Response to Reviewer 3 Comments

In their review the authors describe the role of a subgroup of actin binding proteins in cardiac hypertrophy. They highlight the importance of the topic and appropriate figures and tables to facilitate an overview.

Point 1: It remains unclear why they chose the 7 ABPs mentioned in this review.

Response 1: We thank this reviewer for this critical point. ABPs mainly discussed in this revised manuscript are listed separately based on their functions in regulating actin dynamics. We have chosen 1-2 representative ABPs from the same functional type to elaborate in this revised manuscript.

Point 2: A clear mechanistic link is often missing but rather associations are pointed out.

Response 2: We are grateful to this reviewer for this point. Different ABPs may have distinct roles in myocardial hypertrophy. For example, the overexpression of profilin 1 or CapZ can lead to cardiac hypertrophy while gene mutations in MYH7 and MYH6 is associated with hypertrophic cardiomyopathy and dilated cardiomyopathy. However, whether gene mutations in MYH7 and MYH6 induce cardiac hypertrophy or not requires further studies. Therefore, the elaboration on ABPs is based on their research progress in the revised manuscript.

Point 3: A few misleading comments are made and important details are missing or inprecise.

Response 3: We have corrected the relevent contents in the revised manuscript as suggested.

Overall, this is an interesting topic but the review needs major revision:

Point 4: It starts with a misleading description of what hypertrophy is:

Intro: definition of hypertrophy would help, and separating it from its association to fibrosis, etc. The subtitle of figure 1 suggests a misunderstanding: an enlarged cardiomyocyte is not a feature, especially not a “most significant” feature but part of its definition. Maybe also provide a clinical definition.

Response 4: We thank the reviewer for this good suggestion. We have removed "The enlarged cardiomyocyte is one of the most significant structural features of cardiac hypertrophy" from the legend of revised Figure 1 (Page 2, line 33) and added the clinical definition in the revised manuscript (Page 1, line 23-27) and revised Figure 1.

Point 5: Figure 1: “impaired protein” is a vague description – what does this mean? Impaired function? Degradation? Aggregation? This could be explained in detail in the text.

Response 5: We thank the reviewer for pointing this mistake of description. We have removed the vague description of "impaired protein" in the revised Figure 1.

Point 6: Line 35: morphogenesis is determined by microfilament cytoskeleton; separate from this idea: hydraulic pressure and mechanical force are potential influencer; putting these 3 together in a list is not logical. They are on a different mechanistic level

Response 6: We agree with the reviewers and have removed the description of hydraulic pressure and mechanical force from the relevent section in the revised manuscript. (Page 2, line 44)

Point 7: Line 56: eNOS S1177 can be a result of profilin-1 overexpression, but there are other causes as well. The wording is not clear.

Response 7: We have rephrased this statement in the revised manuscript. (Page 4, line 80-83)

Point 8: Figure 2: shorten title

Response 8: We have shortened the title of the revised Figure 2.

Point 9: Line 78: reference missing

Response 9: We have added the related reference in the revised manuscript. (Page 5, line 109)

Point 10: Line 128: Figure 5 description should be provided in a short and precise manner

Response 10: We are grateful to the reviewer for this critical point. We have rewritten the relevant description in the revised manuscript. (Page 9, line 189-192)

Point 11: Line 69+90+124: maybe the authors can elaborate why F-actin accumulation leads to cardiac hypertrophy: is this due to aggregation of dysfunctional proteins? Failing autophagy?

Response 11: We appreciate this reviewer so much for this wonderful suggestion. Relevant content has been added in the revised manuscript. (Page 2, line 50-55)

Point 12: Concluding remarks:
The authors conclude that the few ABPs mentioned in this review may be a therapeutic target for cardiac hypertrophy. The authors miss to describe the plethora of ABPs that are not described in detail here like integrins, MLC, titin, troponin, CamKII, Dystrophin, Hsp, and many more that exist and already have shown to have major therapeutic implications.

Response 12: We thank this reviewer for this critical point and have added relevent contents in the revised manuscript. (Page 9-10, line 205-233, page 10, line 241-243)

Point 13: Kind suggestion: maybe it would also be interesting to add the role of actin and ABPs in physiological hypertrophy and its similarities/differences to pathological hypertrophy if data is available.

Response 13: We thank this reviewer for the good suggestion and have added the relevant section in the revised manuscript. (Page 9, line 215-216)

Point 14: English: major revision needed
Line 15: associated
Line 22: characterized by
Line 28: English can be improved …
Line 35: related to
Line 37: involves in – is involved in
Line 38: contain – might be the wrong verb
Line 54: shown
Line 56: cardiomyopathy
Line 63: glycation+
Line 72: consists of
Line 74: is (not was)
Line 79: content change …. change of protein abundance?
Line 84: attenuates ?
Line 83-86: sentence is not understandable
Line 93: "formin is a kind of …" very colloquial English
Line 95: promotes
Line 101-102: attenuated in mDia1 knockout mice.
Line 131: it has been shown
Line 132: fetal gene reactivation
Line 144: caused by multiple pathological stimuli…
Line 145: -which

Response 14: We are grateful to this reviewer for pointing these errors of English language. We have corrected them in the revised manuscript. (Page1 , line15, line27; page2, line 34-36, line43, line 46-47, line47-48; page3, line73; page4, line80, line93; page5, line104, line107, line113, line122, line120-125; page6, line134, line137; page7, line147; page9, line197, line199; page10, line246-247, line249)