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Letter to the Editor: "Histone Deacetylase 7 Inhibition in a Murine Model of Gram-Negative Pneumonia-Induced Acute Lung Injury" *Shock* 53:344–351, 2020

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To the Editor:

In the article of Kasotakis et al. "Histone deacetylase 7 inhibition in a murine model of gram-negative pneumonia-induced acute lung injury" recently accepted by "Shock" (Shock 53:344–351,2020) (1), the authors described the specific involvement of histone deacetylase, HDAC7, in acute lung injury (ALI) induced by *E coli* in murine model. While the authors reported a very interesting and novel finding regarding the role of class IIa deacetylases, specifically HDAC7, in ALI *in vivo*, this study raised several concerns such as:

According to the paper, trichostatin A (TSA), a potent inhibitor of HDACs, inhibits HDAC7 expression, which is very surprising. Original paper on the mechanism of TSA-mediated HDACs inhibition clearly demonstrated that this mechanism involved inhibition of HDACs activity by direct binding with HDACs catalytic region (2); therefore, it is highly unlikely that TSA affects HDAC7 expression. Further, to the best of my knowledge, there are no papers describing the effect of TSA on the HDACs expression. In supporting paper cited (Reference 40) (3), the authors did not study the effects of TSA on HDACs expression, they examined the role of HDAC3 and 7 in the expression of HDAC's downstream targets relevant to their study. Further, while Kasotakis et al. (1) claimed that this paper supported selectivity of TSA toward HDAC3 and 7 *in vivo*, the cited manuscript described the role of HDAC 3 and 7 in cancer cells model, not *in vivo*. Therefore, the statement that "TSA … appears to be more selective HDAC inhibitor *in vivo"* is not supported by the data of literature. It is well established that TSA inhibits a wide spectrum of HDACs (classes I and II) *in vitro* (4) and efficiently inhibits HDACs in murine model (5), but not specifically HDAC7 or 3.

Based on the results in Figure 4, the authors claimed that *E coli* effects are due, at least in part, to the changes in HDAC7 expression. However, depletion of HDAC7 (HDAC7 silencing + *E coli*) did not change the level of HDAC7 mRNA expression compare with *E coli* alone, although the authors stated that it does: "this transcription is inhibited further with both TSA and highly selective HDAC7-siRNA inhibition," see Discussion. Further, while the authors claimed in the Discussion that "HDAC7 mRNA is not statistically different from control siRNA-treated animals," I cannot find any data on the effects of HDAC7

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siRNA or TSA alone on HDAC7 mRNA expression. The authors hypothesized that apparent discrepancy between the lack of effect on HDAC7 mRNA level (no effect) and protein production (decrease) can be explained by some restoration of mRNA level due to rapid turnover; however, I assume that the authors used an excess of siRNA to efficiently inhibit HDAC7 production. Therefore, siRNA is still present and should decrease the level of mRNA independently of turnover. Therefore, it is highly unlikely that this explanation is valid. Further, the specific role of HDAC7 in *E coli*-induced ALI was mainly supported by experiments with *in vivo* effects of HDAC7 siRNA on HDAC7 protein expression. Any siRNA designed to decrease expression of specific mRNA, but not protein, therefore, it is unclear, how the protein level of HDAC7 decreased without decreasing HDAC7 mRNA level.

Both *E coli* and TSA decreased HDAC7 mRNA level, but very surprisingly, *E coli* increased HDAC7 protein expression. The authors stated that mechanism of this remarkable difference is unknown and will be examined in the feature studies. However, I assume that measurements of HDAC7 protein and mRNA level were performed in the same time frame; therefore, it is quite strange that while the level of mRNA decreased, protein expression increased. In addition, TSA but not siHDAC7 has the same (inhibitory) effect on protein and mRNA levels, which is not fit with the conclusion that TSA acts mainly via HDAC7-mediated mechanism.

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