Warm stress modulates embryonic cortical development

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. Jiao JianWei (焦建伟) at the CAS Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, uncovered the relationship between heat stress and embryonic cerebral development, which was published in *Science Advances* (2020, 6(1)).

During pregnancy, various stimuli can lead to abnormal neural development. Among them, heat stress is an important stimulus for both the mother and fetus during pregnancy, and maternal thermal homeostasis is critical for fetal survival and ontogenesis. Studies have shown that maternal fever during the gestation period is associated with congenital heart defects and neural tube defects. However, it is largely unknown whether heat stress, such as hyperthermia, disturbs neurogenesis and cortical development.

After warm challenge in pregnant mice, the proliferation ratio of neural stem cells in the embryonic cerebral cortex increased, while the proportion of differentiated neurons decreased. Besides, heat-treated mice showed a marked augmentation of TRPM2 expression, which is a heat-activated calcium channel, in the VZ/SVZ of the neo-cortex. It has been previously reported that TRPM2 is associated with a variety of neurodevelopmental/neurological disorders, including bipolar disorder, neuropathic pain, and Parkinson's disease.

In the latest study, in order to further explore whether TRPM2 plays a unique role in neurogenesis during embryonic brain development, the researchers studied its function by specifically knocking down TRPM2 in neural stem cells. They found that *TRPM2*-deficient mice exposed to heat show reduced neural stem cell proliferation and a premature shift in RG differentiation, but it will not cause this phenotype in the maternal environment at normal temperatures. Further research has shown that TRPM2 affects embryonic neural development by regulating the transcription factor SP5 in hyperthermia. Previous reports indicate that SP5 plays an important role in affecting the pluripotency of mouse embryonic stem cells.

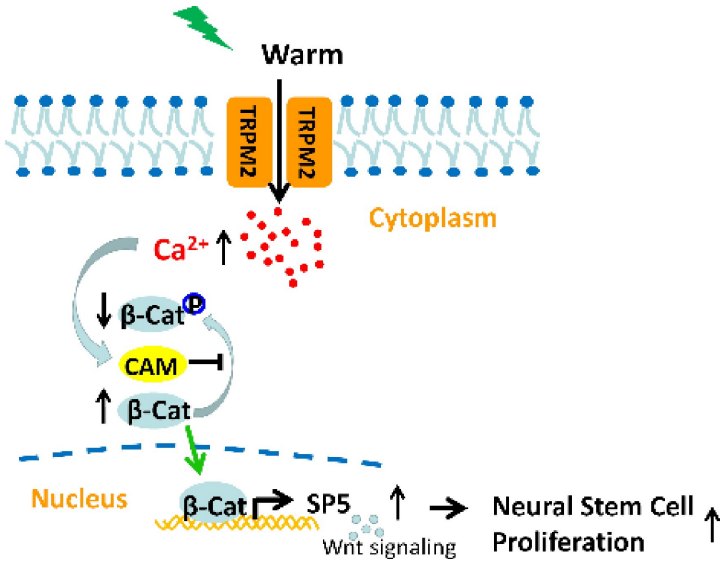

Figure TRPM2 regulates brain development in hyperthermia.

In terms of specific mechanisms, researchers revealed an important role of TRPM2 in modulating SP5 expression by inhibiting the phosphorylation of β-catenin in sustaining neural progenitor self-renewal during heat stress. Additionally, the heat-induced proliferation defects caused by TRPM2 knockdown or knockout can be partially rescued by the overexpression of SP5.

Collectively, these findings reveal that the heat sensor protein TRPM2 has a novel role in modulating cortical neurogenesis during hyperthermia conditions. These findings provide new insights to further elucidate neurological disorders associated with heat stress and reveal new strategies for treatment.