoA1 mimetic therapies are considered lipid modifying, ApoA1 may directly reduce plaque inflammation. Through anti-inflammatory effects and removal of cholesterol by reverse cholesterol transport, these agents may modulate plaque macrophage phenotype and plaque vulnerability [83]. ApoA1 Milano achieved proof-of-concept for plaque regression [84] and is now in Ph I, with a new formulation. CSL-112, a synthetic reconstituted HDL, and RVX-208, an Apo-A1 inducer, which also has potential direct anti-inflammatory actions through an epigenetic mechanism, are both in Phase II IVUS plaque regression studies with data expected in 2013 (reviewed in Vucic and Rosenson, Current Atherosclerosis Reports 2011 [85]). ATI-5261 (Artery Therapeutics) is a 26-mer HDL mimetic peptide in preclinical development.

A number of experimental therapies have targeted LDL oxidation. Darapladib, an Lp-PLA2 inhibitor in Phase III outcomes studies [86] may reduce plaque inflammation by inhibiting LDL oxidation, and has shown favorable effects on necrotic core in animal and human studies [87, 88], COR-2, an OxLDL scavenger (soluble CD68, J&J) and INV-311 (inVasc therapeutics), a myeloperoxidase inhibitor, are in preclinical development.

Exploratory drugs being developed to reduce myocardial ischemia/reperfusion injury might secondarily be active in plaque destabilization. Examples include complement targeting therapies, J&J CB-159, a protease targeting the inflammatory cascade, and Elafin (Proteo), an inhibitor of leukocyte elastase and proteinase 3. Similarly, apoptosis inhibitors being developed to improve myocyte survival after STEMI, including growth factors and Akt activators, might have effects promoting survival of plaque-resident cells.

While no therapies currently being explored directly target autophagy, rapamycin and related drugs may in part function through this mechanism; stent-based delivery of everolimus in rabbit atheroma has demonstrated clearance of macrophages via autophagic death [89].

Table 1 Pipeline of plaque stabilization therapies

Drug Target	Product Name	Company/Originator	Status for CAD/ Dyslipidemia/ Atherosclerosis	Reference	Description
Apolipoprotein A-I Modulators	RVX-208	Resverlogix	Phase II	[90]	Small-molecule inhibitor of the Bromodomain and Extraterminal Domain (BET) proteins that increases transcription of the ApoA-I protein
Apolipoprotein A-I Modulators	CER-001	Cerenis	Phase II	NCT01201837	Synthetically produced functional HDL mimetic based on natural apolipoprotein A-I
Apolipoprotein A-I Modulators	MDCO-216	Medicines Company	Phase I	[84]	ApoA-I Milano / phospholipid complex; Pfizer licensed to The Medicines Co. in December 2009; high-risk ACS to be lead indication
Apolipoprotein A-I Modulators	KM-011 / FX-5A	KineMed	Preclinical	http://www.kinemed.com/Media/Kinemed_FX_5A_RAID_AWARD_Press_Release_April_10_2012.pdf	ApoA-I HDL mimetic peptide designed to reverse atherosclerosis
Apolipoprotein A-I Modulators	unspecified	Esperion	preclinical	http://www.esperion.com/products-research/product-candidates.php	Oxidation-resistant ApoA1 biologic being developed in collaboration with Cleveland Clinic
Cytokine Modulators	CT-2009	Carolus Therapeutics	Preclinical	[91]	Peptide antagonist to the RANTES/platelet factor 4 (PF4) heterodimer
Cytokine Modulators	XOMA-052	Servier/Xoma	Phase II	[92]	Humanized monoclonal antibody to IL-1beta; Orphan Drug status for Behçet's disease in the U.S. and Europe; licensed to Servier in January 2011. Aug. 2012: BI chosen as manufacturing partner for Gevokizumab
Cytokine Modulators	CV-18C3	XBiotech	Preclinical	NCT01270945	Monoclonal antibody to IL-1alpha
Cytokine Modulators	Canakinumab	Novartis	Phase III	[95]	Anti-IL1-B mAb in large secondary prevention Ph III CV outcomes study
HDL mimetics	CSL-112	CSL	Phase II	NCT01129661	Reconstituted high-density lipoprotein (rHDL)
Innate inflammation	CB-159	J&J/Catalyst Biosciences	Preclinical	NCT01201837	Protease targeting the complement component C3
Innate inflammation	VB-201	VBL Therapeutics	Phase II	[56]	Lead candidate oxidized phospholipid analog from a series of lecinoxoids with anti-inflammatory, TLR antagonizing properties.
Innate inflammation	OPN-305	Opsona	Preclinical	[93]	Fully humanized anti-TLR antibody
Innate inflammation	IMO-3100	Idera	Preclinical		Dual TLR7/TLR9 antagonist; lead indications are autoimmune disorders, including psoriasis, lupus, and rheumatoid arthritis
Innate inflammation	sCD14	Bridge BioResearch	Preclinical	US Patent WO2004082578A2	Soluble formulation of CD14 protein: lipopolysaccharide modulator
Macrophage activation	GSK-856553	GlaxoSmithKline	Phase II	[94]	Anti-inflammatory p38 MAPK inhibitor
Macrophage activation	unspecified	Syndexa	Preclinical	N/A	Small-molecule compounds that can Modulate the inflammatory responses associated with JNK activity and ER biology
Monocyte trafficking	PA-508	ProtAffin	Preclinical	[95]	Anti-inflammatory, decoy MCP-1 protein
Monocyte trafficking	inclacumab	Roche	Phase II	NCT01327183	Anti-P-selectin mAb

Table 1 (continued)

Drug Target	Product Name	Company/Originator	Status for CAD/ Dyslipidemia/ Atherosclerosis	Reference	Description
PLA2 Inhibitors	SB-480848	GlaxoSmithKline	Phase III	[96]	Inhibitor of lipoprotein-associated phospholipase A2 (Lp-PLA2); from HGSI acquisition.
T-cell activation	Methotrexate	NIH	Phase IV	[66]	Cardiovascular Inflammation Reduction (CIRT) CV outcomes trial ongoing.
Complement modulators	TP10	Celldex	Phase II	[97]	C1 receptor inhibitor (soluble complement receptor 1) completed Phase II in post-CABG ischemia/reperfusion injury, now being developed for renal indications.

Conclusion

Despite advances in therapy, patients remain vulnerable after presenting with ACS, and preventing recurrent infarction in this high-risk period remains a major unmet need. Advances in our understanding of immunology and plaque biology lead to the promise of developing novel therapeutics for novel targets with key roles in plaque vulnerability after ACS. In particular, immune modulation to target the production and release of HSC after ACS, HSC differentiation to inflammatory monocytes, and inflammatory monocyte ingress into plaque represent new approaches to therapy. Cellular actors in the post-ACS "activated" plaque represent downstream targets of therapy. A balancing of benefit and risk of novel therapies will likely require an ability to individually tailor therapy to patients, depending on both the systemic and local (plaque) factors driving their risk of recurrent events.

Conflicts of Interest Amos Baruch declares no conflicts of interest.
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- • Of importance
- •• Of major importance

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