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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 ВИНИТИ 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 ВИНИТИ 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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ 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 შეღებვის 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 ფჩხილებში 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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PHENOTYPIC SWITCHING OF VASCULAR SMOOTH MUSCLE CELLS: KEY MECHANISM IN ATHEROSCLEROSIS PROGRESSION

Chigareva Irina S.[1], Karelova Alina D.[1], Zeinalova Narmin E.[1], Abdulkhadzhiev Akhmed A.[2], Isaev Akhmed Kh.[2], Kurbanov Gadzhi K.[3], Israpilov Ibragim R.[2], Dagaeva Imani I.[2], Dashaeva Maryam I.[2], Petchina Anastasia I.[1], Delimkhanov Rustam S.-Kh.[4], Musaev Emin R.[4], Pandyashkina Karina G.[1]

[1]*North-Western State Medical University named after I.I. Mechnikov, Saint-Petersburg, Russia*

[2]*Kadyrov Chechen State University, Grozny, Russia*

[3]*S.M. Kirov Military Medical Academy, Saint-Petersburg, Russia*

[4]*Ingush State University, Magas, Russia*

Abstract.

Vascular smooth muscle cells (VSMCs) have emerged as key contributors to atherosclerosis through their remarkable phenotypic plasticity. In response to vascular injury, inflammation, and metabolic stress, VSMCs transition from a differentiated contractile phenotype to a synthetic, proliferative, and migratory state. Recent evidence reveals that VSMCs also transdifferentiate into macrophage-like, osteogenic, and mesenchymal-like phenotypes, actively shaping plaque composition and stability. This review provides a comprehensive analysis of the molecular mechanisms underlying VSMC phenotypic modulation, including PDGF-BB, TGF-β, KLF4, TCF21, and non-coding RNAs. We also explore the dual roles of VSMCs in promoting vascular repair and contributing to disease progression. Understanding these processes offers novel insights into plaque pathobiology and presents promising therapeutic targets to stabilize atherosclerotic lesions and prevent adverse cardiovascular events.

Key words. Vascular smooth muscle cells, phenotypic switching, atherosclerosis, plaque stability, PDGF, TGF-β, KLF4, TCF21, microRNAs, vascular remodeling.

Introduction.

Atherosclerosis remains a leading contributor to cardiovascular disease (CVD) morbidity and mortality, accounting for millions of deaths annually worldwide [1]. Traditionally viewed as a lipid-driven and immune-mediated disorder of the intima, recent decades have fundamentally reshaped our understanding of the disease as a complex, multicellular process involving dynamic interactions among endothelial cells, immune cells, and vascular smooth muscle cells (VSMCs) [2,3]. Among these, VSMCs, long thought to be passive, contractile structural elements, have emerged as active participants in both the initiation and progression of atherosclerotic lesions.

VSMCs originate from the mesenchyme and reside predominantly in the medial layer of the arterial wall, where they contribute to vascular tone and elasticity through a highly differentiated, contractile phenotype characterized by the expression of α-smooth muscle actin (α-SMA), smooth muscle myosin heavy chain (SM-MHC), calponin, and transgelin (SM22α) [4]. Under physiological conditions, VSMCs exhibit low rates of proliferation and migration, maintaining vessel homeostasis. However, in response to pathological stimuli such as mechanical injury, oxidative stress, modified lipids (e.g., oxidized LDL), and inflammatory cytokines, VSMCs undergo a process of phenotypic switching, a highly regulated, plastic transformation in which they lose contractile markers and acquire synthetic, migratory, and pro-inflammatory characteristics [5,6].

The synthetic phenotype is marked by upregulation of matrix metalloproteinases (MMPs), osteopontin (SPP1), vimentin, and increased production of extracellular matrix components, facilitating tissue remodeling and neointima formation [7]. Importantly, VSMCs also acquire the capacity to proliferate and migrate into the intima, where they contribute to plaque development, fibrous cap formation, and potentially, plaque destabilization [8]. Moreover, evidence from fate-mapping and single-cell RNA sequencing studies has revealed that VSMCs can adopt alternative phenotypes beyond the synthetic type, including macrophage-like, osteogenic, chondrogenic, and even mesenchymal stem-like states [9-11].

This phenotypic plasticity, once considered aberrant, is now viewed as an essential feature of VSMCs that enables context-dependent responses during vascular injury and repair. However, this same plasticity can drive maladaptive remodeling in chronic inflammatory settings like atherosclerosis [12]. Notably, the balance between beneficial and detrimental VSMC phenotypes appears to be regulated by intricate signaling networks, including PDGF-BB/PDGFRβ, TGF-β/Smad, Notch, KLF4, and myocardin pathways, as well as a host of non-coding RNAs and epigenetic mechanisms [13-15].

Despite the accumulating evidence, critical questions remain. What dictates whether VSMCs contribute to plaque stability or rupture? Can pharmacologic targeting of phenotypic modulation reverse or halt disease progression? Do VSMC-derived cells contribute to immune surveillance or simply mimic immune phenotypes without functional equivalency?

Given the central and multifaceted role of VSMCs in vascular disease, a thorough re-examination of their contribution to atherogenesis is urgently needed. This review provides a comprehensive synthesis of the molecular mechanisms underlying VSMC phenotypic switching, its functional consequences in atherosclerosis, and emerging therapeutic avenues aimed at modulating this process. Understanding these dynamics holds great promise for the development of novel, cell-targeted strategies to mitigate the burden of atherosclerotic cardiovascular disease.

Contractile vs. Synthetic Phenotype.

Vascular smooth muscle cells (VSMCs) are uniquely capable of undergoing dynamic phenotypic transitions in response to environmental stimuli. This plasticity, central to both vascular repair and disease progression, is classically described as a switch between two major phenotypes: contractile and

synthetic. However, accumulating evidence suggests that this binary framework represents only part of a broader and more complex phenotypic spectrum [4,5,9].

Contractile Phenotype: Maintaining Vascular Homeostasis. In healthy adult vessels, VSMCs adopt a highly differentiated, contractile phenotype, characterized by the expression of cytoskeletal and contractile proteins that are essential for regulating vascular tone, elasticity, and mechanical integrity. Key markers include:

1. α-smooth muscle actin (α-SMA).
2. Smooth muscle myosin heavy chain (SM-MHC / MYH11).
3. Calponin.
4. Transgelin (SM22α).
5. Desmin.

This phenotype is regulated by a transcriptional network involving serum response factor (SRF) and myocardin, as well as its coactivators, myocardin-related transcription factors (MRTFs), which bind to CArG elements within the promoters of contractile genes [4,16,17]. Under physiological conditions, VSMCs in this state exhibit low rates of proliferation, migration, and matrix secretion.

Synthetic Phenotype: Remodeling and Repair – or Disease. Following vascular injury or chronic exposure to atherogenic factors such as oxidized LDL, mechanical stretch, PDGF-BB, or inflammatory cytokines, VSMCs lose their contractile identity and adopt a synthetic phenotype [5,6,12]. This state is marked by downregulation of contractile genes, upregulation of matrix-remodeling and inflammatory molecules, including:

1. Osteopontin (SPP1).
2. Matrix metalloproteinases (MMP-2, MMP-9).
3. Vimentin.
4. Fibronectin.
5. Type I and III collagen.

Synthetic VSMCs exhibit enhanced proliferation and migration, and they actively participate in neointimal formation, ECM remodeling, and plaque development [6,12]. While initially beneficial for repair, prolonged activation promotes maladaptive remodeling and contributes to plaque instability, calcification, and vascular stiffening [9,18].

Beyond the Dichotomy: VSMC Heterogeneity in Atherosclerosis. Advances in single-cell RNA sequencing and fate-mapping techniques have revealed that VSMC phenotypic modulation is not limited to a simple contractile-synthetic shift. Instead, VSMCs can acquire multiple alternative phenotypes:

1. Macrophage-like VSMCs (CD68+, LGALS3+), involved in lipid uptake and foam cell formation [6,10].
2. Chondrocyte-like or osteoblast-like VSMCs, contributing to vascular calcification (Runx2+, ALPL+) [11,18].
3. Mesenchymal stem-like states, associated with progenitor-like behavior and multilineage potential [9,13].

This plasticity underscores the complexity of VSMC contributions to plaque biology and highlights the importance of context-dependent signals in shaping disease outcomes. It also raises critical questions about the functional significance of these transdifferentiated states – whether they are adaptive, pathogenic, or both.

Molecular Pathways of Phenotypic Switching.

The ability of vascular smooth muscle cells (VSMCs) to undergo phenotypic switching is tightly regulated by a complex network of signaling pathways, transcription factors, and epigenetic regulators. These molecular mechanisms interpret environmental stimuli and govern the transition from a contractile to a synthetic or alternative phenotype, thereby playing a pivotal role in vascular remodeling and atherosclerosis.

One of the key pathways involved in initiating phenotypic modulation is the platelet-derived growth factor-BB (PDGF-BB)/PDGFRβ axis. Binding of PDGF-BB to its receptor leads to activation of downstream effectors such as PI3K/AKT, MAPK/ERK, and STAT pathways, which collectively promote VSMC proliferation, migration, and dedifferentiation. Importantly, this signaling cascade suppresses the myocardin–serum response factor (SRF) complex, which is central to maintaining the contractile gene expression program. As a result, expression of α-smooth muscle actin (α-SMA), smooth muscle myosin heavy chain (SM-MHC), and calponin is downregulated, and synthetic markers such as osteopontin and matrix metalloproteinases are upregulated [4,5,6,19].

Transforming growth factor-β (TGF-β) signaling, in contrast, exerts dual and context-dependent effects on VSMCs. Under physiological conditions, TGF-β promotes contractile differentiation through Smad2/3-dependent transcriptional activation of smooth muscle-specific genes. However, in the pro-inflammatory environment of the atherosclerotic plaque, TGF-β may contribute to phenotypic modulation and even osteogenic reprogramming, depending on crosstalk with other pathways such as bone morphogenetic protein (BMP), PDGF, and Notch signaling [20]. This context specificity underscores the need for a nuanced understanding of TGF-β's role in vascular pathology.

The transcriptional landscape of VSMC phenotypic switching is further shaped by several key regulatory proteins. Myocardin, a potent coactivator of SRF, is essential for the expression of contractile genes and maintenance of the differentiated phenotype [17]. In contrast, the transcription factor Kruppel-like factor 4 (KLF4) antagonizes myocardin–SRF signaling and drives VSMCs toward a synthetic or macrophage-like state. KLF4 expression is induced by oxidative stress, inflammatory cytokines, and vascular injury, and has been shown to be essential for the loss of contractile identity in atherosclerosis models [8,21]. Another critical regulator is TCF21, a transcription factor identified through genome-wide association studies as a susceptibility locus for coronary artery disease. TCF21 promotes VSMC migration and phenotypic modulation by repressing contractile gene expression and facilitating the acquisition of alternative cell fates [13,22].

Actin dynamics also contribute significantly to phenotypic control via myocardin-related transcription factors (MRTFs). In contractile VSMCs, polymerized actin permits MRTF-A and MRTF-B to enter the nucleus and coactivate SRF-dependent transcription. Conversely, in synthetic VSMCs, actin depolymerization traps MRTFs in the cytoplasm, leading to reduced expression of contractile proteins [17,23].

This mechanotransduction mechanism links cytoskeletal architecture to gene regulation and plays a vital role in response to biomechanical stress.

Finally, epigenetic mechanisms including non-coding RNAs have emerged as potent modulators of VSMC phenotype. The microRNAs miR-143 and miR-145 are highly expressed in contractile VSMCs and promote differentiation by enhancing myocardin–SRF signaling [14,24]. Conversely, miR-221 and miR-222 are upregulated in response to PDGF and suppress the contractile program while facilitating cell cycle entry and proliferation [24]. In addition to miRNAs, long non-coding RNAs (lncRNAs) such as SMILR and SENCR have been shown to regulate proliferation and phenotype switching, further adding complexity to the regulatory network [25].

VSMC phenotypic plasticity is orchestrated by a tightly regulated molecular framework integrating growth factor signaling, transcriptional modulation, cytoskeletal dynamics, and epigenetic control. This intricate machinery not only enables VSMCs to respond to injury but also contributes to the pathogenesis of vascular disease when dysregulated. Targeting specific nodes within these networks represents a promising avenue for therapeutic intervention in atherosclerosis.

Phenotypic Plasticity and Disease Progression.

The phenotypic plasticity of vascular smooth muscle cells (VSMCs) plays a fundamental role in the initiation, progression, and complications of atherosclerotic disease. Once regarded as passive structural components of the medial layer, VSMCs are now recognized as dynamic contributors to multiple stages of plaque development through their ability to switch phenotypes, migrate, proliferate, and modulate the extracellular matrix [4,5,9].

During early atherogenesis, VSMCs are recruited from the media into the intima in response to endothelial dysfunction and local release of cytokines, growth factors, and lipids. In this environment, contractile VSMCs dedifferentiate into synthetic cells that exhibit enhanced proliferative and migratory capacity, contributing to neointimal hyperplasia and the formation of the fibrous cap [5,6]. These synthetic VSMCs secrete large amounts of extracellular matrix proteins, such as collagen and fibronectin, which provide structural stability to developing lesions. However, as inflammation and oxidative stress accumulate within the plaque, VSMCs undergo further phenotypic modulation that may undermine plaque integrity.

A growing body of evidence, derived from lineage-tracing experiments and single-cell transcriptomic profiling, has demonstrated that VSMCs contribute not only to fibrous cap formation but also to the pool of so-called "non-smooth muscle" cells within the plaque. These include cells with macrophage-like, osteoblast-like, and mesenchymal-like characteristics, which arise through transdifferentiation from medial VSMCs [9,10,11,26]. For example, VSMC-derived cells can express macrophage markers such as CD68 and Lgals3, take up lipids, and exhibit foam cell morphology. However, despite their phenotypic resemblance to monocyte-derived macrophages, these cells lack full phagocytic competence and display distinct transcriptomic profiles [26,27]. As such, they may exacerbate plaque inflammation without performing essential immune functions.

Similarly, osteochondrogenic transdifferentiation of VSMCs has been implicated in medial and intimal calcification, a hallmark of advanced atherosclerotic lesions and a predictor of cardiovascular events [18,28]. VSMC-derived osteogenic cells express bone-associated markers such as Runx2 and alkaline phosphatase and contribute to vascular stiffness and plaque instability. The plasticity that allows VSMCs to adopt these diverse phenotypes may represent an adaptive attempt to stabilize injured vasculature but becomes maladaptive under conditions of chronic injury and metabolic stress.

Importantly, the contextual signals within the plaque microenvironment, including oxidized lipids, inflammatory cytokines, and disturbed flow, determine the direction and extent of VSMC phenotypic transitions. The balance between contractile and non-contractile states appears to be critical in maintaining plaque stability. Studies have shown that VSMCs populating the fibrous cap tend to retain a partially contractile phenotype and contribute to lesion stabilization, whereas those undergoing full dedifferentiation or transdifferentiation are more likely to contribute to plaque vulnerability [12,26,29].

These findings have significant clinical implications. The ability of VSMCs to adopt protective versus pathogenic roles depending on environmental stimuli suggests that targeted modulation of their phenotype could represent a novel therapeutic strategy. Promoting a “stable” synthetic phenotype, capable of matrix synthesis without excessive inflammation, or reinforcing the contractile identity of cap-forming VSMCs may reduce the risk of plaque rupture and thrombosis. However, such strategies must be carefully designed to avoid impairing necessary repair functions or promoting excessive fibrosis or calcification.

Therapeutic Implications.

The recognition that vascular smooth muscle cells (VSMCs) actively contribute to atherosclerosis through phenotypic modulation has prompted a paradigm shift in therapeutic strategies. Rather than targeting lipids or inflammation alone, future interventions may aim to preserve or restore protective VSMC phenotypes, thereby stabilizing plaques and preventing adverse cardiovascular events. However, translating these insights into clinical therapies remains challenging due to the dual, and sometimes opposing, roles of VSMC phenotypes in vascular health and disease.

The concept of targeting VSMC phenotype is supported by experimental studies showing that promoting contractile gene expression or limiting pro-inflammatory transdifferentiation can attenuate lesion progression and increase fibrous cap stability [12,26]. One approach involves modulating key signaling pathways implicated in VSMC phenotype switching. For example, inhibition of PDGF-BB/PDGFRβ signaling has been shown to suppress VSMC proliferation and reduce neointimal formation in animal models [19,30]. However, systemic blockade of PDGF pathways may impair physiological repair responses and cause off-target effects, underscoring the need for cell-specific delivery systems.

In contrast, enhancement of TGF-β signaling has been explored as a means to promote the contractile phenotype, particularly via activation of Smad2/3-dependent transcription [20]. Yet, the

pleiotropic and context-dependent effects of TGF-β complicate its therapeutic application, as it may simultaneously induce pro-calcific or fibrotic responses, especially in the presence of oxidative stress or disturbed flow [18,28].

Targeting transcriptional regulators represents another strategy. For instance, KLF4, a key driver of VSMC plasticity and inflammation, has emerged as a promising target. Genetic silencing of Klf4 in lineage-tracing studies prevented the loss of contractile markers and reduced the formation of foam cell–like VSMCs [8,21]. Similarly, modulation of TCF21, which promotes a migratory, synthetic phenotype, has shown potential in promoting fibrous cap integrity while limiting necrotic core expansion [22,29]. Nonetheless, manipulating transcription factors in vivo remains technically complex and may carry risks related to tissue specificity and long-term safety.

Emerging research also highlights the therapeutic potential of epigenetic interventions, particularly non-coding RNAs that govern VSMC phenotype. Restoration of miR-143/145 levels has been shown to reinforce the contractile state and reduce lesion size in murine models, whereas inhibition of miR-221/222 suppressed proliferation and matrix degradation [24,31]. In parallel, targeting long non-coding RNAs such as SMILR, which promotes proliferation, may offer additional regulatory leverage [25]. The challenge lies in the development of efficient and selective delivery platforms for RNA therapeutics to VSMCs within the plaque microenvironment.

Beyond molecular targeting, biomaterial-based and drug-eluting technologies provide an avenue for localized control of VSMC behavior. Stents coated with agents that inhibit phenotypic modulation or promote matrix synthesis are under investigation, aiming to avoid late stent thrombosis and restenosis by optimizing VSMC response [32].

Despite these advances, several barriers hinder the clinical translation of VSMC-targeted therapies. These include the lack of specific markers distinguishing beneficial versus detrimental phenotypic states, the contextual dependence of phenotypic effects, and the dynamic, plastic nature of VSMC identity. Moreover, most studies have been conducted in murine models, which may not fully replicate the heterogeneity and complexity of human atherosclerosis.

Nevertheless, the therapeutic modulation of VSMC phenotype represents a promising frontier in vascular medicine. A better understanding of the molecular cues governing VSMC plasticity, and how to harness them selectively, could yield novel interventions that complement lipid-lowering and anti-inflammatory therapies, ultimately improving cardiovascular outcomes.

Conclusion.

Over the past decade, the vascular smooth muscle cell (VSMC) has been redefined from a passive contractile unit to a central, dynamic player in atherosclerosis. The ability of VSMCs to switch phenotypes in response to environmental cues represents both a critical adaptive mechanism and a contributor to disease pathology. This phenotypic plasticity underlies their involvement in a range of processes, including lesion formation, extracellular matrix remodelling, fibrous cap maintenance, inflammation, and calcification.

As highlighted in this review, the phenotypic modulation of VSMCs is orchestrated by a multifaceted network of signalling pathways, transcriptional regulators, and epigenetic mechanisms. Key pathways such as PDGF-BB/PDGFRβ and TGF-β/Smad, transcription factors including KLF4 and TCF21, and regulatory RNAs like miR-143/145 and miR-221/222, collectively shape VSMC behavior in the atheroprone environment. These molecular circuits not only determine whether VSMCs promote repair or degeneration but also offer potential targets for therapeutic modulation.

Importantly, VSMCs do not simply oscillate between two phenotypes. Rather, they display a broad continuum of intermediate and alternative states, including macrophage-like, osteogenic, and stem-like phenotypes. This complexity, revealed through single-cell technologies and lineage-tracing studies, challenges traditional dichotomies and emphasizes the need for more precise phenotypic classifications in both experimental and clinical research.

Despite significant progress, many questions remain unresolved. It is still unclear how to selectively promote beneficial VSMC phenotypes without exacerbating calcification or fibrosis, or how to design interventions that can adapt to the dynamic and heterogeneous nature of plaques. Furthermore, the translational gap between animal models and human pathology must be bridged to develop clinically effective therapies.

Nevertheless, the targeting of VSMC phenotypic switching holds considerable promise. By understanding and manipulating the mechanisms that govern VSMC identity, it may be possible to develop novel interventions that stabilize atherosclerotic plaques, reduce the risk of rupture, and complement existing lipid-lowering and anti-inflammatory therapies. In this light, VSMCs emerge not as bystanders, but as therapeutic gatekeepers in the battle against atherosclerotic cardiovascular disease.

REFERENCES

1. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action. J Am Coll Cardiol. 2020;76:2980-2981.
2. Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868-874.
3. Basatemur GL, Jørgensen HF, Clarke MCH, et al. Vascular smooth muscle cells in atherosclerosis. Nat Rev Cardiol. 2019;16:727-744.
4. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004;84:767-801.
5. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. Circ Res. 2016;118:692-702.
6. Allahverdian S, Chehroudi AC, McManus BM, et al. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. Circulation. 2014;129:1551-1559.
7. Alexander MR, Owens GK. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. Annu Rev Physiol. 2012;74:13-40.
8. Shankman LS, Gomez D, Cherepanova OA, et al. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. Nat Med. 2015;21:628-637.

9. Chappell J, Harman JL, Narasimhan VM, et al. Extensive proliferation of a subset of differentiated, yet plastic, medial vascular smooth muscle cells contributes to neointima formation. Circ Res. 2016;119:1313-1323.
10. Wirka RC, Wagh D, Paik DT, et al. Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. Nat Med. 2019;25:1280-1289.
11. Pan H, Xue C, Auerbach BJ, et al. Single-cell genomics reveals a novel cell state during smooth muscle cell phenotypic switching in atherosclerosis. Circulation. 2020;142:2060-2072.
12. Grootaert MOJ, Bennett MR. Vascular smooth muscle cells in atherosclerosis: time for a re-assessment. Cardiovasc Res. 2021;117:2326-2339.
13. Alencar GF, Owsiany KM, Burris HK, et al. The stem cell pluripotency gene TCF21 promotes atherosclerosis by modulating smooth muscle cell plasticity. Nat Commun. 2020;11:1-15.
14. Liu R, Jin Y, Tang WH. MiRNAs and smooth muscle cell phenotype modulation in atherosclerosis. Curr Atheroscler Rep. 2019;21:32.
15. Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. Cardiovasc Res. 2012;95:156-164.
16. Miano JM. Myocardin in biology and disease. J Biomed Res. 2015;29:3-19.
17. Parmacek MS. Myocardin-related transcription factors: critical coactivators regulating cardiovascular development and adaptation. Circ Res. 2007;100:633-644.
18. Speer MY, Yang HY, Brabb T, et al. Smooth muscle cells give rise to osteochondrogenic precursors and chondrocytes in calcifying arteries. Circ Res. 2009;104:733-741.
19. Rzucidlo EM, Martin KA, Powell RJ. Regulation of vascular smooth muscle cell differentiation. J Vasc Surg. 2007;45:A25-A32.
20. Chen PY, Qin L, Li G, et al. Smooth muscle cell reprogramming in aortic aneurysms. Cell Stem Cell. 2020;26:542-557.e11.
21. Shankman LS, Gomez D, Cherepanova OA, et al. KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. Nat Med. 2015;21:628-637.
22. Wirka RC, Wagh D, Paik DT, et al. Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. Nat Med. 2019;25:1280-1289.
23. Salmon M, Gomez D, Greene E, et al. Cooperative binding of KLF4, SRF, and myocardin drives the phenotypic modulation of smooth muscle cells. Circ Res. 2012;110:571-584.
24. Boettger T, Beetz N, Kostin S, et al. Acquisition of the contractile phenotype by murine arterial smooth muscle cells depends on the Mir143/145 gene cluster. J Clin Invest. 2009;119:2634-2647.
25. Ballantyne MD, Pinel K, Dakin R, et al. Smooth muscle enriched long noncoding RNA (SMILR) regulates cell proliferation. Circulation. 2016;133:2050-2065.
26. Misra A, Feng Z, Chandran RR, et al. Integrative genomics reveals phenotypic modulation of human smooth muscle cells by aging and disease. Nat Commun. 2018;9:3561.
27. Wang Y, Dubland JA, Allahverdian S, et al. Smooth muscle cells contribute the majority of foam cells in murine atherosclerosis. J Clin Invest. 2021;131:e138824.
28. Durham AL, Speer MY, Scatena M, et al. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovasc Res. 2018;114:590-600.
29. Gomez D, Baylis RA, Durgin BG, et al. Interleukin-1β has atheroprotective effects in advanced atherosclerotic lesions in mice. Nat Med. 2021;27:1213-1224.
30. Raines EW. PDGF and cardiovascular disease. Cytokine Growth Factor Rev. 2004;15:237-254.
31. Cordes KR, Sheehy NT, White MP, et al. miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. Nature. 2009;460:705-710.
32. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006;48:193-202.