

Article: Type IV P-type ATPases: Recent Updates in Cancer Development, Progression and Treatment

Comments:

In this article the authors attempt to highlight the role of Type IV lipid flippases in cancer.

As indicated in the summary and in the abstract, this is a quite interesting field, and that could be relevant in the context of cancer. Then a review like this could be insightful to obtain a better picture of function of these enzymes and the lipids they modify in cancer cells.

The review, unfortunately, has some inconsistencies and fails to offer the readers a clear and consistent picture of these lipid enzymes in cancer. Many data appear solely enumerated, with a simple description and without proper integration with the rest of the data to give a full context, which makes it difficult to communicate a complete organized idea. Since in many cases the expression of the enzyme is downregulated in cancer cells, the options to develop a possible therapy would require expressing the enzymes, strategies that are not mentioned or elaborated. Modifications are suggested for improving clarity.

This is a list of observations:

L35-37. This sentence looks very interesting, but then is not connected in the rest of the section. The authors talk again about this issue in the next section but also without conclusion. Consider to either remove from here or to elaborate more to give a general conclusion of this issue here or move these observations to the 4.2 section.

L42. "P4-ATPases" This is the first mention to the family, please mention before that is a flippase. Are there other P1-P3 members? P4 are present only in mammals. Please rewrite for improved clarity.

L4-52. The ideas here seem contradictory, "there is limited information" but this review summarized the "recent updates".

L54, what are the bases of this classification? Substrate specificity?

L67-75. Although very interesting, it is difficult to get the idea. As described here, then the important thing in cancer is the presence of CD47 and not that of flippases. Please organize better the structure of the paragraph.

L79-82. Please rewrite to explain that in cancer cells the activity of the enzyme is low.

L88-90. This is a hypothesis of the authors? Please explain about the mechanisms and provide references.

Table 2:

This table is an excellent idea as intended to be abstract of the information described in the section 3, and also for section 4. As described in all the section there are a lot of information and sometimes the results are contradictory. Since this is the aim of the review, please consider to clarify better the reported feature column: for example, in gene expression, is it increasing or going down?

Some enzymes are not included, although then are discussed in the next section, for example ATP8B3. Please correct and include in this table all the enzymes. This could facilitate to pick up the information.

L134 GI cancer: indicates the full name

L311. Please explain if the enzyme levels are high or not, and which could be the connections with oxaliplatin.

L320-329. Are the studies described here included in table 2? Please correct.

L346, please describe briefly the hypothesis about how ATP11b could support PDL-1 expression.

L350. ATP8B levels/ expression increases or diminishes? Please indicate how this could alter macrophage function.