Peer Review File
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In response to Reviewer A:

Comment 1: In the abstract, please briefly indicate the significance of review or why there is a need for this review.

Reply 1: Thank you for your suggested improvements to our manuscript abstract in this and the following comments.

Changes in the text: We have modified the abstract to emphasize the need for this review with the following statements:

"This new structural information necessitates a review of past literature to determine how reported structural features fit into the newly solved structure. In this review, we provide the first comprehensive summary of known structural features of CD36 within the context of its newly solved three-dimensional structure." (see Page 4, lines 55-58).

Comment 2: In the abstract, the authors should consider to summarize the novel insights and main findings. Also, a brief comment on existing studies to indicate their limitations and unaddressed issues is needed.

Reply 2: This review synthesizes previous findings related to CD36 structure and summarizes the impacts of structure on function. The new insight is examining the structural features of CD36 in the context of the newly solved structure, which we have addressed in the following statement in the abstract (as mentioned above in Comment 1): "In this review, we provide the first comprehensive summary of known structural features of CD36 within the context of its newly solved three-dimensional structure." (see Page 4, lines 55-58). We have also included comments to address the limitations of existing studies, as indicated below and in Comment 4.

Changes in the text: The abstract now reads:

"The mechanisms underlying these and other functions of CD36 have not been fully defined at the structural level, largely because previous studies were limited by the lack of a high-resolution CD36 structure" (see Page 4, lines 51-53).

"While the extracellular CD36 structure greatly enhances our mechanistic understanding of ligand binding and transport, a full-length structure that includes the transmembrane and intracellular domains will be critical to understand the positioning of CD36 on the plasma membrane and how it may interact with other proteins. Nonetheless, this solved structure builds on our previous understanding of CD36 ligand binding sites and post-translational modifications and paves the way for future mechanistic studies to better understand CD36 function" (see Pages 4-5, lines 61-67).

Comment 3: In the conclusion part of the abstract, the authors would consider to provide comments on further research topics to address unaddressed issues.

Reply 3: In the abstract, we have briefly mentioned that additional areas of study will be suggested. We discuss future directions in the main text in the relevant sections, and we now provide examples in the final conclusion section.

Changes in the text: The abstract now reads:

"In this review, we emphasize structural features relevant to platelet biology, highlighting new insights and suggesting additional areas of study into CD36 structure-function relationships" (see Page 5, lines 67-69).

Comment 4: The authors may consider to have comments on the methodology rigorousness and limitations of previous studies.

Reply 4: We appreciate the suggestion to add comments addressing the limitations of previous studies.

Changes in the text: The following statements were modified/added:

"However, due to the lack of a CD36 structure, many of these studies relied upon structural feature prediction software and homology modelling" (see Page 7, 101-102).

"Until recently, structure-function studies of CD36 were hindered by the lack of a high-resolution CD36 structure, and researchers relied on various biochemical techniques (e.g. mutagenesis) to predict biologically-relevant structural features of CD36. However, interpretation of mutagenesis studies can be limited in cases where a mutation unexpectedly reduces protein stability or expression" (see Page 8, lines 124-128).

Comment 5: In the part of conclusion, please have more detailed comments on further studies.

Reply 5: We have modified the conclusion to provide examples of further areas of study, all of which are discussed further in the main text.

Changes in the text: The following sentences were added to the conclusion:

"For example, additional studies must be performed to address the purpose of CD36 acetylation and to clarify if CD36 phosphorylation occurs *in vivo*. The structural features mediating CD36 dimerization are understudied, as is the function of CD36 dimerization or multimerization (e.g. increased membrane retention). Most importantly, high-resolution structures of the transmembrane and cytosolic domains will provide new insight into the structural mechanisms that facilitate interactions between CD36 and other protein partners and how these interactions may drive downstream signaling events." (see Page 20, lines 378-386).

Comment 6: Comments on clinical implications of CD36 are inadequate. The authors may consider provide more.

Reply 6: Thank you for your suggestion. It was our intention to focus on the structural aspects of CD36 that are important for its function. Therefore, we believe that adding a discussion of CD36 clinical implications would be beyond the scope of this structure-focused review. It is also our understanding that another invited review within this special edition of the journal, entitled *CD36 Gene Variants and Their Clinical Relevance*, will cover clinical topics related to CD36, such as human mutations in the CD36 gene.

In response to <u>Reviewer B:</u>

Comment 1: Since it is a narrative review of the literature, it is important to describe it in the text, together with the literature search strategy and the limitations.

Reply 1: We appreciate the suggestion to describe our methods for the literature search.

Changes in the text: We have included additional details on the search strategy in the introduction, which now reads:

"In this narrative literature review, structural features relevant to platelet biology will be emphasized. To obtain relevant literature, our search results were limited to publications within the PubMed database using the keywords *"CD36"* in combination with other words that include *"structure", "platelet", "mutant", and "oligomerization"* (see Page 7, lines 104-108).

In response to <u>Reviewer C:</u>

Comment 1: I wonder if the authors would consider adding to Figure 1 by pointing out the position of the immunodominant epitope (amino acids 155-183) on CD36 that is recognized by several CD36 specific monoclonal antibodies.

Reply 1: Thank you for this great suggestion. We now highlight this region in Figure 1 (in addition to Figure 2).

Changes in the text: We have included mention of this immunodominant region and the suggested references in the Figure 1 legend, which now reads:

"The epitope recognized by several CD36 monoclonal antibodies (amino acids 155-183) (40, 41) is highlighted in orange" (see Page 30, lines 694-696).

We have added these same two references to the main text (see Page 10, line 178).

Additionally, we added the parenthesized information to the Figure 2 legend to clarify that this is the same region highlighted in Figure 1:

"The oxLDL binding region (amino acids 155-183), which overlaps with the binding sites of PfEMP1 and anionic phospholipids, is highlighted in orange" (see Page 30, 706-708).