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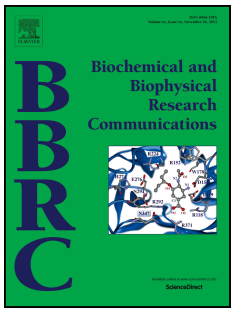

HDAC6 deficiency induces apoptosis in mesenchymal stem cells through p53 K120 acetylation

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October 10, 2017

Dr. W. Baumeister

Editor-in-Chief

Dear Dr. Baumeister

Please find enclosed manuscript entitled “HDAC6 deficiency induces apoptosis in mesenchymal stem cells through p53 K120 acetylation” which we would like to submit as a short communication in Biochemical and Biophysical Research Communications (BBRC).

The transplantation of mesenchymal stem cells (MSCs) has garnered significant attention as a novel therapeutic approach involving immunoregulatory and regenerative medicine due to their ability to differentiate into multiple cell lineages. However the poor survival of MSCs in pro-apoptotic microenvironment after transplantation limits clinical application, thus the molecular mechanisms underlying MSC survival is an active area in this field. Here, we report the novel role of HDAC6 in regulating MSC apoptosis. We found that loss of HDAC6 leads to apoptosis in MSCs without affecting cell cycle profiling utilizing primary cultured MSCs obtained from HDAC6 KO mouse model. Mechanistically, we demonstrate that HDAC6 regulates p53 K120 acetylation, which reportedly plays an important role in pro-apoptotic role of p53. Further, we show that loss of HDAC6 impairs normal mitochondrial metabolic activity, which is linked to aberrant accumulation of ROS in HDAC6-deficient MSCs. Our results suggest that modulation of HDAC6-p53 axis could be a novel approach to improve MSC survival to overcome major limitation of MSC-based therapy.

We would like to note that during preparation of our manuscript another group reported HDAC6 promotes cancer cell survival through deacetylation of p53 K120 (Bitler et al. ARID1A-mutated ovarian cancers depend on HDAC6 activity, Nat Cell Biol 19 (2017) 962-973). Our study also supports the notion that HDAC6 plays a key role in determining cell fate in not only in cancer also in stem cells through regulating p53 acetylation. Taken together, this paper would appeal to the broad readership of BBRC, including those interested in stem cell biology and its translational application.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

Thank you for your consideration.

Sincerely,