Author's reply to the review report-Reviewer 3

The reviewer rightly points out that in the introduction a justification must be provided that indicates the novelty of this study and therefore its justification for publication. To improve this aspect, we point out in the last paragraph of the introduction that the effect of caspase-3 has focused mostly on its final effects on cell death, but little on cell adhesion, this is important since the loss of adhesion Cellular is a key factor that from a mechanical point of view is crucial in the formation of the blister, which is the clinical and histopathological characteristic of pemphigus, this is pointed out at the introduction section, lines 40 to 57.

1. The reviewer suggests moving paragraph 2.2 casp-3-shRNA expression in transformants to material and methods section 4.5. This has been done.

2. The reviewer suggests performing additional assays to qRT-PCR that demonstrate that caspase-3 expression is inhibited by Casp-3 shRNA. For this purpose, two tests were carried out: One to evaluate the effect of shRNA on the expression of the Caspase-3 protein by Western blot. Second: cellular localization by immunofluorescence with an anti-Caspase-3 monoclonal antibody. By both methods, the Caspase-3 protein was demonstrated in untransfected cells and treated with PV-IgG, however this expression of caspase-3 in cells transfected with sHRNA was significantly reduced. Another assay was performed with the M30 antibody that recognizes a neoepitope on cytokeratin 18 (J Cell Biol 148(6)2000 1239-54), confirming that caspase-3 was activeblot and immunofluorescence. Lines 29, section 2.3 lines 128 to 132. Figure 3 (modified) and figure legend, lines 135 to 149.

3. The reviewer asks about the criteria we followed for the synthesis of sense and antisense sequences. As noted in section 4.5, several sequences were designed in the aforementioned software, of which three sets were chosen and the three sets

were synthesized, however only one was chosen using the following criteria: The sequence that produced the highest percentage of transfection and more ease of selection of shRNA positive cells, another selection criterion was to avoid the presence of more than four A's or T's in the target sequences to avoid the problem of premature transcription termination. Another criterion is the presence of more than 50% of cytokines and guanines in the sequence of the oligo chosen for greater stability and affinity (Methods Mol Biol. 2010; 629: 141–158.). We clarify that three sets of sequences were synthesized and we chose a single sequence to perform the experiments. Section 4.5 lines 312 to 313; 319 to 323.

4. We clarify that we did not use another gene other than alpha-tubulin as a control for the qRT.PCR.

5. The reviewer suggested studying the expression of other markers, however, due to time constraints, we were only able to study the M30 marker of caspase-3 activity, as previously stated. Section 4.12 lines 396 to 406.

We thanks for your suggestions and observations that were taken into account and we feel the improved manuscript is ready for evaluation.