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POSTER 17: Piwil2 prevents loss of function of hematopoietic stem cell during proliferative stress

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Hematopoietic stem cells (HSCs) are rare and quiescent self-renewing cells that can give rise to the entire blood system under steady state conditions. In response to hematopoietic or immune stresses, they become activated and proliferate to replenish the hematopoietic and immune system.

PIWI proteins play a crucial role in maintaining genomic integrity by silencing transposable elements. Initially discovered in germline stem cells, their importance has been observed in somatic stem cells in drosophila and lower organisms with high self-renewing capacity such as planaria or hydra 1,2. Additionally, in mammals, PIWI proteins have been found to be involved in tumor development and more recently in neural stem cells 3,4. In somatic cells, they perform diverse functions in genomic maintenance and cell differentiation through various mechanisms of gene expression and epigenetic regulation.

In mice, there are three PIWI proteins named piwil1, piwil2, and piwil4. We have discovered that piwil2 is specifically expressed in mouse hematopoietic and stem cell progenitors (HS/PCs) and not in more differentiated progenitors such as Mega-Erythorid and Granulo-Mono pogenitors (MEP and GMP). By using a mouse model with an altered function of piwil2 (piwil2D21), we observed a defect in the reconstitution capacity of HSCs of these mice, despite a similar number of HS/PCs compared to what was quantified in wild-type (WT) mice.

Further investigations revealed that immune and hematopoietic stresses, which induce HSC proliferation, such as LPS (a bacterial compound) and 5-FU (a chemotherapeutic drug), increase the expression of piwil2 in HSCs. Interestingly, we observed a decrease of proliferative capacities quantified by EDU incorporation, and number of HSCs from piwil2 D 21 mice after serial LPS stimulation. This is along with an increase in genomic instability, indicated by an increase in gH2AX foci numbers in HSCs. These findings suggest that when the function of piwil2 is impaired, HSCs become more susceptible to proliferative stress. Further research is needed to fully understand the role of piwil2 in genomic maintenance of HSCs.

Overall, our study highlights the crucial role of Piwil2 in maintaining genomic integrity of HSCs in response to proliferative stresses and underscores the important somatic function of PIWI proteins in mammals.

1 Ross, R. J., Weiner, M. M. & Lin, H. PIWI proteins and PIWI-interacting RNAs in the soma. *Nature* (2014). 2 Sousa-Victor, P. *et al.* Piwi Is Required to Limit Exhaustion of Aging Somatic Stem Cells. *Cell Rep* (2017). 3 Liu, Y. *et al.* The emerging role of the piRNA/piwi complex in cancer. *Mol Cancer* (2019). 4 Gasperini, C. *et al.* Piwil2 (Mili) sustains neurogenesis and prevents cellular senescence in the postnatal hippocampus. *EMBO Rep* (2023).