Biomedical Reviews 2023; 34: 181-184

ISSN 1314-1929 (online)

BMR Biomedical Reviews

Proof-of-concept

COLCHICINE AND THERAPY OF CARDIOVASCULAR DISEASE: NOT MERELY A THEORY

George N. Chaldakov[1]*, Maria D. Zhelyazkova-Savova[2], Daniela Panayotova[3], Anton B. Tonchev[1], Manlio Vinciguerra[4], Stanislav G. Yanev[5], Marco Fiore[6], and Peter Ghenv[7]

[1]Departments of Anatomy and Cell Biology and Translational Stem Cell Biology, Research Institute, Medical University, Varna, Bulgaria, [2]Department of Preclinical and Clinical Pharmacology, Medical University, Varna, Bulgaria, [3]Cardiology Division, Department of Cardiac Surgery, University St Marina Hospital, Varna, Bulgaria, [4]Department of Translational Stem Cell Biology, Research Institute, Medical University, Varna, Bulgaria, [5]Institute of Neurobiology, Bulgarian Academy of Sciences, Sofia, Bulgaria, [6]Institute of Biochemistry and Cell Biology, CNR, Rome, Italy, [7]Department of General and Clinical Pathology, Medical University, Varna, Bulgaria

The cytoskeleton is a sophisticated cellular system consisted of actin filaments, intermediate filaments and microtubules (MT) accompanied by a large number of associated structural and motor proteins. Microtubules are dynamically assembling and disassembling structures. They are pivotal for many cell functions, e.g. intracellular traffic of membrane-bound organelles in endocytosis and protein secretion, also a variety of inflammatory and signal transduction pathways. Tubulin is the major building protein of MT. Depended on doses, agents that bind to tubulin inhibit its assembly, that is, MT formation, or disassemble the preformed MT. Such tubulin-binding agents are named MT-disassembling agents or antitululins, colchicine being a classical member of these agents. Herein, we describe in brief the scientific saga of colchicine as related to the therapy of cardiovascular diseases such as acute coronary syndromes, myocardial infarction, atrial fibrillation, pericarditis, and hypertrophic cardiomyopathy. ***Biomed Rev* 2023; 34:181-184**

Keywords: colchicine, microtubules, tubulin, antitubulins, cardiovascular diseases, therapy, concept

Received 25 November 2023, revised 12 December 2023, accepted 12 December 2023.
*Correspondence to: chaldakov@yahoo.com

INTRODUCTION

The cytoskeleton is a sophisticated cellular machinery consisted of actin filaments, intermediate filaments and microtubules (MT) accompanied by a large number of associated structural and motor proteins such as actin, myosin, spectrin, titin, septin, dystrophin, desmin, vimentin, keratin, and MT-associated proteins (MAP1, 2, 4, 6, 7, tau proteins, kinesins, dyneins, *etc*). The motor protein kinesin is an MT-activated adenosine triphosphatase (ATP-ase), an anterograde, MT's plus end-directed motor. The dynein is also such an ATPase, but operates as a retrograde, MT's minus end-directed motor. Microtubules are unstable, dynamically assembling and disassembling structures. They are pivotal for many cell functions, e.g. intracellular traffic of membrane-bound organelles in endocytosis and protein secretion and a variety of inflammatory and signal transduction pathways. Tubulin, the major building protein of MT, is a heterodimer consisting of α and ß subunits. Depended on doses, agents that bind to tubulin block its assembly resulting in the inhibition of MT formation or disassemble the preformed MT – cytoplasmic and mitotic. Such tubulin-binding agents are usually
termed MT-disassembling agents or *antitululins*, colchicine being a classical member of this group of agents.

Herein, we describe in brief the conceptual saga of the antitululin colchicine as related to the therapy and/or secondary prevention of cardiovascular diseases (CVD), which are *bona fide* inflammatory diseases (1, 2).

An old wine in a new bottle

Colchicine is one of the oldest remedies still in use. It is derived from the *Colchicum autumnale* plant. The name "colchicine" comes from the ancient and legendary kingdom of Colchis where *C. autumnale* plants were widespread. Colchicine is an effective anti-inflammatory drug that has been used for decades for the inhibition of acute inflammatory processes - firstly in gouty arthritis and later in familial Mediterranean fever, Behçet's disease, liver cirrhosis, scleroderma, psoriasis, aphthous stomatitis, Sweet's syndrome, amyloidosis, and epidermolysis bullosa.

Antitubulins - a concept for therapy of cardiovascular diseases

Based on the results published for the first time during the 1970's and early 1980's by one of us (GNC), we had proposed that antitubulins, particularly colchicine, could be effective in the therapy of CVD (3-13).

Recently, this concept was repeatedly appreciated by other colleagues in patients with CVD such as acute coronary syndromes, myocardial infarction, atrial fibrillation, pericarditis, and hypertrophic cardiomyopathy administered at 0.5 mg/day or twice daily, the so-called LoDoCo (low-dose colchicine) therapy (14-29).

Intriguingly, George Cooper's group has demonstrated that the excess presence of MT in cardiomyocytes is related to myocardial contractile dysfunction suggesting that this may be one mechanism contributing to the development of heart failure caused by cardiac hypertrophy (25). Accordingly, colchicine treatment leads to striking improvement in contractile function of cardiomyocytes. Likewise, chronic beta-adrenergic blockade instituted early might delay or prevent the appearance of the pathological microtubule phenotype (25).

Moreover, advancement in pharmaceutical design may lead to the production of highly specific pharmaceuticals targeting key molecules such as MAPs, kinesins and dyneins involved in the regulation of MT functions, thus raising a hope for further development of antitubulin therapy for CVD.

Atherosclerosis complications (erosion and rupture of the plaque fibrous cap) resulted in acute coronary syndromes, myocardial infarction or stroke. Of note, arterial smooth muscle cells (SMC) of the innermost media undergo phenotypic modulation towards a secretory state involved in (pro)collagen and other matrix proteins production. The risk of plaque rupture is inversely correlated with the presence of secretory phenotype SMC and collagen fibrils within the plaque fbrous cap (8-10).

CONCLUSION

We argue that one of the present challenges in vascular biology is to consider antitubulins, particularly colchicine's anti-inflammatory action for therapy of CVD, concomitatly addressing how we could boost SMC secretion of matrix proteins for atherosclerotic plaque fibrous cap stabilization (8-10, 14, 22). This would immensely aid efforts in CVD therapy, including in thoracic aortic aneurysms related to Marfan syndrome (30). In acute coronary syndromes patients undergoing percutaneous coronary intervention (PCI), it is feasible to discontinue aspirin therapy and administer low-dose colchicine on the day after PCI in addition to P2Y12 inhibitors (ticagrelor or prasugrel), wrote Seung-Yul Lee and colleagues (23, see also 24). Recently, the US Food and Drug Administration approved colchicine 0.5 mg tablets as the first anti-inflammatory drug shown to reduce the risk for myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with either established atherosclerosis or multiple risk factors for CVD.

In effect, antitubulin concept for CVD therapy is no more a theory now. Thus, we may, just for an intellectual fun, suggest this new approach to be named Burnstock-Chaldakov therapy for CVD.

Isn't *"Fact is the sweetest dream of labor knows.*
My long scythe whispered and left the hay to make".
***Robert Frost**, from "Mowing"*

Photography: Credit Nikolai G. Chaldakov

ACKNOWLEDGEMENTS

We appreciate the valuable and stimulating noosphere created by our brain-and-heart friends (BHF) Tzanka B. Jurukova, Michael S. Davidoff, Anna Kadar, Takashi Fujiwara, Haralambi Shomilov, and Alexander Stoychev. We apologize to the authors of many relevant articles that were not quoted here for reasons of brevity.

REFRENCES

1. Ross R. Atherosclerosis - An inflammatory disease. *N Engl J Med* 1999;340: 115-126. doi: 10.1056/nejm199901143400207

2. Libby P. Inflammation in atherosclerosis No longer a theory. *Clin Chem* 2021; 67:131-142.doi:10.1093/clinchem/hvaa275

3. Chaldakov GN. Antitubulins - a new therapeutic approach for atherosclerosis? *Atherosclerosis* 1982;44: 385-390. doi: 10.1016/0021-9150(82)90013-2

4. Chaldakov GN. Anti-inflammatory drugs and ischemic heart disease: New considerations (A cell biologist's proposal to cardiologists). *J Am Coll Cardiol* 1991; 17(6):1445-1447.

5. Chaldakov GN. Proposal for clinical trials using anti-inflammatory drugs in the therapy of angina pectoris, myocardial infarction and coronary restenosis after angioplasty and bypass grafting. *Med Hypotheses* 1992;37(2):74-75. doi:10.1016/0306-9877(92)90043-c

6. Chaldakov GN, Nikolov SD. Ultrastructure of the arterial smooth muscle cell. In: Wolf S, Werthessen NT, editors. The Smooth Muscle of the Artery. New York City, NY: Plenum Press. *Adv Exp Med Biol* 1975; 57:14-20.

7 . Chaldakov GN, Nikolov S, Vancov V. Fine morphological aspects of the secretory process in arterial smooth muscle cells. II. Role of microtubules. *Acta Morphol Acad Sci Hung* 1977;25: 167-174.

8. Ghenev PI, Aloe L, Kisheva AR, Singh M, Panayotov P, Fiore M, *et al*. QUO VADIS, ATHEROGENESIS? Part 1. Smooth muscle cell secretion – how foe becomes friend in the fight against the atherosclerotic plaque. *Biomed Rev* 2017;28:134-138.

9. Chaldakov GN, Zhelyazkova-Savova MD, Panayotova D, Fiore M, Yanev S. Phenotypic modulation of smooth muscle cells and matrix metalloproteinases as targets for atherosclerotic plaque stabilization. *Biomed Rev* 2020;31: 49-60. doi: 10.14748/bmr.v31.7704

10. Chaldakov GN, Ghenev PI. Colchicine, inflammation and fibrosis in cardiovascular disease: Merging three classical tales. *Biomed Rev* 2017; 28: 110-115. doi: 10.14748/bmr.v28.4

11. Chaldakov GN. Colchicine, a microtubule-disassembling drug, in the therapy of cardiovascular diseases. *Cell Biol Int* 2018;42(8):1079-1084.doi:10.1002/cbin.10988

12. Yanev S, Fiore M, Hinev A, Ghenev PI, Hristova MG, Panayotov P, *et al*. From antitubulins to trackins. *Biomed Rev* 2016;27:59-67.

13. Chaldakov GN, Aloe L, Kádár A, Ghenev P, Fiore M, Pancheva RZ, *et al*. Homage to George E. Palade. Cell protein secretion in vascular biology: overview and updates. *ABMJ* 2021; 4(1): 31-43. doi: 10.2478/abmj-2021-0004

14. Cecconi A, Vilchez-Tschischke JP, Mateo J, Sanchez Gonzalez J, España S, *et al*. Effects of colchicine on atherosclerotic plaque stabilization: a multimodality imaging study in an animal model. *J Cardiovasc Transl Res* 2021;14(1):150-160.doi:10.1007/s12265-020-09974-7

15. Lee JZ, Singh N, Howe CL, Low S-W, Huang JJ, Ortega G, *et al*. Colchicine for prevention of post-operative atrial fibrillation. A meta-analysis. *J Am Coll Cardiol Clin Electrophyisol* 2016;2(1):78-85. doi:10.1016/j.jacep.2015.09.016

16. Nidorf M, Thompson PL.. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007; 99(6):805-7. doi:10.1016/ j.amjcard.2006.10.039.

17. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013; 61:404-410

18. Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J* 2021; 1–16 doi:10.1093/eurheartj/ehab221

19. Robertson S, Martinez GJ, Payet CA, Barraclough JY, Celermajer DS, Bursill C. Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP3 inflammasome monocyte activation. *Clin Sci (Lond)* 2016; 130:1237-1246. doi: 10.1042/ CS20160090

20. Martinez GJ, Robertson S, Barraclough J, Xia Q, Mallat Z, Bursill C. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. *J Am Heart Assoc* 2015;4:e002128. doi: 10.1161/ JAHA.115.002128

21. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, *et al*. Efficacy and safety of lowdose colchicine after myocardial infarction. *N Engl J Med* 2019;381(26):2497-2505. doi: 10.1056/NEJMoa1912388

22. Vaidya K, Arnott C, Martínez GJ, Ng B, McCormack S, Sullivan DR, Colchicine therapy and plaque stabilization in patients with acute coronary syndrome. *J Am Coll Cardiol Img* 2017; doi: https://doi.org/ 10.1016/j.j-cmg.2017.08.013

23. Seung-Yul ee, Young-Hoon Jeong, Kyeong Ho Yun, *et al.* P2Y12 Inhibitor monotherapy combined with colchicine following PCI in ACS patients. *Cardiovsc Intv* 2023;16(15):1845-1855.doi:10.1016/ j.jcin.2023.05.035

24. Costa F, Micari A. Aspirin-free strategy after ACS implementing colchicine: looking for a substitution? *J Am Coll Cardiol Intv* 2023;16 (15) 1856–1859.

25. Zile MR, Koide M, Hiroshi Sato H, Cooper IV G. Role of microtubules in the contractile dysfunction of hypertro-phied myocardium. *J Am Coll Cardiol* 1999; 33(1): 250-260.

26. Abrantes AM, Nogueira-Garcia B, Alves M, Teixeira Passos LS, Botelho C, et al. Low Dose Colchicine in Coronary Artery Disease - Systematic Review and Meta-Analysis. 2021;8(8):457-64.

27. Imazio M, Andreis A, Brucato A, Adler Y, De Ferrari GM. Colchicine for acute and chronic coronary syndromes. 2020;106(20):1555-60.

28. Andreis A, Imazio M, De Ferrari GM. Colchicine for the treatment of cardiovascular diseases:old drug, new targets. J Cardiovasc Med 2022;22(1):1-8.

29. Schattner A. Colchicine - new horizons for an ancient drug. Review based on the highest hierarchy of evidence. Eur J Intern Med 2022;96:34-41.

30. Mullen M, Jin XY, Child A, Stuart AG,Dodd M, Aragon-Martin JA, Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet* 2019;394:2263–2270 doi:10.1016/S0140 6736(19)32518-8