Dr. XXXXX, Editor in Chief

Nature

November XX, 2021

Dear Dr. XXXXX,

We would like to submit the attached manuscript entitled ‘Highly conserved evolution of the hypoxic response in metazoans’ for consideration for publication in Nature.

This original research paper details the diurnal response of a basal marine metazoan, the Scleractinian coral *Stylophora pistillata*, to constant prolonged (2 weeks) severe hypoxia for the first time.

We believe that this research will be of great interest to readers of Nature because our manuscript describes transcriptional responses to hypoxia in lower metazoans that can shed light on the evolution and development of similar processes that have been thoroughly studied in mammals as it relates to tumors. In addition, we make observations that are of great interest to the readers interested in interactions between oxygen levels and circadian rhythm genes that have been reported in humans. We also substantiate the conserved nature of the basic hypoxic response and provide evolutionary clues to gene interactions.

Specifically, our study indicates that hypoxia enhances *S*. *pistillata*s’ dependence on symbiosis-derived inputs. These inputs might be essential to corals and other organisms energetically dependent on photosynthetic symbionts to survive prolonged hypoxia. Therefore, additional factors (e.g., thermal stress) leading to coral bleaching might reduce the ability of corals to withstand prolonged hypoxia.

Combining phylogenetic and transcriptomic analyses enabled the identification of two distinct evolution-function patterns related to hypoxia: conserved (HIF/circadian rhythm) and unique (PHDs). Adopting this strategy may allow for further elucidation of evolution-function mechanisms related to coral biology.

Thank you very much for your kind consideration of our submission. My fellow authors and I would be happy to supply any additional information required.

Sincerely,