Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors:
- Title needs to be rewritten as it is not grammatically correct. It also should reflect the nature of work rather than a definitive statement while there is no experimental evidence.
Response: Thank you for this very critical comment, the grammatical oversight was a mistake on the part of our team. Also our team strongly agrees with the addition of a subtitle to reflect the fact that this study is only a theoretical level of analysis, and we have revised the title. Once again, on behalf of my team, thank you for your meticulous review.

- PKA pathway is one of the downstream pathways of the cAMP and not the only one. Accordingly, it is not accurate to call the cAMP pathway "known as PKA system".
Response: Thank you very much for this careful comment. The PKA system is only one of the downstream signaling pathways of cAMP, so here we have an oversight. in the manuscript. We have revised the corresponding part of the manuscript and would like to thank you again for your careful review and rigorous scientific attitude.

- Authors need to analyse their data for potential upstream receptors that activate the ADCY1-9 and the cAMP pathway that leads to the activation of observed downstream effects (e.g., wound healing). They also need to check the expression of this (these) receptor(s) in the platelet (from public data of bulk or single cell RNA-seq).
Response: This comment of yours is considered extremely important by our team after deliberation and it is a great improvement to our study. We combed through the sequencing data of platelets in the GEO database (GSE178158) and analyzed ADCY1-9 expression levels using whole blood (GSE134080) as a control. Differential adenylate cyclase promoter region sequences were then parsed, and transcription factors that could bind efficiently were predicted based on the promoter sequences. Eventually, ADCY4 and ADCY7 were found to be lowly expressed in platelets, and their upstream promoters might be STAT4, GR-beta, respectively. And both STAT4 and GR-beta were lowly expressed in platelets. Because the available platelet sequencing data were minimal and ADCY4 was not expressed at all in the GSE178158 cohort, we further obtained cartilage tissue sequencing data from osteoarthritic disease cohorts GSE51588 and GSE114007 for correlation analysis. An extremely strong positive correlation was found between ADCY4 and STAT4 expression levels, while ADCY7 and GR-beta were also extremely strongly positively correlated. The correlations have been added to the manuscript and form Figure 4A-4G. Once again, on behalf of our team, we would like to express our gratitude to you for this revolutionary suggestion for our research.

- It would be also very good to analyse their data to find the central nodes of secretion factors in pletlets that is induced by the activation of these downstream pathways (e.g., wound healing, etc), and confirm the expression of these factors in the platelets. These factors are potentialy the essential factors that mediate the effect of activated platelets.

Identification of either the receptors of secreted factors offer a more tractable target for theraputic purposes.

Response: Our team is looking forward to your interest in our follow-up research, and we agree that you have very compelling ideas in terms of scientific thinking, and we thank you for this valuable comment. We used the Human Protein Atlas database to find out which proteins are secreted proteins and then correlated them according to their expression levels in the cohort of osteoarthritic diseases. LAMA5, which is highly positively correlated with ADCY4 expression levels, and SEMA3C, which is highly positively correlated with ADCY7 expression levels, were found. Further differential analysis revealed that LAMA5 and SEMA3C were highly expressed in osteoarthritic disease samples and were lowly expressed in platelets, which was fully consistent with the trend for ADCY4 and ADCY7. It is therefore suspected that ADCY4 and ADCY7 contribute to the progression of osteoarthritic diseases through two secreted proteins, LAMA5 and SEMA3C, respectively. Corresponding content has been added to the manuscript and forms Figures 4H and 4I.