Dance Round

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

COLCHICINE, INFLAMMATION AND FIBROSIS IN CARDIOVASCULAR DISEASE: MERGING THREE CLASSICAL TALES

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ABSTRACT

*Colchicine, isolated from Colchicum autumnale, is a drug for acute gouty arthritis known from thousands of years whose use has survived to modernity. Over the past decades, the use for this very old drug extended beyond gout therapy. This was due to the advance in knowledge of (i) association of hyperuricemia and gout with cardiovascular disease, (ii) cytoskeletal microtubules (MT), and (iii) anti-inflammatory and antifibrotic effects of colchicine, a classical MT-disassembling agent (antitubulin). Here, we present the Bulgarian contribution to colchicine potential in the therapy of cardiovascular disease that has emerged in the early 1970's in the Laboratory of Electron Microscopy, Medical Institute, Varna, Bulgaria, studying the secretory (fibrogenic) function of vascular smooth muscle cells. From this time onward, low-dose colchicine (LoDoCo, 0.5 – 1.0 mg/daily) was increasingly administered orally for therapy of cardiovascular disease such as acute coronary syndromes, cardiac surgery postoperative atrial fibrillation, pericarditis, cardiac hypertrophy-associated heart failure, and systemic necrotizing vasculitis. Thus colchicine might be a new tool in the present therapeutic armamentarium for these diseases. It is simply an example of MT-disassembling drugs. Further studies will definitely be required before gaining real confidence in this kind of antitubulin therapy. This may lead to developing new and more specific antitubulins for therapy of cardiovascular disease. **Biomed Rev 2017; 28: 105-110.***

Keywords: microtubules, tubulin, colchicine, antitubulins, cardiovascular diseases, inflammation, fibrosis

INTRODUCTION

The colorful saga of *Colchicum autumnale* (commonly known as autumn crocus) stretches back over 3 000 years. Ancient writers have described it as the remedy for patients suffering debilitating pain due to acute gout arthritis. Today, this therapeutic effect of *Colchicum autumnale*, from which colchicine has been isolated more than 100 years ago, is known to be due to its anti-inflammatory action. Over the past decades, advances in the knowledge of (i) cy-

toskeletal microtubules (MT) и (ii) cellular effects of colchicine as MT-disassembling agent have led to potential new uses for this very old drug. For instance, colchicine has been used to treat familial Mediterranean fever (and related amyloidosis and recurrent pericarditis), Behçet's disease, acute febrile neutrophilic dermatosis (Sweet's syndrome), epidermolysis bullosa acquisita, aphthous stomatitis, also liver cirrhosis, scleroderma, idiopathic pulmonary fibrosis and other fibro-inflammatory diseases (1-4).

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Figure 1. Schematic illustration of microtubule-organizing center (MTOC) composed of centrosome represented by two centrioles (=) and pericentriolar dense material (γ -tubulin ring complexes) (•) located in trans-Golgi zone. Subplasmalemmal cytoskeleton (1 xxx), microtubules (2) nuclear lamina (3 xxx), intermediate filaments (4). From (32).

Here, we present briefly the Bulgarian contribution to possible potential of MT-disassembling drugs (antitubulins), such as colchicine, in the therapy of cardiovascular disease, e.g. acute coronary syndromes, myocardial infarction, peripheral atherosclerosis, atrial fibrillation, pericarditis, and cardiac hypertrophy-associated heart failure.

MICROTUBULES AND COLCHICINE

Cytoplasmic and mitotic spindle microtubules (MT) are 25 nm in outer diameter cytoskeletal structures composed of self-assembling heterodimers of α - and β -tubulin in collaboration with MT-associated proteins (MAP 1-3 and *tau* protein) and GTP/GDP. Microtubules originate from MT-organizing center (Fig. 1).

Colchicine binds with high affinity to specific domain of β -tubulin, resulting in (i) inhibition of tubulin assembly into MT, (ii) disassembly of preformed MT, and/or (iii) inhibition of membrane-bound tubulin sensitive cellular processes. We prefer the term *tubulin-targeting agents* (MT-disassembling agents, antitubulins) (1, 8, 9) instead of *MT-targeting agents* (10). In brief, tubulin and MT have been emerging as promising targets for new anti-inflammatory (2, 11-14), antifibrotic (1, 3-9), and anticancer (10) drugs.

In effect, colchicine inhibits various MT-dependent cellular processes, for example: (i) in interphase cells –

Figure 2. Electron micrographs of secretory-state (secretory phenotype) aortic smooth muscle cells of the rabbit. The cells possess less filaments and well-developed rough endoplasmic reticulum and Golgi complex-derived secretion granules (vacuoles), spherical-shaped (arrows) and elongated-shaped (arrowheads). a-e, x20 000. From (1, 9).

Figure 3. Electron micrographs of secretory-state (secretory phenotype) aortic smooth muscle cells of the rabbit. **a.** Golgi-associated clathrin-coated vesicles (arrows). **b.** Elongated vacuole linked via filamentous arms (two arrows) to microtubule. **c.** Plasmalemma-derived coated pits (three arrows). **d.** Group of Golgi vesicles are sandwiched between microtubules. **e.** Rough endoplasmic reticulum-associated microtubules (arrowheads) and filaments (F). **a, c, d,** x50 000; **b,** 80 000; **e,** 20 000. From (1, 9).

protein secretion including that of collagen and other matrix proteins realized by vascular smooth muscle cells (1, 5-9; Fig. 2-4), and (ii) in mitotically dividing cells – proliferation, the latter being out of the scope of present article. Colchicine also exerts anti-inflammatory action mediated *via* (i) inhibition of the secretion of proinflammatory cytokines and growth factors, and (ii) inhibition of NLRP3 inflammasome-mediated inflammation, nucleotide-binding oligomerization domain-like receptors, pyrin domain-containing 3 (NLRP3) inflammasome being a cytoplasmic protein complex, which senses

pathogenic invasion through the activation of caspase-1 (cysteine-**asp**artic protease), which converts pro-interleukin (IL)-1 β and pro-IL-18 into IL-1 β and IL-18 respectively (2, 14a for colchicine and NLRP3 inflammasomes; 14b for Canakinumab – human monoclonal antibody neutralizing the action of IL-1 β , the production of which being significantly increased in cells with cholesterol crystal deposition, reminding of urate crystal deposition in gout, also other crystal deposition diseases (14c). Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) are recent clinical

Figure 4. Electron micrographs of secretory-state (secretory phenotype) aortic smooth muscle cells of the rabbit treated with a sub-antimitotic dose of colchicine. The cells responded to the treatment by (a) an accumulation of secretion granules (circles), or (b) vacuolar type dilation of rough endoplasmic reticulum cisternae, some of them approaching the cell periphery (1, 2, 3). a, b, $\times 10\,000$. From (1, 9).

trials for patients with acute coronary syndromes.

THE BULGARIAN CONTRIBUTION

The concept of possible therapeutic potential of MT-disassembling drugs, such as colchicine, has emerged in the Laboratory of Electron Microscopy, Department of Anatomy and Histology, Medical Institute, Varna, Bulgaria, studying the secretory function of vascular smooth muscle cells (Fig. 2-4; 1, 3, 5-9; also see 4, 15). Preliminary proof for the possible antiseecretory (antifibrotic) effect of colchicine was presented in a lecture delivered by one of the authors (GNC) at the International Symposium on Smooth Muscle of the Artery, held Heidelberg, Germany, October 1973, which was published in 1975 (5).

From this time onward, colchicine was increasingly administered for therapy of cardiovascular diseases (16-26). It has also been demonstrated that excess MT density is important for myocardial contractile dysfunction, suggesting that this may be one mechanism contributing to the development of heart failure due to cardiac hypertrophy (27, 28). Noteworthy, colchicine may restore the contractile activity of cardiomyocytes (27, 28; also see 15, 29).

CONCLUSION

The use of low-dose colchicine (referred to as LoDoCo)

might be a new tool, both anti-inflammatory and antifibrotic, in the present therapeutic armamentarium for cardiovascular disease. In 2010 FDA approved Colcris (brand of colchicine) for use. However, a pharmaceutical company raised its price from as low as 10 cents per pill (generic colchicine) to \$5 per pill. \$5 versus 10 cents per pill of colchicine – a 5 000% increase of its price, one more example of today's global commercialization schemes.

Colchicine is simply an example of MT-disassembling drugs. Further experimental and clinical studies will definitely be required before gaining real confidence in this kind of antitubulin therapy. This may lead to developing new and more specific drugs with anti-inflammatory and antifibrotic effects in cardiovascular disease, targeting also (i) the MT-based motor proteins kinesin and dynein (see 32), (ii) post-translational modification of tubulin, (iii) membrane-bound tubulin, (iv) non-tubulin-binding action of colchicine (requiring testing of lumicolchicine, an analogue of colchicine which does not bind tubulin, nor disrupt microtubules, also see 15), and (v) resolvins (pro-resolving lipid mediators) (reviewed in 33).

Considering the importance of atherosclerotic plaque's fibrous cap for the vulnerability of the plaque, we must proceed cautiously with antifibrotic action of colchicine (30, 31).

Anyway we must recall Robert Frost's poem *The Secret Sits*:

*We dance round in a ring and suppose,
But the Secret sits in the middle and knows.*

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in the present *Dance Round*.

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