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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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BEYOND CONTRACTILITY: PHENOTYPIC SWITCHING OF VASCULAR SMOOTH MUSCLE CELLS IN ATHEROSCLEROSIS

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Abstract.

Atherosclerosis is a complex and dynamic vascular disease driven by chronic inflammation, lipid accumulation, and profound cellular remodeling within the arterial wall. Among the cellular components of the atherosclerotic plaque, vascular smooth muscle cells (VSMCs) play a pivotal and increasingly recognized role. VSMCs display a high degree of phenotypic adaptability, enabling dynamic responses to vascular injury and metabolic stress.

Under conditions of vascular injury, oxidative stress, and inflammatory signaling, VSMCs undergo extensive phenotypic modulation characterized by loss of the contractile program and acquisition of synthetic, proliferative, and migratory properties. Recent lineage-tracing studies have further demonstrated that VSMCs can adopt diverse alternative phenotypes, including macrophage-like, foam cell-like, osteogenic, and mesenchymal-like states, thereby actively contributing to plaque growth, calcification, and structural remodeling.

This review summarizes current knowledge on the molecular mechanisms governing VSMC phenotypic modulation in atherosclerosis, highlighting key transcriptional regulators and signaling pathways such as PDGF signaling, TGF- β pathways, KLF4, TCF21, and regulatory non-coding RNAs. We also discuss the dual and context-dependent roles of VSMCs in plaque development, emphasizing their contribution to both disease progression and plaque stabilization through extracellular matrix production and fibrous cap formation.

Elucidating the mechanisms that control VSMC phenotypic plasticity may provide new opportunities for therapeutic intervention aimed at limiting plaque progression and improving plaque stability in atherosclerotic cardiovascular disease.

Key words. Vascular smooth muscle cells, phenotypic plasticity, phenotypic switching, atherosclerosis, plaque stability, transcription factors, PDGF signaling, TGF- β signaling, microRNAs, vascular remodeling.

Introduction.

Atherosclerosis remains the principal pathological basis of cardiovascular disease (CVD) and continues to represent a leading cause of morbidity and mortality worldwide [1]. For many years, atherosclerosis was primarily regarded as a lipid-driven inflammatory disorder of the arterial intima. However, advances in vascular biology have substantially expanded this

view, revealing a complex and highly dynamic disease process involving coordinated interactions among endothelial cells, immune cells, and vascular smooth muscle cells (VSMCs) within the arterial wall [2,3]. Among these cellular components, VSMCs have emerged as critical regulators of plaque development, progression, and stability.

VSMCs originate from mesenchymal precursors and are predominantly located within the medial layer of the arterial wall, where they maintain vascular tone and structural integrity. In healthy vessels, VSMCs exhibit a highly differentiated contractile phenotype characterized by the expression of specific cytoskeletal and contractile proteins, including α -smooth muscle actin (α -SMA), smooth muscle myosin heavy chain (SM-MHC), calponin, and transgelin (SM22 α) [4]. Under physiological conditions, these cells display minimal proliferative and migratory activity, thereby contributing to the maintenance of vascular homeostasis.

In response to vascular injury or pathological stimuli such as oxidative stress, inflammatory mediators, and modified lipoproteins VSMCs undergo profound phenotypic modulation. This process, commonly referred to as phenotypic switching, involves shift from a differentiated contractile state to a proliferative and matrix-producing phenotype [5,6]. During this transition, VSMCs downregulate contractile markers while upregulating genes associated with matrix remodeling and cellular plasticity.

The synthetic phenotype is associated with increased expression of molecules such as matrix metalloproteinases (MMPs), osteopontin (SPP1), and vimentin, as well as enhanced production of extracellular matrix components that contribute to neointimal formation and structural remodeling of the arterial wall [7]. These changes enable VSMCs to migrate from the media into the intima, where they play a crucial role in plaque formation and fibrous cap development. Depending on the local microenvironment, these processes may contribute either to plaque stabilization or to structural weakening of the lesion [8].

Recent advances in lineage-tracing techniques and single-cell transcriptomic analyses have revealed an even greater degree of VSMC plasticity than previously appreciated. Rather than existing solely in contractile or synthetic states, VSMCs can adopt multiple alternative phenotypes, including macrophage-like, osteogenic, chondrogenic, and mesenchymal stem-like phenotypes [9-11]. These findings have fundamentally changed

the conceptual framework of atherosclerosis by demonstrating that VSMC-derived cells constitute a substantial proportion of cells within atherosclerotic plaques.

Phenotypic plasticity of VSMCs is now recognized as a central adaptive mechanism that allows the vascular wall to respond to injury and maintain structural integrity. Nevertheless, under conditions of chronic inflammation and persistent metabolic stress, this adaptive response may become maladaptive, promoting pathological remodeling and accelerating disease progression [12]. The regulation of VSMC phenotypic transitions is controlled by complex signaling networks involving growth factors, transcription factors, and epigenetic regulators. Key pathways implicated in this process include PDGF-BB/PDGFR β signaling, TGF- β /Smad pathways, Notch signaling, and transcriptional regulators such as KLF4 and myocardin, along with multiple classes of non-coding RNAs [13-15].

Despite rapid progress in understanding VSMC biology, several important questions remain unresolved. It is still unclear which molecular mechanisms determine whether VSMC phenotypic transitions promote plaque stabilization or contribute to plaque vulnerability. Furthermore, the functional significance of VSMC-derived macrophage-like cells and their relationship to classical immune cells remain incompletely understood. Addressing these questions is essential for identifying new therapeutic strategies aimed at modulating VSMC behavior in atherosclerotic disease.

In this review, we provide an updated overview of the molecular mechanisms that govern VSMC phenotypic switching and discuss the functional consequences of this process in atherosclerosis. We also highlight emerging therapeutic approaches targeting VSMC phenotypic modulation and consider their potential role in preventing plaque progression and improving plaque stability in atherosclerotic cardiovascular disease.

Contractile and Synthetic Phenotypes of Vascular Smooth Muscle Cells.

Vascular smooth muscle cells (VSMCs) possess a remarkable capacity for phenotypic modulation in response to environmental cues. This plasticity represents a central feature of vascular biology, allowing the arterial wall to adapt to injury, hemodynamic stress, and inflammatory stimuli. Traditionally, VSMC behavior has been described within a binary framework consisting of two major phenotypes: the contractile phenotype and the synthetic phenotype. However, increasing experimental evidence indicates that this simplified dichotomy represents only part of a broader spectrum of phenotypic states that VSMCs may adopt under physiological and pathological conditions [4,5,9].

In healthy adult vessels, VSMCs predominantly exhibit a highly differentiated contractile phenotype that is essential for maintaining vascular tone, structural integrity, and mechanical stability of the arterial wall. This phenotype is characterized by the expression of specific cytoskeletal and contractile proteins, including α -smooth muscle actin (α -SMA), smooth muscle myosin heavy chain (SM-MHC / MYH11), calponin, transgelin (SM22 α), and desmin. The expression of these markers reflects a transcriptional program that maintains the specialized contractile

function of VSMCs within the medial layer of the vessel wall. Regulation of this program is largely controlled by the serum response factor (SRF)–myocardin signaling axis. Myocardin and myocardin-related transcription factors (MRTFs) act as key coactivators of SRF, binding to CArG box elements within the promoters of smooth muscle-specific genes and promoting the expression of contractile proteins [4,16,17]. Under physiological conditions, VSMCs in this differentiated state display minimal proliferative activity, limited migratory capacity, and relatively low levels of extracellular matrix secretion, thereby supporting vascular homeostasis.

Following vascular injury or exposure to pro-atherogenic stimuli, VSMCs undergo a profound phenotypic transition commonly referred to as phenotypic switching. Factors such as oxidized low-density lipoprotein (oxLDL), mechanical stress, platelet-derived growth factor-BB (PDGF-BB), and inflammatory cytokines can disrupt the contractile transcriptional program and promote the emergence of a synthetic phenotype [5,6,12]. This state is characterized by downregulation of classical contractile markers and increased expression of genes associated with cellular proliferation, migration, and extracellular matrix remodeling. Synthetic VSMCs demonstrate elevated levels of molecules such as osteopontin (SPP1), matrix metalloproteinases (particularly MMP-2 and MMP-9), vimentin, fibronectin, and fibrillar collagens including types I and III. These changes enable VSMCs to actively participate in neointimal formation and structural remodeling of the vascular wall [6,12].

Functionally, synthetic VSMCs exhibit enhanced proliferative and migratory properties, allowing them to move from the medial layer into the intima where they contribute to plaque formation and fibrous cap development. In the early phases of vascular injury, this response may serve an adaptive role by promoting repair and stabilizing the vessel wall. However, persistent activation of the synthetic phenotype in chronic inflammatory conditions such as atherosclerosis can drive maladaptive remodeling. Excessive extracellular matrix remodeling, increased proteolytic activity, and pro-inflammatory signaling may contribute to plaque progression, vascular stiffening, and ultimately plaque destabilization [9,18].

Recent technological advances, particularly lineage-tracing approaches and single-cell RNA sequencing, have revealed that VSMC phenotypic modulation extends far beyond the classical contractile–synthetic paradigm. Instead, VSMCs appear capable of adopting a diverse array of alternative phenotypic states during atherosclerosis. Among the most extensively described are macrophage-like VSMCs expressing markers such as CD68 and LGALS3, which can participate in lipid uptake and foam cell formation within the atherosclerotic plaque [6,10]. Other VSMC-derived phenotypes include osteogenic or chondrocyte-like cells characterized by the expression of osteogenic transcription factors such as Runx2 and alkaline phosphatase (ALPL), contributing to vascular calcification [11,18]. Additionally, subsets of VSMCs have been shown to acquire mesenchymal stem-like characteristics, displaying progenitor-like properties and multilineage differentiation potential [9,13].

The discovery of this extensive phenotypic heterogeneity has significantly reshaped the understanding of VSMC biology

in atherosclerosis. Rather than acting solely as structural components of the vessel wall, VSMCs are now recognized as highly dynamic participants in plaque evolution. Their ability to transition between multiple phenotypic states suggests that local environmental cues within the plaque microenvironment play a decisive role in determining the functional outcomes of VSMC modulation. Consequently, deciphering the mechanisms that regulate these transitions remains a critical objective for understanding plaque biology and identifying novel therapeutic targets.

Molecular Pathways of Phenotypic Switching.

The remarkable phenotypic plasticity of vascular smooth muscle cells (VSMCs) is governed by a complex network of signaling pathways, transcription factors, cytoskeletal regulators, and epigenetic mechanisms. These molecular systems integrate environmental stimuli such as inflammatory mediators, growth factors, biomechanical stress, and lipid accumulation, thereby controlling the transition from a contractile phenotype toward synthetic or alternative cellular states. Dysregulation of these regulatory networks plays a central role in vascular remodeling and the progression of atherosclerosis.

Among the most prominent drivers of phenotypic modulation is the platelet-derived growth factor-BB (PDGF-BB)/PDGFR β signaling axis. Activation of PDGFR β by PDGF-BB triggers multiple downstream pathways, including PI3K/AKT, MAPK/ERK, and STAT signaling cascades, which collectively stimulate VSMC proliferation, migration, and dedifferentiation. A critical consequence of PDGF signaling is the suppression of the myocardin–serum response factor (SRF) transcriptional complex, which normally maintains the contractile gene expression program. Disruption of this regulatory axis leads to decreased expression of contractile markers such as α -smooth muscle actin (α -SMA), smooth muscle myosin heavy chain (SM-MHC), and calponin, while promoting the upregulation of genes associated with extracellular matrix remodeling and cellular plasticity, including osteopontin and matrix metalloproteinases [4-6,19].

In contrast to PDGF signaling, transforming growth factor- β (TGF- β) exerts complex and context-dependent effects on VSMC phenotype. Under physiological conditions, TGF- β signaling through Smad2/3 promotes contractile differentiation by enhancing the transcription of smooth muscle–specific genes. However, within the inflammatory and metabolically altered microenvironment of the atherosclerotic plaque, TGF- β may contribute to phenotypic modulation and even osteogenic reprogramming of VSMCs. These divergent effects are largely determined by interactions with other signaling pathways, including bone morphogenetic protein (BMP), PDGF, and Notch signaling, highlighting the highly context-dependent nature of TGF- β activity in vascular pathology [20].

At the transcriptional level, several key regulatory factors orchestrate the shift between contractile and synthetic phenotypes. Myocardin acts as a master regulator of smooth muscle differentiation by functioning as a potent coactivator of SRF and driving the expression of contractile genes required for the maintenance of the differentiated VSMC phenotype [17]. In contrast, the transcription factor Kruppel-like factor

4 (KLF4) plays a central role in promoting phenotypic switching. KLF4 antagonizes myocardin–SRF signaling and facilitates the transition toward synthetic or macrophage-like states. Its expression is strongly induced by oxidative stress, inflammatory cytokines, and vascular injury, and experimental studies have demonstrated that KLF4 activation is essential for the loss of contractile identity observed during atherosclerosis development [8].

Another important transcriptional regulator of VSMC phenotypic modulation is transcription factor 21 (TCF21). Identified through genome-wide association studies as a genetic susceptibility locus for coronary artery disease, TCF21 promotes VSMC migration and phenotypic remodeling by repressing contractile gene expression and facilitating cellular dedifferentiation. Evidence suggests that TCF21-driven transitions may contribute to the emergence of fibroblast-like VSMC-derived cells within atherosclerotic plaques, which participate in extracellular matrix deposition and fibrous cap formation [10,13].

Cytoskeletal dynamics also play an essential role in regulating VSMC phenotype. Actin polymerization status directly influences the activity of myocardin-related transcription factors (MRTF-A and MRTF-B), which function as cofactors of SRF. In contractile VSMCs, polymerized actin allows MRTFs to translocate into the nucleus and activate SRF-dependent transcription of contractile genes. Conversely, actin depolymerization leads to cytoplasmic sequestration of MRTFs, resulting in reduced transcription of contractile proteins and promoting the transition toward a synthetic phenotype [17,23]. This mechanotransduction mechanism provides a critical link between cytoskeletal organization, biomechanical forces, and gene regulation.

Beyond non-coding RNAs, classical epigenetic mechanisms also play a critical role in regulating VSMC phenotypic plasticity. DNA methylation, histone modifications, and chromatin remodeling contribute to the transcriptional control of genes associated with contractile differentiation and phenotypic switching. Increased activity of DNA methyltransferases (DNMTs) has been associated with suppression of contractile genes such as MYH11 and ACTA2, thereby promoting transition toward synthetic phenotypes. In parallel, histone deacetylases (HDACs) regulate chromatin accessibility and influence the expression of genes involved in proliferation, migration, and extracellular matrix remodeling. Experimental studies have shown that dysregulated histone acetylation and chromatin remodeling facilitate VSMC dedifferentiation and contribute to pathological vascular remodeling during atherosclerosis [7,23]. The microRNAs miR-143 and miR-145 are highly expressed in differentiated contractile VSMCs and promote maintenance of the contractile phenotype by reinforcing myocardin–SRF signaling and suppressing proliferative pathways [14,24]. In contrast, miR-221 and miR-222 are upregulated in response to PDGF signaling and promote phenotypic switching by inhibiting contractile gene expression and facilitating cell cycle progression [24]. The major molecular and epigenetic mechanisms involved in VSMC phenotypic switching in atherosclerosis are summarized in Figure 1.

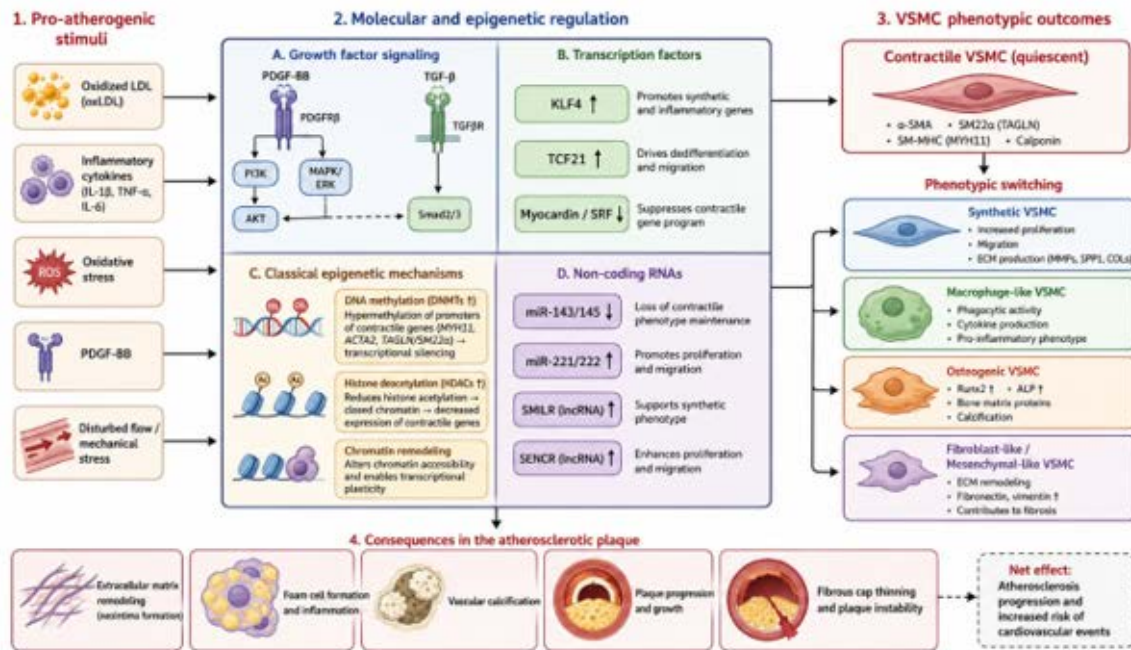


Figure 1. Molecular and epigenetic mechanisms regulating vascular smooth muscle cell (VSMC) phenotypic switching in atherosclerosis. Pro-atherogenic stimuli, including oxidized LDL, inflammatory cytokines, oxidative stress, and disturbed flow, activate signaling pathways, transcription factors, and epigenetic regulators that suppress the contractile phenotype and promote transition toward synthetic, macrophage-like, osteogenic, and mesenchymal-like VSMC states, contributing to plaque progression, calcification, and instability.

Table 1. Major Phenotypes of Vascular Smooth Muscle Cells in Atherosclerosis.

Phenotype	Key Markers	Functional Characteristics	Role in Atherosclerosis
Contractile VSMC	α -SMA, SM-MHC (MYH11), calponin, SM22 α	Maintains vascular tone, low proliferation and migration	Stabilizes vessel wall and fibrous cap
Synthetic VSMC	Osteopontin (SPP1), vimentin, fibronectin, MMPs	High proliferation, migration, ECM production	Contributes to neointima formation and plaque growth
Macrophage-like VSMC	CD68, LGALS3	Lipid uptake, foam cell formation	Associated with lipid accumulation, impaired phagocytic function, and increased plaque complexity
Osteogenic VSMC	Runx2, ALPL, osteocalcin	Mineral deposition and calcification	Promotes mineral deposition and contributes to vascular stiffening and altered biomechanical properties of the plaque
Mesenchymal stem-like VSMC	Sca-1, stem cell-associated markers	Progenitor-like properties, multilineage potential	May contribute to plaque heterogeneity

Table 2. Key Molecular Regulators of VSMC Phenotypic Switching.

Pathway / Regulator	Mechanism	Effect on VSMC Phenotype	Key References
PDGF-BB / PDGFR β	Activates PI3K/AKT and MAPK signaling	Promotes dedifferentiation and proliferation	[5,19,30]
TGF- β / Smad	Smad-dependent transcription	Maintains contractile phenotype but context-dependent	[20]
KLF4	Represses myocardin-SRF complex	Induces synthetic and macrophage-like states	[8]
TCF21	Transcriptional regulator	Promotes fibroblast-like phenotypes	[10]
MRTF / SRF	Regulates contractile gene transcription	Maintains contractile differentiation	[17]

Table 3. Epigenetic Regulators of VSMC Phenotypic Switching.

Epigenetic Factor	Type	Functional Role
DNMT1	DNA methyltransferase	Suppresses contractile gene expression and promotes synthetic phenotype
HDACs	Histone deacetylases	Regulate chromatin accessibility and promote VSMC dedifferentiation
Histone acetylation	Histone modification	Modulates transcriptional plasticity and VSMC phenotype
miR-143/145	microRNA	Maintains contractile phenotype
miR-221/222	microRNA	Promotes proliferation and synthetic phenotype
SMILR	lncRNA	Regulates VSMC proliferation
SENCR	lncRNA	Maintains vascular cell differentiation

Table 4. Therapeutic Targets for Modulating VSMC Phenotype.

Target	Mechanism	Potential Therapeutic Effect
PDGFR β inhibitors	Block VSMC proliferation	Reduce neointima formation
KLF4 inhibition	Preserve contractile phenotype	Reduce foam cell formation
miR-143/145 restoration	Promote differentiation	Improve plaque stability
Drug-eluting stents	Local drug delivery	Control VSMC proliferation

Long non-coding RNAs (lncRNAs) have also emerged as important modulators of VSMC behavior. Molecules such as smooth muscle-induced lncRNA enhances replication (SMILR) and smooth muscle and endothelial cell-enriched migration/differentiation-associated lncRNA (SENCR) regulate VSMC proliferation, migration, and phenotypic transitions through interactions with transcription factors and chromatin-modifying complexes [25]. These findings illustrate the growing importance of epigenetic mechanisms in shaping VSMC responses to vascular injury.

Collectively, phenotypic switching of VSMCs is orchestrated by a tightly integrated molecular framework involving growth factor signaling, transcriptional control, cytoskeletal dynamics, and epigenetic regulation. While these mechanisms enable adaptive responses to vascular injury, their dysregulation contributes to pathological vascular remodeling and the progression of atherosclerotic disease. Understanding the key regulatory nodes within these networks may provide new opportunities for therapeutic strategies aimed at modulating VSMC phenotype and improving plaque stability.

Phenotypic Plasticity and Disease Progression.

The phenotypic plasticity of vascular smooth muscle cells (VSMCs) has emerged as a central determinant of atherosclerotic plaque development and progression. Once considered passive structural elements of the arterial wall, VSMCs are now recognized as highly dynamic participants in multiple stages of atherogenesis. Their ability to undergo phenotypic transitions, migrate from the media to the intima, proliferate, and remodel the extracellular matrix allows them to shape both the architecture and biological behavior of atherosclerotic lesions [4,5,9].

During the early stages of atherogenesis, endothelial dysfunction promotes the accumulation of lipids and inflammatory mediators within the arterial intima. In response to these stimuli, VSMCs migrate from the medial layer into the intima, where they undergo phenotypic modulation characterized by loss of the contractile phenotype and acquisition of a synthetic state. These synthetic VSMCs display enhanced proliferative and migratory capacities and contribute to neointimal expansion and fibrous cap formation [5,6]. In addition, they produce substantial amounts of extracellular matrix components, including collagen and fibronectin, which help maintain structural stability of developing plaques.

As atherosclerosis progresses, however, the inflammatory and oxidative environment within the plaque drives further phenotypic diversification of VSMCs. Evidence from lineage-tracing studies and single-cell transcriptomic analyses has demonstrated that VSMCs represent a major source of several non-classical cell populations within atherosclerotic lesions. These include cells with macrophage-like, osteogenic, and mesenchymal-like characteristics that arise through transdifferentiation of medial VSMCs [9,10,11,26].

Increasing evidence suggests that phenotypically modulated VSMCs actively participate in bidirectional communication with immune cells within the atherosclerotic plaque microenvironment. Pro-inflammatory cytokines released by monocyte-derived macrophages and T lymphocytes, including TNF- α , IL-1 β , and IFN- γ , promote VSMC dedifferentiation and suppress the expression of contractile genes. In turn, synthetic and macrophage-like VSMCs can produce inflammatory mediators, chemokines, and matrix-degrading enzymes that further amplify local inflammatory responses.

In addition to soluble mediators, direct cell-cell interactions and extracellular vesicle-mediated signaling have emerged as important regulators of plaque biology. These intercellular communication networks may contribute to chronic inflammation, extracellular matrix remodeling, and plaque destabilization. Thus, VSMCs should not be regarded solely as structural vascular cells, but rather as dynamic immunomodulatory participants in atherosclerotic disease progression.

Among the most extensively studied are macrophage-like VSMCs, which express markers such as CD68 and LGALS3 and are capable of lipid uptake and foam cell formation. Despite their phenotypic resemblance to monocyte-derived macrophages, these cells display distinct transcriptional signatures and reduced phagocytic capacity, suggesting that they may contribute to inflammatory amplification within plaques without performing classical immune functions [26,27]. Consequently, VSMC-derived macrophage-like cells may represent an important source of dysfunctional foam cells during atherogenesis.

Another important phenotypic trajectory involves osteogenic or chondrocyte-like transdifferentiation of VSMCs. This process has been implicated in vascular calcification, a common feature of advanced atherosclerotic lesions and an independent predictor of cardiovascular events. Osteogenic VSMCs express bone-associated markers such as Runx2 and alkaline phosphatase and contribute to mineral deposition within the arterial wall, promoting vascular stiffness and altering plaque mechanical properties [18,28].

The remarkable phenotypic flexibility of VSMCs likely represents an adaptive mechanism that allows the vascular wall to respond to injury and maintain structural integrity. However, under conditions of persistent inflammation, oxidative stress, and lipid accumulation, this adaptive response may become maladaptive, driving pathological vascular remodeling and plaque destabilization [29-32].

Accumulating evidence suggests that sex-related biological differences may also influence VSMC phenotypic modulation during atherosclerosis. Estrogen signaling has been shown to exert protective vascular effects by suppressing VSMC proliferation, reducing inflammatory activation, and promoting maintenance of the contractile phenotype through estrogen

receptor-dependent pathways. In contrast, loss of estrogen activity, particularly after menopause, has been associated with enhanced vascular remodeling and increased susceptibility to atherosclerotic progression. Experimental studies further indicate that sex-dependent differences in gene expression and hormonal signaling may contribute to variations in plaque composition, calcification, and vascular stiffness between males and females. Nevertheless, the precise mechanisms linking sex hormones and VSMC plasticity remain incompletely understood and require further investigation [33,34].

Importantly, the direction of VSMC phenotypic transitions is strongly influenced by the local plaque microenvironment. Factors such as oxidized lipoproteins, inflammatory cytokines, disturbed hemodynamic flow, and extracellular matrix composition collectively shape VSMC behavior. Studies have shown that VSMCs located within the fibrous cap often retain features of the contractile phenotype and contribute to plaque stabilization by producing structural matrix proteins. In contrast, VSMCs that undergo extensive dedifferentiation or transdifferentiation are more frequently associated with plaque vulnerability and progression [12,26,29].

These observations highlight the context-dependent roles of VSMCs in atherosclerosis. While certain phenotypic states contribute to vascular repair and plaque stabilization, others promote inflammation, calcification, and structural weakening of the lesion. Understanding the signals that determine these divergent outcomes remains a major challenge in vascular biology and represents a key step toward developing new therapeutic approaches aimed at modulating VSMC behavior in atherosclerotic disease.

Much of the current understanding of VSMC phenotypic plasticity has been derived from lineage-tracing studies performed in murine models of atherosclerosis, particularly ApoE^{-/-} and LDLR^{-/-} mice. These experimental systems have provided direct evidence that medial VSMCs can undergo extensive phenotypic transitions toward macrophage-like, osteogenic, and mesenchymal-like states during plaque development.

In human atherosclerotic plaques, however, direct lineage-tracing approaches are not feasible. Consequently, evidence for VSMC transdifferentiation in humans relies primarily on single-cell transcriptomics, immunophenotypic analyses, and co-expression of smooth muscle and macrophage-associated markers within plaque-derived cells. Several studies have demonstrated the presence of ACTA2⁺/CD68⁺ and MYH11⁺/LGALS3⁺ cell populations in advanced human lesions, supporting the translational relevance of VSMC phenotypic modulation observed in experimental models. Nevertheless, the precise contribution of these populations to plaque progression and instability in humans remains incompletely understood.

Therapeutic Implications.

Recognition of the active role of vascular smooth muscle cells in atherosclerosis has led to a growing interest in therapeutic strategies aimed at modulating VSMC phenotype. While current treatments for atherosclerotic cardiovascular disease primarily target lipid metabolism and systemic inflammation, emerging evidence suggests that stabilizing protective VSMC phenotypes

may represent an additional therapeutic avenue for preventing plaque rupture and adverse cardiovascular events.

Experimental studies have demonstrated that preservation of the contractile phenotype or controlled promotion of a matrix-producing synthetic phenotype can enhance fibrous cap integrity and reduce lesion progression [12,26]. These findings have stimulated efforts to identify molecular targets that regulate VSMC phenotypic transitions.

One potential strategy involves modulation of growth factor signaling pathways implicated in VSMC dedifferentiation. Inhibition of the PDGF-BB/PDGFR β signaling axis has been shown in experimental models to reduce VSMC proliferation and neointimal formation [19,30]. However, systemic inhibition of PDGF signaling may interfere with physiological repair processes and produce off-target effects, highlighting the importance of developing cell-specific or locally targeted delivery systems.

In contrast, activation of TGF- β signaling has been explored as a means to reinforce the contractile phenotype through Smad2/3-dependent transcriptional pathways. Nevertheless, the pleiotropic and context-dependent nature of TGF- β signaling complicates its therapeutic application. Depending on the cellular environment, TGF- β may also promote fibrosis or osteogenic differentiation, particularly under conditions of oxidative stress or disturbed flow [18,28].

Transcription factors that regulate VSMC plasticity have also attracted significant attention as potential therapeutic targets. The transcription factor KLF4 plays a central role in driving phenotypic switching toward synthetic and macrophage-like states. Experimental deletion of Klf4 in lineage-tracing models has been shown to preserve contractile gene expression and reduce the formation of foam cell-like VSMCs within atherosclerotic plaques [8]. Similarly, modulation of TCF21 activity has been proposed as a strategy to influence the balance between stabilizing fibroblast-like VSMC derivatives and pathogenic phenotypic states within plaques [22,29].

Epigenetic regulation represents another promising therapeutic direction. Non-coding RNAs, particularly microRNAs, have emerged as key regulators of VSMC phenotype. Restoration of miR-143 and miR-145 expression has been shown to promote the contractile phenotype and reduce lesion size in experimental models, whereas inhibition of miR-221 and miR-222 suppresses VSMC proliferation and matrix degradation [24,31]. Long non-coding RNAs such as SMILR have also been implicated in the regulation of VSMC proliferation and may represent additional therapeutic targets [25].

Beyond molecular targeting, biomaterial-based strategies provide opportunities for localized modulation of VSMC behavior. Drug-eluting stents designed to regulate VSMC proliferation and phenotype are being explored as a means to reduce restenosis and improve long-term vascular healing following percutaneous interventions [32].

Despite these promising developments, several challenges remain before VSMC-targeted therapies can be translated into clinical practice. The phenotypic states of VSMCs are highly dynamic and context-dependent, and reliable markers distinguishing protective from pathogenic phenotypes remain limited. In addition, most mechanistic insights have been

derived from experimental models, and the extent to which these findings apply to human atherosclerosis remains an area of active investigation.

Nevertheless, therapeutic modulation of VSMC phenotype represents an emerging frontier in cardiovascular medicine. A deeper understanding of the molecular and environmental cues that govern VSMC plasticity may enable the development of targeted interventions that complement lipid-lowering and anti-inflammatory therapies, ultimately improving outcomes in patients with atherosclerotic cardiovascular disease.

Emerging therapeutic strategies increasingly focus on localized and cell-specific modulation of pathogenic VSMC phenotypes in order to minimize systemic adverse effects. Nanoparticle-based drug delivery systems have attracted considerable attention as potential tools for targeted delivery of small molecules, siRNAs, and microRNA mimics directly into atherosclerotic plaques. Such approaches may allow selective suppression of pathogenic signaling pathways, including KLF4-mediated phenotypic switching, while preserving physiological vascular repair mechanisms.

In parallel, advances in biomaterial engineering have led to the development of next-generation drug-eluting stents capable not only of inhibiting excessive VSMC proliferation, but also of modulating VSMC phenotype toward more stable and reparative states. These technologies may ultimately provide more precise therapeutic control over vascular remodeling following arterial injury and during plaque progression.

Recent advances in spatial transcriptomics and multimodal single-cell technologies are further expanding current understanding of VSMC heterogeneity within atherosclerotic plaques. Unlike conventional single-cell sequencing, these approaches preserve spatial information and allow characterization of localized cellular interactions within the plaque microenvironment. Such technologies may help identify spatially distinct pathogenic and protective VSMC subpopulations, thereby improving the precision of future therapeutic targeting.

Conclusion.

Over the past decade, vascular smooth muscle cells (VSMCs) have emerged as central regulators of atherosclerotic plaque biology rather than passive structural components of the arterial wall. Their capacity for phenotypic plasticity enables them to respond dynamically to vascular injury and environmental stress, contributing to diverse processes such as lesion formation, extracellular matrix remodeling, fibrous cap formation, inflammation, and vascular calcification. Consequently, VSMCs play a pivotal role in determining the structural integrity and clinical fate of atherosclerotic plaques.

As discussed in this review, phenotypic modulation of VSMCs is governed by an intricate regulatory network involving growth factor signalling pathways, transcriptional regulators, cytoskeletal dynamics, and epigenetic mechanisms. Signalling axes such as PDGF-BB/PDGFR β and TGF- β /Smad, transcription factors including KLF4 and TCF21, and regulatory non-coding RNAs collectively shape VSMC behavior within the atherosclerotic microenvironment. These molecular pathways influence whether VSMCs adopt phenotypes that promote

plaque stability through extracellular matrix production or contribute to inflammation, lipid accumulation, and structural destabilization.

Importantly, recent advances in lineage-tracing techniques and single-cell transcriptomics have revealed that VSMC phenotypic modulation extends far beyond the traditional contractile–synthetic paradigm. Instead, VSMCs exhibit a diverse spectrum of intermediate and alternative states, including macrophage-like, osteogenic, and stem-like phenotypes. Recognition of this phenotypic diversity has significantly reshaped current concepts of plaque biology and highlights the need for more refined classification of VSMC-derived cell populations in atherosclerosis.

Despite these advances, several critical challenges remain. A deeper understanding of the signals that determine whether VSMC phenotypic transitions promote plaque stabilization or disease progression is still required. Furthermore, translating experimental findings into clinically effective therapies remains difficult due to the complex, context-dependent nature of VSMC plasticity and the limitations of current experimental models.

Nevertheless, targeting the molecular mechanisms that govern VSMC phenotypic switching represents a promising therapeutic direction. Interventions aimed at preserving protective VSMC phenotypes or preventing maladaptive transdifferentiation may complement existing lipid-lowering and anti-inflammatory strategies. Ultimately, improved insight into VSMC biology may open new avenues for stabilizing atherosclerotic plaques and reducing the burden of cardiovascular disease.

Future progress in this field will likely depend on integration of lineage-tracing studies, spatial transcriptomics, and human plaque analyses to better define functionally distinct VSMC subpopulations. Improved understanding of the molecular determinants that drive protective versus pathogenic phenotypic transitions may ultimately enable development of precision therapies aimed at stabilizing atherosclerotic plaques without impairing physiological vascular repair.

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