WHITE PAPER

Guide to atherosclerosis pathogenesis, cellular actors, and pathways

Introduction

Atherosclerosis is a common condition where arteries become narrowed due to a build-up of fatty material, usually cholesterol, and other substances such as calcium. This build-up is known as plaque, and it can block or reduce blood flow through the arteries. This can lead to a range of serious health complications, including heart attack or stroke, which makes the disease an important contributing factor to death and morbidity in developed countries. Atherosclerosis is known to be driven by lipid and lipoprotein metabolism, with risk factors including high blood pressure, high cholesterol, diabetes, smoking, and obesity. However, ongoing research suggests that atherosclerosis may not be exclusively driven by metabolism, and that it may also have an inflammatory influence, where immune cells and mediators play an active role in the disease. Treatment for atherosclerosis includes lifestyle changes such as exercise, quitting smoking, and eating a healthy diet, as well as medications such as cholesterol-lowering drugs.

Atherosclerosis begins with the development of atherosclerotic lesions in the endothelial lining or arteries, where local cell dysfunction and disturbed blood flow allow the deposition of fatty material (low-density lipoproteins or LDL) and local oxidation into harmful and inflammatory components. As a defense, local endothelial cells express cytokines and inflammatory mediators that recruit monocytes from the blood and promote their differentiation into macrophages, which can remove and break down LDLs. Atherosclerosis develops when the removal abilities of macrophages are insufficient, leaving them saturated with absorbed LDL that eventually causes cellular death. The LDL-full macrophages are known as foam cells due to the foamy appearance they get from their lipoprotein content. At this stage, the atherosclerotic lesion is called a fatty streak due to its appearance to the naked eye.[1–5]

Progression from fatty streaks to fibrotic plaques involves the infiltration and proliferation of more macrophages into smooth muscle tissues under the endothelial lining, where they promote inflammation and production of extracellular collagen matrix. At this point, plaques become vulnerable due to persistent inflammation, leading to unstable structures made of a necrotic core of dead cells, covered by a thin fibrous cap that bulges out into the artery lumen and narrows it down.[4]

During the entire process, macrophage death and the inefficient removal of apoptotic cells in the lesion/plaque escalates the inflammation, leading to increased smooth muscle cell death, decreased extracellular matrix production, and collagen degradation on the outside of the plaque. Rupture of the surrounding fibrous cap frees the contents of the plaque, which can detach and enter the circulation. Here, it carries catastrophic potential for thrombus formation, which can lead to stroke and serious cardiovascular events.[4,6–8]

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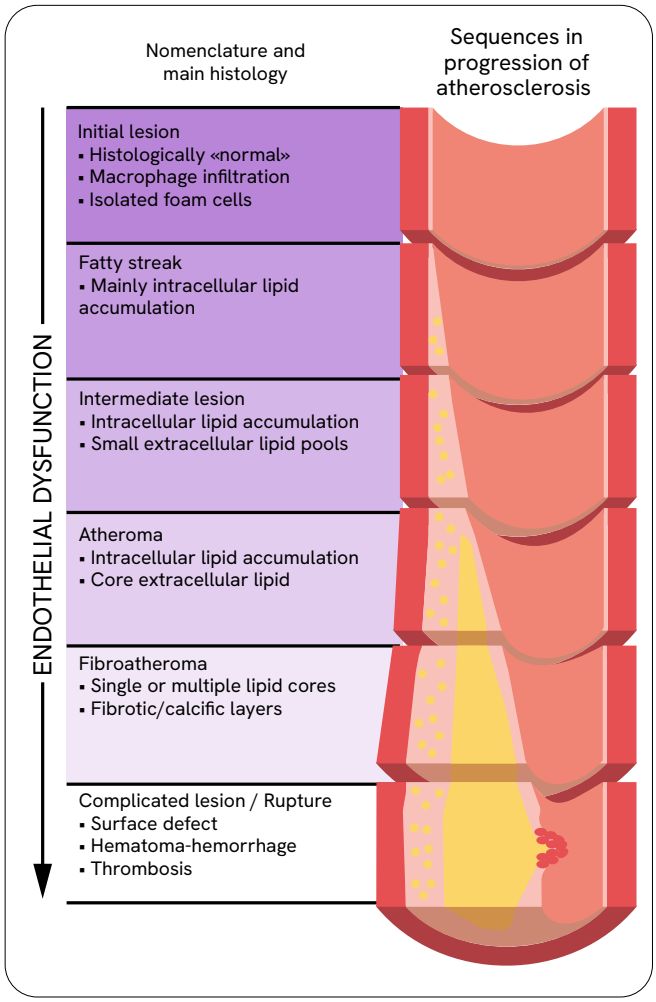

Figure 1: Simplified progression of atherosclerosis

Pathogenesis

Initial lesion and fatty streak stages of atherosclerosis

The inner lining of arteries comprises endothelial cells that regulate contractility, hemostasis, and inflammatory signals locally. Structural or functional defects of this endothelial lining are considered the first and earliest stage of atherosclerotic lesions. Such defects can have multiple forms like unusual cell morphology, thin glycocalyx layers, lack of cell-to-cell spatial organization, etc. They are most commonly observed in arterial regions where shear stress is low and blood flow disturbed and/or turbulent. On the contrary, regions with laminar blood flow are not susceptible to atherosclerotic lesions.[4,9,10]

On top of structural parameters, the susceptibility of endothelial cells to atherogenic behaviors is linked to a range of molecular factors that shift from being regulatory to pathogenic when disrupted or altered. For instance, the role of Nitric Oxide (NO) and its synthesizing enzyme Endothelial Nitric Oxide Synthase (eNOS) have been described as promoters of atherosclerosis-resistant regions, with laminar flow, due to its effect on vasodilation and artery diameter. When eNOS is reduced, the lack of NO reduces artery diameter, alters blood flow, and threatens the integrity of the endothelial lining, which becomes more likely to sustain tears and breakage over time. Similar issues can arise from local inflammation promoted by mediators like NF-kB and other cytokines, but also oxidized LDL, pathogens, and reactive oxygen species, all of which can come from lifestyle habits. [11,12]

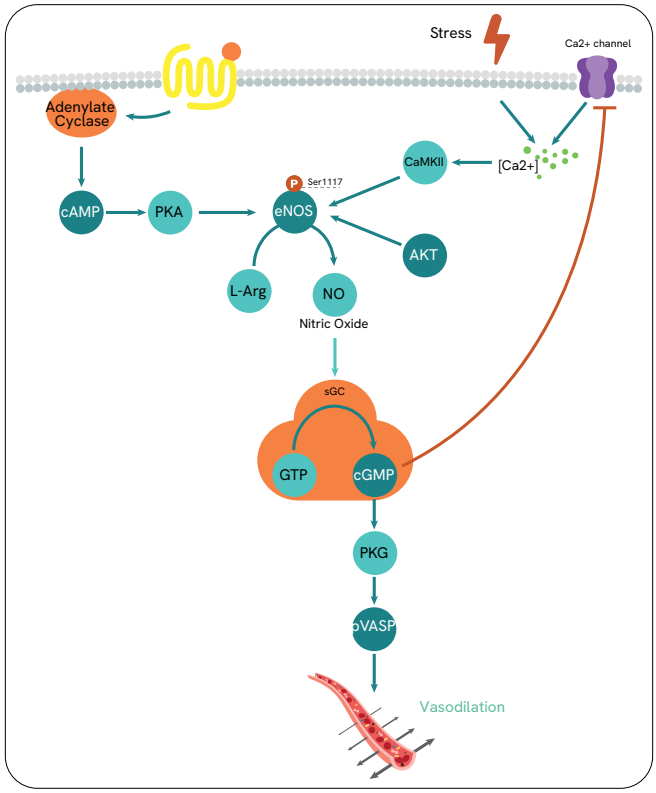

Figure 2: Nitric oxide role in artery diameter and blood flow

Over time, defects in the endothelial lining increase the risk of tears in the barrier, which creates spots where LDL circulating in the blood can stick, accumulate, and then oxidize into inflammatory compounds.

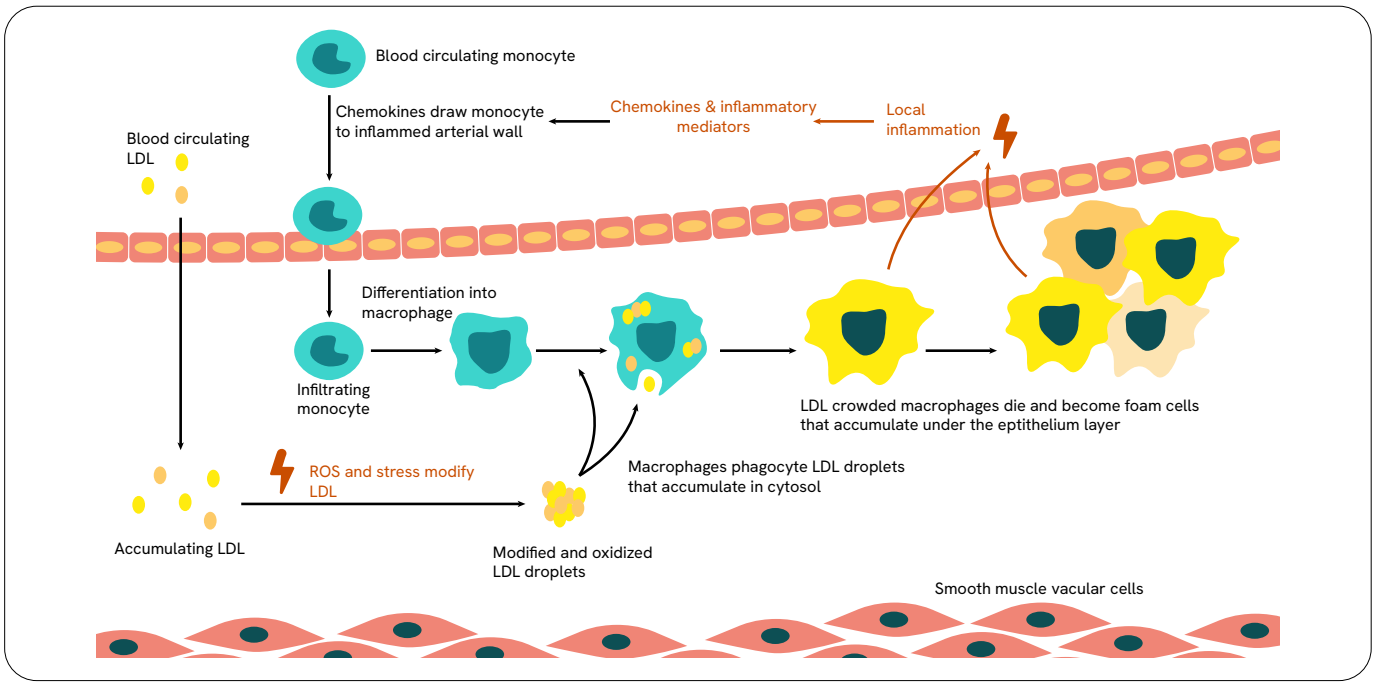

Figure 3: Formation of the atherosclerotic lesion and fatty streak

Advanced atherosclerotic lesions, plaque stage, and plaque rupture

Even though fatty streaks are the first step up from atherosclerotic lesions, they are not determinant as they still have the potential to regress. Atherosclerosis only sets in when lesions progress and start to incorporate durable cellular and molecular components that promote ongoing inflammation.

A key event is when macrophages recruited at the site of inflammation begin expressing growth factors that stimulate smooth muscle cell proliferation under the inflamed endothelial lining. This results in large numbers of muscle cells with poor LDL absorption capacity growing into the lesion. Over time, this proliferating population of cells dies and accumulates into the lesion, along with macrophage-turned foam cells, all of which constitute a necrotic core in the wound. At the same time, macrophage activity promotes tissue remodeling and matrix expression around the lesion, which becomes surrounded by a thin fibrous cap made of collagen. The increase in the lesion's intimal volume size pushes and bulges into the artery, reducing its diameter and increasing blood pressure locally. This promotes vascular remodeling around the site with more specialized cell types, including local fibroblasts that secrete extracellular matrix components and which stiffen tissues in an inflammatory environment.[11]

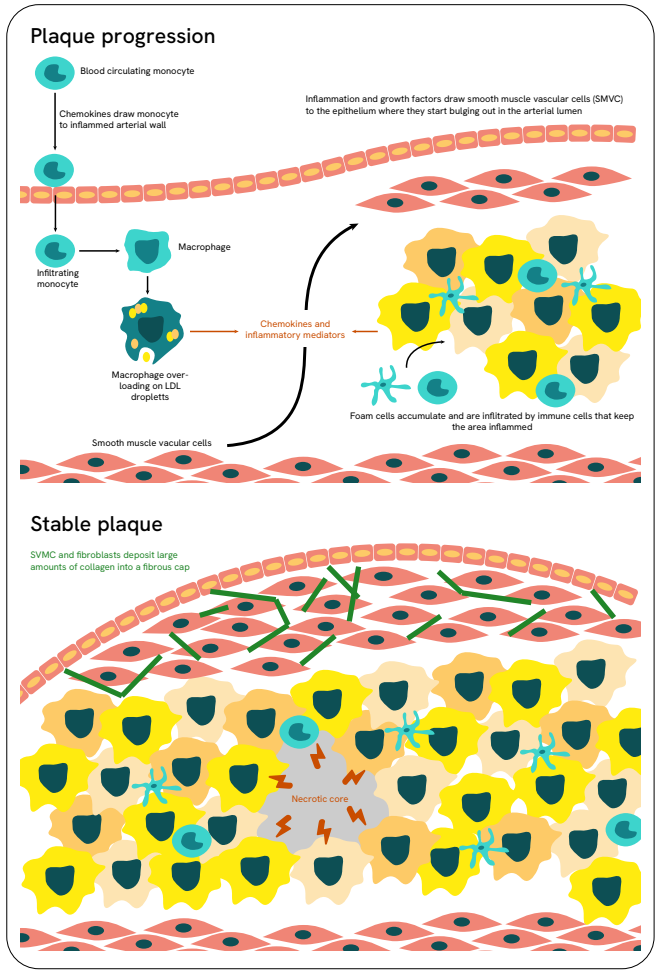

Figure 4: Plaque progression to a stable plaque stage

At this stage, the lesion is now a plaque or atheroma, and it is defined as a combination of cholesterol, fat, calcium, and other substances that accumulate in the artery walls. Plaque size is the main parameter that qualifies the disease has progressed past the lesion and fatty streak stages. A plaque is deemed vulnerable when its necrotic core grows and its fibrous cap thins. The thinner and more deteriorated the fibrous cap, the more at-risk the plaque is since its rupture likelihood grows. When rupturing, plaques cause the acute release of procoagulant and prothrombotic factors from the necrotic core to platelets and procoagulant factors in the lumen, causing the formation of thrombus responsible for myocardial infarction, unstable angina, sudden cardiac death, and stroke.[7,8,11]

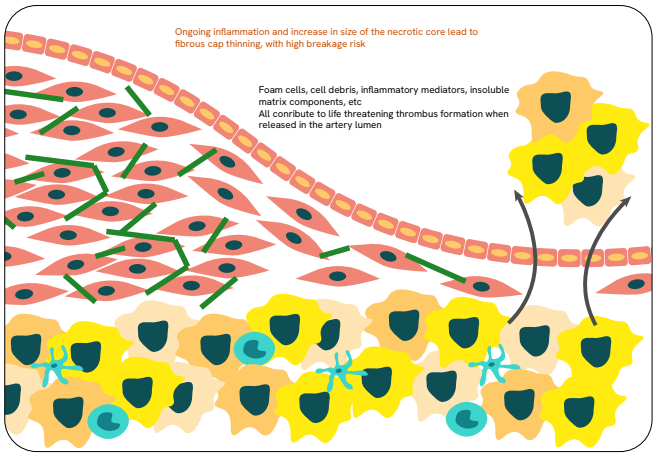

Figure 5: Vulnerable/unstable plaque stage

Macrophages: the culprit?

As endothelial cells are triggered and become inflamed from infiltrating modified LDLs, they issue 'calls for help' to the immune system in the form of inflammatory mediators. Such signaling proteins include MCP-1 (monocyte chemoattractant protein 1) and IL-8 (interleukin 8) that draw monocytes from the blood into the endothelial lining where they can adhere due to VCAM-1 (vascular cell adhesion molecule 1) and ICAM-1 (intercellular adhesion molecule 1) and differentiate into macrophages. In atherosclerosis, macrophages' role is to remove the cause of inflammation, clear dead cells and cytotoxic compounds, and create the conditions typical of wound healing before promoting cell growth and tissue reparation.

In the fatty streak stage, macrophages internalize and then break down LDLs (often carried by apolipoprotein E or apoE) inside lysosomes. In the meantime, macrophages capture and process free cholesterol through their endoplasmic reticulum (which puts pressure on this system over time) to be esterified into cholesteryl esters (CE) and stored as droplets in the cytosol. These droplets are white in appearance and as they accumulate, they give macrophages the foamy look that earns them the name of foam cells. Eventually, lipid droplet accumulation becomes excessive and forces foam-cell metabolism to halt, which kills them. Several mechanisms can improve the management of LDLs by macrophages, such as oxidation or glycation, which make them more susceptible to capture by scavenger receptors and lectin-like receptors. Aggregation of apolipoproteins by enzymes has also been suggested to improve absorption by macrophages. [1-3,13-15]

Macrophages are therefore in the paradoxical position of being both the clearance system in charge of driving wound management, sanitation, and healing, but also key actors in disease progression when they deviate toward a foam-cell phenotype. There can be multiple reasons for that transition, all rooted in inflammatory signals like oxidative stress, modified lipoproteins, other lesion factors that can induce inflammation via receptors, and accumulating lipids in foam-cell cytosol that trigger the escalation of inflammation until cell death. Along with inflammatory factors, certain innate immunity mechanisms like the inflammasome have been implicated in atherosclerosis progression associated with cardiovascular complications. IL-1β (interleukin 1-beta) and IL-18 (interleukin 18) play a particular role here since they are the main drivers of inflammasome-induced inflammatory signaling. Recent clinical results (CANTOS trial, 2020) showed that anti-IL-1β canakinumab treatment reduced cardiovascular events in patients. [16]

Of note, macrophages are not the only immune cells involved; they have several relatives that also contribute to the development of atherosclerotic lesions, such as dendritic cells, mast cells, and specialized T-cell subsets. Dendritic cells act as antigen-presenting cells and promote the recruitment and activation of adaptive T-cells. They are also potent secretors of chemoattractants and cytokines that sustain inflammation.

Mast cells or mastocytes are tissue-resident sentinels and a source of IL-6 (interleukin 6) and INF-γ (interferon gamma), which are both pro-inflammatory mediators that contribute to a lasting inflammatory response. T-cells have more specific roles in line with their adaptive immunity affiliation. They exist in several subsets, with beneficial or adverse effects in atherosclerosis settings. While helpers like Th1-cells tend to have pro-inflammatory and atherogenic effects, regulators (T-reg) express anti-inflammatory mediators like TGF-β (transforming growth factor beta) and IL-10 (interleukin 10) that de-escalate immune cells local activity and inflammatory behaviors.[17-20]

The necrotic core in atheromas or plaques results from two macrophage defects: accelerated turnover and insufficient removal of cellular remnants. This leads to the accumulation of apoptotic cells, both foamy macrophages and smooth muscle cells, which stagnate in the plaque intima before breaking down and releasing their intracellular oxidative and inflammatory components. This subsequently propagates more inflammation, oxidative stress, and death to neighboring cells.

There are multiple reasons for accelerated macrophage death, such as oxidative stress, activation of their death receptors by inflammatory mediators, and local nutrient deprivation. Chronic endoplasmic reticulum stress (part of lipid-removing avenues in macrophages) triggers the unfolded protein response (UPR), which is also a promoter of cell death over time and is increasingly present as the disease progresses. The reason for insufficient removal of cellular remnants is thought to be due to phagocytosis and degradation mechanisms becoming impaired via decreases in the expression and/or function of capture receptors, as well as the large amount of locally apoptotic cells that compete for binding to these capture receptors. There can also be cases of immune checkpoint high jacking where apoptotic cells evade phagocytosis by upregulating the expression of “no-kill” signals such as CD47. [21-23]

These defects in macrophages promote the transition from a stable plaque to an unstable plaque over time, which is a key event in atherosclerosis progression. As vascular smooth muscle cells (VSMC) expend and die into the necrotic core, their accumulation grows inside the artery lumen. Inflammation-driven constant remodeling of the surrounding collagen matrix combined with the lack of collagen renewing due to dying VSMC also causes the fibrous cap to become thinner. Fortunately, there are mechanisms that combat the progression to unstable plaque and offer opportunities for future therapeutic research. For instance, HDLs (high-density lipoproteins) are suggested to reduce inflammation by promoting the anti-inflammatory and wound healing M2 phenotype of macrophages over the pro-inflammatory M1 phenotype, which improves plaque stability over time. The role of regulatory T-cells (Treg) is also highlighted for expressing pro-M2 phenotype IL-13 (interleukin 13) and for their own anti-inflammatory properties mediated through IL-10, adenosine, and CTL-4.[14,15,24]

Signaling pathways

In addition to vasodilation and blood flow regulation mechanisms like nitric oxide/eNOS, other signaling pathways have significant implications in the development of atherosclerosis and are potential therapeutic targets. The main pathway of interest, both in terms of research and therapeutic targeting, is the renin-angiotensin-aldosterone system (RAAS). RAAS is a hormone signaling pathway that regulates blood pressure and fluid balance. In atherosclerosis patients, dysregulation of the RAAS system causes an increase in blood pressure, which results in structural and functional defects in the endothelial lining of arteries, thereby promoting atherosclerosis-vulnerable arterial regions.

RAAS signaling is normally triggered by decreases in arterial blood flow and involves several hormones and enzymes, including angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and aldosterone. ACE is an enzyme that converts angiotensin I (Ang I) into the powerful vasoconstrictor Ang II (Figure 2). Beyond vasoconstriction, Ang II stimulates the release of aldosterone, a hormone that helps regulate fluid balance and blood pressure. It also promotes the production of cholesterol and other substances in the arterial wall, leading to plaque formation. Dysregulation of the RAAS pathway is understood to cause cholesterol and other fatty substances to accumulate in the arteries, which then promotes and drives atherosclerosis development.[10,25-27]

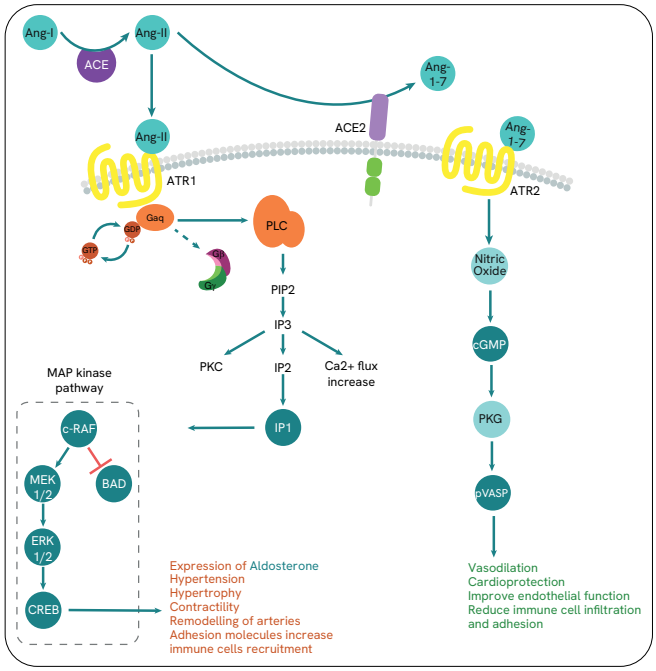

Figure 6: Renin-Angiotensin Aldosterone System (RAAS) signaling.

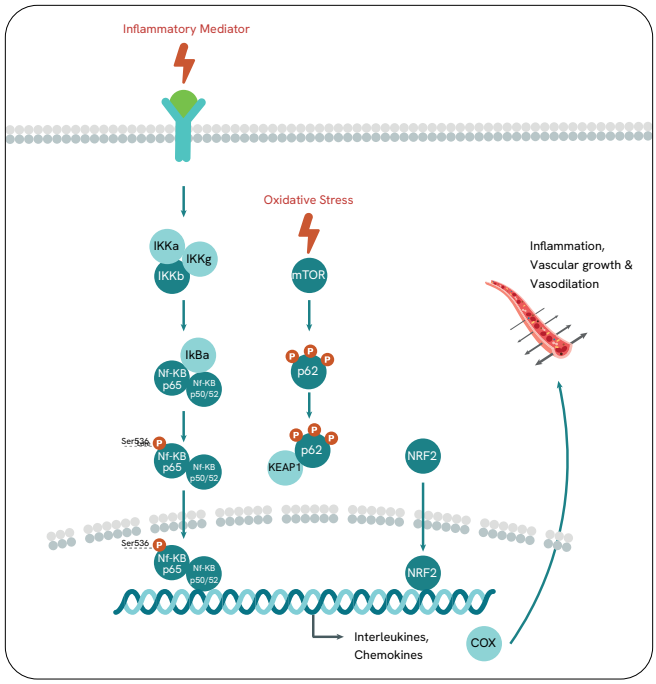

Figure 7: Simplified representation of NF-kB, COX and Nrf2 pathways

Other signaling pathways involved in the pathogenesis of atherosclerosis include the nuclear factor kappa B (NF-κB), cyclooxygenase (COX), and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways. These all have pro-inflammatory outputs in the form of cytokines, prostaglandins, etc. Their role in atherosclerosis progression is not as flagrant as that of RAAS, but they contribute to chronic inflammation at the lesion site, which is key in early-stage disease development. [9,10,25-27]

Therapeutic strategies

Therapeutic strategies seek to mitigate the risk factors associated with atherosclerosis development and/or directly impede disease progression in patients. This systematically includes lifestyle changes such as switching the patient's diet and exercise regimens to decrease LDL levels in the blood and avoid chronic inflammation. In addition to lifestyle changes, patients are often given medications to manage lipid metabolism and blood pressure. Care of high-risk patients necessitates more directed medications to reduce potential atherosclerotic vascular events. Aspirin or clopidogrel are examples of drugs that increase blood fluidity and reduce the risk of thrombus and coagulation that could otherwise cause heart attacks and strokes.

Medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins, and non-steroidal anti-inflammatory drugs (NSAIDs) can also be used to target the signaling pathways involved in the pathogenesis of atherosclerosis. Surgical techniques like endarterectomy (removal of plaque from the arterial walls) or stenting (introduction of a tubular structure inside a vessel to keep it open and prevent its obstruction) are reserved for more severe cases, where the state of the atherosclerotic vessel is such that the previously described strategies are insufficient for eliminating the deposited arterial plaques. However, surgeries on vessels are not always effective and can carry significant risks.

The effectiveness of lifestyle changes and medications in treating atherosclerosis depends on the individual. It is important to keep in mind that the current state of available medications does not allow them to be a substitute for lifestyle modifications. Furthermore, current medications can only address the problem once atherosclerotic tissues develop .[10,27,28]

Current atherosclerosis research is focused on the mechanisms promoting disease progression and the development of new therapeutic solutions to prevent such progression. Key areas of interest include the role of cholesterol-lowering drugs like statins and monitoring

the results achieved by changes in patient lifestyle (exercise, diet, etc.). Pharmaceutical approaches involve exploring the potential of drugs that target the RAAS pathway to inhibit the ACE enzyme and/or block the signaling abilities of Ang II.

There have also been advances in understanding the underlying causes of disease. As such, recent studies have looked at atherosclerosis from a molecular perspective and shone a light on new players in disease pathogenesis. The role of inflammation has notably been re-evaluated as one of the key drivers of disease, and other more obscure factors are suspected to be playing a greater role. Newcomers include epigenetic modifications, such as DNA methylation of genes involved in lipid metabolism and the link between an inflammatory environment, the gut microbiota, and pro-disease metabolites.

Recent developments and underlying causes

Recent developments in our understanding of atherosclerosis from a molecular perspective include the discovery of new players in disease pathogenesis. For example, research has shown that chronic inflammation, mediated by cytokines, is involved in the development of atherosclerosis. In addition, new evidence suggests that epigenetic modifications, such as DNA methylation, also play a role in disease development. Finally, the role of gut microbiota has been highlighted in some studies, suggesting that targeting the gut microbiome may be a potential therapeutic target for future investigation.

DNA methylation

DNA methylation is an epigenetic modification that involves the addition of methyl groups to DNA molecules. In the context of atherosclerosis, DNA methylation has been found to play a role in disease development. For example, DNA methylation is involved in regulating the expression of genes involved in lipid metabolism, such as the low-density lipoprotein receptor (LDL-R) gene, the apolipoprotein B (ApoB) gene, and the lipoprotein lipase (LPL) gene. In addition, DNA methylation has been linked to the upregulation of pro-inflammatory genes, such as the intercellular adhesion molecule-1 (ICAM-1) gene, the vascular cell adhesion molecule-1 (VCAM-1) gene, and the platelet-derived growth factor (PDGF) gene. These genes encode proteins that play a role in the pathogenesis of atherosclerosis.[29,30]

Gut Microbiome

Recent research has highlighted the role of the gut microbiome in the development of atherosclerosis, with studies identifying a link between imbalances in the gut microbiome (dysbiosis) and disease development. For example, gut dysbiosis can lead to an increase in pro-inflammatory cytokines that contribute to atherosclerosis. Certain species of gut bacteria are of particular interest due to the atherogenic metabolites they produce, such as Bacteroides fragilis, Enterococcus faecalis, and Escherichia coli. Metabolites produced by these bacterial include secondary bile acids, trimethylamine-N-oxide (TMAO), and trimethylamine (TMA). Similarly, fungal species like Candida albicans have also been linked to the development of atherosclerosis.

The mechanisms that underlie how these metabolites alter the course of atherosclerosis development are not fully understood. However, secondary bile acids can lead to an increase in cholesterol levels, while TMAO and TMA promote the accumulation of lipids in arterial walls. TMAO and TMA are also indicators of plaque stability, as higher levels in patients corelate with more unstable plaque characteristics. It has been suggested that TMAO might operate via the activation of Toll-like receptors or NLRP3 inflammasome signaling (IL-1b and IL-18 downstream activation), both of which are receptors of innate immunity with pro-inflammatory signaling potential. The MAPK pathway is also a candidate for TMAO activation, with pro-inflammatory and pro-cellular death outputs like IL-1, TNF-α, and C-reactive protein. [31–33]

About Revvity's Atherosclerosis Life Science Solutions

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Lipid transportation & Vasoconstriction/relaxation			
Target	Test Points	HTRF Part #	ALPHA Part #
ApoA1 (human) kit	500	64APAPEG	AL389C
ApoB (human) kit	500	64APBPEG	AL392C
ApoE (human) kit	500	64APOEPEG	AL395C
PCSK9 (human) kit	500	63ADK050PEG	AL270C
ApoC3 (human) kit	500	63ADK001PEG	
cGMP kit	500	62GM2PEG	
eNOS phospho S1177 kit	500	64ENOSS7PEG	
eNOS total kit	500	64ENOSTPEG	
Phospholamban phospho S16 (human) kit	500	64PLN16PEG	
Phospholamban phospho T17 (human) kit	500	63ADK074PEG	
Phospholamban total (human) kit	500	63ADK075PEG	
VASP phospho S157 kit	500	63ADK066PEG	
VASP phospho S239 kit	500	63ADK065PEG	
VASP total kit	500	63ADK067PEG	

Cell inflammation & Survival			
Target	Test Points	HTRF Part #	ALPHA Part #
IP-One kit	1000	62IPAPEB	AL3145D
AKT1 phospho S473 kit	500	63ADK078PEG	ALSU-PAKT1-C500
AKT1 total kit	500	63ADK079PEG	ALSU-TAKT1-B500
AKT1/2/3 phospho S473 kit	500		ALSU-PAKT-B500
AKT1/2/3 phospho T308 kit	500		ALSU-PAKT-A500
AKT1/2/3 phospho T450 kit	500		ALSU-PAKT-C500
AKT1/2/3 total kit	500		ALSU-TAKT-B500
mTOR phospho S2448 kit	500	64TORPEG	ALSU-PMTOR-C500
mTOR phospho S2481 kit	500		ALSU-PMTOR-B500
mTOR total kit	500		ALSU-TMTOR-B500
STAT1 phospho S727 kit	500		ALSU-PST1-B500

Cell inflammation & Survival			
Target	Test Points	HTRF Part #	ALPHA Part #
STAT1 phospho Y701 kit	500		ALSU-PST1-A500
STAT1 total kit	500	63ADK096PEG	ALSU-TST1-A500
STAT3 phospho Y705 kit	500		ALSU-PST3-A500
STAT3 total kit	500	64NT3PEG	ALSU-TST3-A500
STAT4 phospho Y693 kit	500		ALSU-PST4-A500
STAT4 total (human) kit	500		ALSU-TST4-A500
STAT5 phospho Y694/699 kit	500		ALSU-PST5-B500
STAT5 total kit	500		ALSU-TST5-A500
STAT6 phospho Y641 kit	500	64AT6PEG	ALSU-PST6-A500
STAT6 total (human) kit	500		ALSU-TST6-A500
AKT phospho S473 kit	500	64AKSPEG	
AKT phospho T308 kit	500	64AKTPEG	MPSU-PAKT-E500
AKT total kit	500	64NKTPEG	
AKT2 phospho S473 kit	500	63ADK080PEG	
AKT2 total kit	500	63ADK081PEG	
AKT3 phospho S473 kit	500	63ADK082PEG	
AKT3 total kit	500	63ADK083PEG	
STAT1 phospho Y701 kit	500	63ADK026PEG	
STAT3 phospho Y705 kit	500	62AT3PEG	
STAT5 phospho Y694 kit	500	64AT5PEG	
STAT6 total (human; mouse) kit	500	64STAT6TPEG	
AKT1/2/3 phospho S473 & AKT1 total kit	500		MPSU-PTAKT-M500
AKT1/2/3 phospho S473 & ERK 1/2 phospho T202/Y205 kit	500		MPSU-PAKER-K500

References

1. Choudhury RP, Lee JM, Greaves DR. Mechanisms of Disease: macrophage-derived foam cells emerging as therapeutic targets in atherosclerosis. Nat Rev Cardiol. 2005 Jun;2(6):309–15.
2. Gui Y, Zheng H, Cao RY. Foam Cells in Atherosclerosis: Novel Insights Into Its Origins, Consequences, and Molecular Mechanisms. Frontiers in Cardiovascular Medicine [Internet]. 2022 [cited 2023 Apr 27];9.
3. Yu XH, Fu YC, Zhang DW, Yin K, Tang CK. Foam cells in atherosclerosis. Clinica Chimica Acta. 2013 Sep 23;424:245–52.
4. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Exp Clin Cardiol. 2002;7(1):40–53.
5. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation. 1994 May;89(5):2462–78.
6. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. Journal of Internal Medicine. 2014;276(6):618–32.
7. Lee RT, Libby P. The Unstable Atheroma. Arteriosclerosis, Thrombosis, and Vascular Biology. 1997 Oct;17(10):1859–67.
8. Halvorsen B, Otterdal K, Dahl TB, Skjelland M, Gullestad L, Øie E, et al. Atherosclerotic plaque stability--what determines the fate of a plaque? Prog Cardiovasc Dis. 2008;51(3):183–94.
9. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis. Neth Heart J. 2017 Apr;25(4):231–42.
10. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. Circulation. 2007 Oct 16;116(16):1832–44.
11. Linton MF, Yancey PG, Davies SS, Jerome WG, Linton EF, Song WL, et al. The Role of Lipids and Lipoproteins in Atherosclerosis. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2023 Apr 14].
12. Hong FF, Liang XY, Liu W, Lv S, He SJ, Kuang HB, et al. Roles of eNOS in atherosclerosis treatment. Inflamm Res. 2019 Jun;68(6):429–41.
13. Öörni K, Kovanen PT. Aggregation Susceptibility of Low-Density Lipoproteins—A Novel Modifiable Biomarker of Cardiovascular Risk. J Clin Med. 2021 Apr 19;10(8):1769.
14. Bobryshev YV, Ivanova EA, Chistiakov DA, Nikiforov NG, Orekhov AN. Macrophages and Their Role in Atherosclerosis: Pathophysiology and Transcriptome Analysis. Biomed Res Int. 2016;2016:9582430.
15. Moore K, Sheedy F, Fisher E. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol. 2013 Oct;13(10):709–21.
16. Everett BM, MacFadyen JG, Thuren T, Libby P, Glynn RJ, Ridker PM. Inhibition of Interleukin-1β and Reduction in Atherothrombotic Cardiovascular Events in the CANTOS Trial. J Am Coll Cardiol. 2020 Oct 6;76(14):1660–70.
17. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol. 2011 Mar;12(3):204–12.
18. Ilhan F, Kalkanli ST. Atherosclerosis and the role of immune cells. World J Clin Cases. 2015 Apr 16;3(4):345–52.
19. Targeting the Immune System in Atherosclerosis: JACC State-of-the-Art Review - ScienceDirect [Internet]. [cited 2023 Apr 27].
20. An overview of the innate and adaptive immune system in atherosclerosis - Mohmmad-Rezaei - 2021 - IUBMB Life - Wiley Online Library [Internet]. [cited 2023 Apr 27].
21. Kojima Y, Weissman IL, Leeper NJ. The Role of Efferocytosis in Atherosclerosis. Circulation. 2017 Jan 31;135(5):476–89.

22. Tajbakhsh A, Rezaee M, Kovanen PT, Sahebkar A. Efferocytosis in atherosclerotic lesions: Malfunctioning regulatory pathways and control mechanisms. Pharmacology & Therapeutics. 2018 Aug 1;188:12–25.

23. Wang L, Li H, Tang Y, Yao P. Potential Mechanisms and Effects of Efferocytosis in Atherosclerosis. Frontiers in Endocrinology [Internet]. 2021 [cited 2023 Apr 27];11.

24. Bi Y, Chen J, Hu F, Liu J, Li M, Zhao L. M2 Macrophages as a Potential Target for Antiatherosclerosis Treatment. Neural Plast. 2019 Feb 21;2019:6724903.

25. Libby P. Inflammation in atherosclerosis. Nature. 2002 Dec 19;420(6917):868–74.

26. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis — from experimental insights to the clinic. Nat Rev Drug Discov. 2021 Aug;20(8):589–610.

27. Wiebe D. The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence. Daniel Steinberg. San Diego, CA, Academic Press-Elsevier, 2007, ISBN: 978-0-12-373979-7. Clinical Chemistry. 2009 Jul 1;55(7):1441–2.

28. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults | Circulation [Internet]. [cited 2023 Jan 25].

29. Tang H, Zeng Z, Shang C, Li Q, Liu J. Epigenetic Regulation in Pathology of Atherosclerosis: A Novel Perspective. Front Genet. 2021 Dec 15;12:810689.

30. Wierda RJ, Geutskens SB, Jukema JW, Quax PH, van den Elsen PJ. Epigenetics in atherosclerosis and inflammation. J Cell Mol Med. 2010 Jun;14(6a):1225–40.

31. Jonsson AL, Bäckhed F. Role of gut microbiota in atherosclerosis. Nat Rev Cardiol. 2017 Feb;14(2):79–87.

32. Sanchez-Rodriguez E, Egea-Zorrilla A, Plaza-Díaz J, Aragón-Vela J, Muñoz-Quezada S, Tercedor-Sánchez L, et al. The Gut Microbiota and Its Implication in the Development of Atherosclerosis and Related Cardiovascular Diseases. Nutrients. 2020 Feb 26;12(3):605.

33. Shen X, Li L, Sun Z, Zang G, Zhang L, Shao C, et al. Gut Microbiota and Atherosclerosis—Focusing on the Plaque Stability. Frontiers in Cardiovascular Medicine [Internet]. 2021 [cited 2023 Apr 26];8.

Revvity, Inc.
940 Winter Street
Waltham, MA 02451 USA

(800) 762-4000
www.revvity.com