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ABSTRACT POSTER FANCONI:

Polμ deficiency results in altered hematopoiesis.

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We present the first data indicating that Polμ is required for correct hematopoiesis. Polμ was previously shown to be required for V_κ-J_κ recombination during B cell development. Here we show that Polμ deficiency results in a severe reduction in bone marrow cellularity (40% reduction), affecting all lineages of hematopoietic cells similarly.

This defect is due to reduced progenitor (myeloid and lymphoid) numbers and potential. Pol$\mu^{-/-}$ progenitors show increased sensitivity to DNA-damaging agents, in accordance with the proposed role for Polμ as an ancillary factor in non-homologous end joining (NHEJ). Pol$\mu^{-/-}$ mice are also more sensitive to γ irradiation.

Taken together, these results provide the first direct evidence for a *in vivo* Polμ role in general (not V(D)J recombination) double strand break (DSB) repair, both at the cellular level and in the whole individual. In addition, we analyzed the hematopoietic stem cell (HSC) compartment in Pol$\mu^{-/-}$ mice. $Lin^-Sca1^+c\text{-}kit^+$ cells are more abundant in Pol$\mu^{-/-}$ mice, but are unable to reconstitute irradiated recipients in bone marrow transplantation assays, suggesting a blockade in HSC differentiation.

The results thus show a critical role for Polμ (and hence NHEJ) in normal hematopoiesis, as it is required for DSB repair in (hematopoietic) stem cells and committed progenitors.