A newfound role of TopBP1 in the maintenance of proliferative hematopoietic stem progenitor cells

With the support by the National Natural Science Foundation of China, the Science and Technology Commission of Shanghai Municipality and the National Thousand Talents Program for Distinguished Young Scholars, the laboratory led by Dr. Pan WeiJun (**潘巍峻**) at the Institute for Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, published their research article entitled "TopBP1 Governs Hematopoietic Stem/Progenitor Cells Survival in Zebrafish Definitive Hematopoiesis" in *PLOS Genetics* (2015, 11(7): e1005346).

DNA damage response pathways are vital to the proliferation of hematopoietic stem/progenitor cells (HSPCs) during embryo development, for they will resolve the replication stress which is deleterious for genome stability and cell survival. However, the detailed mechanism of the response to the replication stress-induced DNA damage during HSPC expansion remains elusive. The researchers reported that a zebrafish mutant *cas003* with nonsense mutation in the *topbp1* gene encoding topoisomerase II β binding protein 1 (TopBP1) would suffer a reduction in the number of HSPCs during definitive hematopoietic cell expansion, with the formation and migration of HSPCs unacted. Moreover, HSPCs in the *topbp1*^{cas003} mutant embryos are more sensitive to hydroxyurea (HU) treatment. Mechanistically, subcellular mislocalization of TopBP1^{cas003} protein results in ATR/Chk1 activation failure and DNA damage accumulation in HSPCs, and eventually induces the p53-dependent apoptosis of HSPCs. Collectively, their work demonstrates a novel and vital role of TopBP1 in the maintenance of HSPCs genome integrity and survival during hematopoietic progenitor expansion.

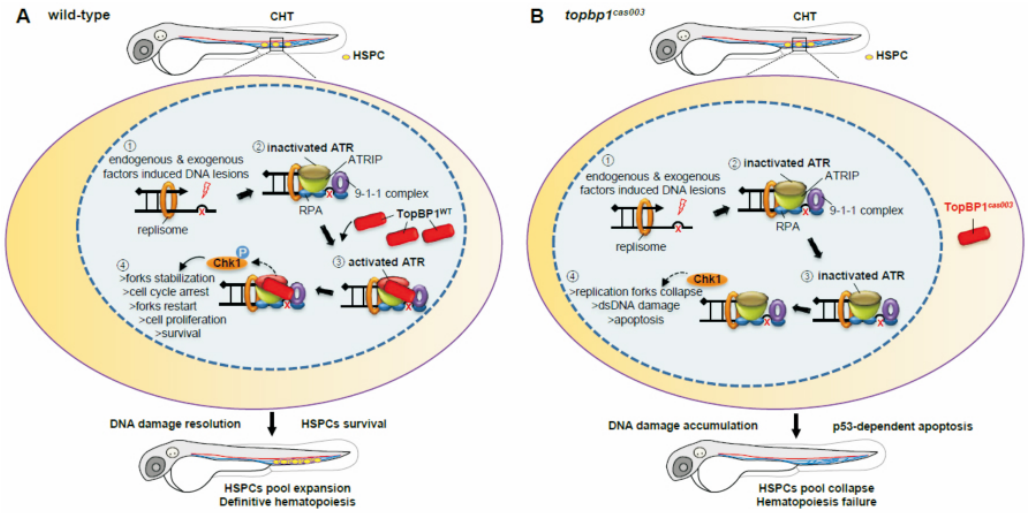

Figure TopBP1 governs HSPCs survival during pool expansion. In zebrafish embryogenesis, the nascent HSPCs undergo extensive pool expansion, while the replication stress causes DNA damage. A In normal HSPCs, the stalled replication forks will generate the typical dsDNA-ssDNA structure. After the loading of replication protein A (RPA), ATR/ATRIP, and 9-1-1 complex, sequential participation of TopBP1 can largely activate ATR kinase activity, and the latter phosphorylate downstream targets such as Chk1. The pChk1 can stabilize replication forks and arrest the cell cycle in order to give more time for DNA damage repair for the replication fork restart. As a result, the HSPCs can survive and go through the pool expansion continuously. B In *topbp1*^{cas003} HSPCs, TopBP1^{cas003} decreases and mislocalizes in cytosol. ATR and Chk1 are prevented from activation in the circumstance of replication stress. Moreover, the stalled replication forks may collapse and trigger p53-dependent apoptosis, which finally results in hematopoiesis failure.