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The oral administration of colchicine prevents the progression of aortic aneurysm

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[Objective]
The pathogenesis of aortic aneurysm (AA) is characterized by the chronic inflammation of the aortic wall with the accumulation of macrophages and the degradation of the extracellular matrix (ECM) including elastin. Colchicine (COL) is an alkaloid derived from the plant Lily family Colchicum autumnale, and it is known for anti-inflammatory effects. Plant extracts containing COL have been used in the treatment of gout from ancient period. Currently, pseudogout, familial Mediterranean fever, Behçet’s disease and pericarditis are also treated by COL. Furthermore, recent evidence suggests the use of COL for secondary prevention of cardiovascular disease, and the phase 3 clinical trial for it has begun. The objective of this study is to investigate whether COL could prevent the progression of aortic aneurysms.

[Methods]
In vitro: Macrophages (J774A.1 cell line) stimulated TNF-a 24 hours before and smooth muscle cell (SMC) were cultured with 10 ng/mL COL, and the gene expression of inflammatory cytokines involved in the AA formation was measured 24 hours later.
In vivo: Male apolipoprotein E-deficient mice (30 - 35 weeks of age) were infused with angiotensin II for 28 days. COL (20 µg/kg/d) or saline (NS, as a control) was administered orally to the mice every day (COL group, n = 8; NS group, n = 8). Aortic diameter was measured by echography every week and all mice were sacrificed and their thoracoabdominal aorta was harvested at the last day of the administration period and elastin content, MMP activitis, and levels of inflammatory cytokines involved in the AA formation were measured.

[Results]
In vitro: The gene expression of IL-1ß, TNF-a, MCP-1, NF-κB, MMP-9 in the macrophages was significantly decreased in the COL group. The gene expression of Lox, TIMP-2 in the SMC were significantly increased in COL group.
In vivo: Aortic diameter measured by echography every week was significantly suppressed in the COL group (2.25 vs 2.81 mm, p < 0.05). The incidence of AA was decreased in the COL group (62.5% vs 100%). COL significantly suppressed the degeneration of aortic elastin in EVG staining (p < 0.05). There is no significant difference in the enzyme activities of MMP-2 and MMP-9 between COL and NS groups, but IL-1ß (54.4 vs 81.4, p < 0.05), TNF-a (31.0 vs 60.6, p < 0.05), MCP-1 (258.2 vs 411.2, p < 0.05), NLRP3 inflammasome (7.1 vs 8.6, p < 0.05), NE (1.5 vs 2.4, p < 0.05), MPO (44.9 vs 48.1, p < 0.05) were decreased in the COL group.

[Discussion]
In AA model mice, COL seems to suppress the progression of AA by anti-inflammation and preservation of the ECM structure through the inhibition of NLRP3 inflammasome. That NLRP3 inflammasome activation leads to the progression of AA in AA model mice was previously reported and this supports our results.

[Conclusions]
This results suggest that the oral administration of COL prevents the progression of AA in AA model mice and it
is expected as a novel therapeutic agent for AA.