Reviewer A

Comment 1: Which stage are we regarding the knowledge of CAVD?

Reply 1: Calcific aortic valve disease (CAVD) is a common cardiovascular disease mainly characterized by thickening and calcification of the aortic valve and inflammatory cell infiltration. Calcific aortic valve disease represents a disease spectrum that spans aortic sclerosis to aortic stenosis. Evidence from studies on the pathogenesis of calcific aortic valve disease supports an active disease process with lipoprotein deposition, chronic inflammation, and leaflet calcification. The treatment of CAVD has been a research hotspot in recent years, especially in the field of drug therapy. However, there is currently no effective drug available to inhibit the progression of valve calcification. Potential drug therapy research directions mainly include the following categories: reducing lipoprotein(a) levels, vitamin K1, bisphosphate, etc. Surgical intervention is divided into surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). In the past decade, with the maturity of new valve treatment technologies represented by TAVR, more and more patients with severe CAVD at high surgical risk have benefited.

Comment 2: How important is your study to the current literature? And why?

Reply 2: At present, no therapeutic approaches have been successfully developed yet to prevent or treat the disease. Therefore, the development of a potent therapy for CAVD has become a major urgent and critical necessity. To attain this noble purpose, it is highly essential for scientists to dive deep into understanding the molecular and cellular mechanisms of CAVD initiation and progression. our study confirmed that circARHGAP10 promoted osteogenic differentiation by competitively binding to miR-335-3p to regulate RUNX2 expression in VICs. The roles and mechanisms of circARHGAO10 were verified in a CAVD animal model. Our study revealed a novel mechanism of circRNA in CAVD and may shed light on circRNA-directed diagnostics

and therapeutics for CAVD.

Comment 3: Please give a clinical perspective and try to identify some points to prevent valve calcification.

Reply 3: Retrospective and prospective analyses have revealed that age, male sex, diabetes mellitus, obesity, hypertension, smoking, and elevated plasma lipoprotein(a) and LDL cholesterol levels are associated with the risk of CAVD. The American Heart Association (AHA) identified seven cardiovascular risk factors and health metrics (BMI, healthy diet, physical activity, smoking, blood pressure, glycaemia and total cholesterol) that should be targeted to achieve ideal cardiovascular health. Therefore, weight loss, smoking cessation are effective measures to prevent valve calcification. At the same time, Evidence suggests that decreasing the plasma levels of lipids such as lipoprotein(a) might be most effective for preventing the onset of aortic valve mineralization.

Reviewer B

Comment 1: Please remove the unnecessary wavy lines in Figure 2F, Figure 4D, Figure 5H, and Figure 7B.

Reply 1: we have modified the figures as advised.

Comment 2: Line 44 point 1, point 4, Line 98, 591: "Our" (upper case); "through competitive binding to" => "by competitively binding to"

Reply 2: we have modified our text as advised.

Changes in the text: see Page 2, line 44, Page4, line 98.

Comment 3: Line 68, 69: "was"; "targeted"; "regulated" (simple past tense for Methods and Results presentation)

Reply 3: we have modified our text as advised.

Changes in the text: see Page 3, line 68-70.

Comment 4: Line 145: "was reversely transcribed to"

Reply 4: we have modified our text as advised.

Changes in the text: see Page 6, line 145.

Comment 5: Line 346: "were presented" (simple past tense for Methods and Results presentation)

Reply 5: we have modified our text as advised.

Changes in the text: see Page 12, line 346.

Comment 6: Line 349: please review "between more than two groups" as this is not the proper presentation

Reply 6: we have modified our text as advised.

Changes in the text: see Page 13, line 349.

Comment 7: Line 414: "interacted" (better keep the simple past tense as in other parts of the paper)

Reply 7: we have modified our text as advised.

Changes in the text: see Page 15, line 414.

Comment 8: Line 423: "was negatively correlated with"

Reply 9: we have modified our text as advised.

Changes in the text: see Page 15, line 423.

Comment 9: Line 453, 457, 469: "was a target gene"; "was regulated" (simple past tense for Methods and Results presentation)

Reply 9: we have modified our text as advised.

Changes in the text: see Page 16-17, line 453, 457, 469, 470.

Comment 10: Line 525: "with aging population"

Reply 10: we have modified our text as advised.

Changes in the text: see Page 18, line 525.