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POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Caspase 8 Deletion Causes Infection/Inflammation-Induced MDS-like Bone Marrow Failure in Mice

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Myelodysplastic syndromes (MDS) are a heterogeneous group of pre-leukemic hematopoietic disorders characterized by persistent cytopenia in peripheral blood (PB) and normo- or hypercellular and morphologic dysplasia in bone marrow (BM) due to ineffective hematopoiesis, as well as resulting in an elevated risk for leukemic transformation. Bacterial or viral infections increase the severity of MDS patients' symptoms. An inflammatory BM micro-environment and programmed cell death of hematopoietic stem/progenitor cells (HSPCs) have been thought to be the major causes leading to ineffective hematopoiesis. Three types of programed cell death, apoptosis, necroptosis and pyroptosis, were observed in BM tissues of MDS patients, suggesting PANoptosis might play a critical role in the pathogenesis of MDS. Caspase 8 (Casp8) is a master regulator of PANoptosis. Casp8 is downregulated in HSPCs from patients with MDS, and is associated with increased Ripk1 protein, which is another master regulator of PANoptosis. To study the role of PANoptosis in normal hematopoiesis and the pathogenesis of MDS, we generated Mx1-Cre and Rosa-ERT ^{2}Cre-mediated inducible C *asp8* knockout mice (*Casp8* $^{-/-}$). *Mx1-CreCasp8* $^{-/-}$ mice died of BM failure within 10 days of three polyI:C injections (administered every other day) due to the massive depletion of HSPCs. This could be completely rescued by *Ripk3* deletion, suggesting that HSPCs were eliminated by necroptosis. *Rosa-ERT* ^{2}*Cre- Casp8* $^{-/-}$ mice are completely normal without any significant changes in BM hematopoiesis after induction by five doses of tamoxifen (TAM) when maintained in specific pathogen-free facilities. However, such mice developed a spontaneous BM failure phenotype when maintained in quarantine facilities. This BM failure can be attenuated by antibiotic treatment, suggesting that the phenotype is infection-induced. In addition, low dose polyI:C injections or treatment with LPS also induces BM failure in *Rosa-ERT* ^{2}*Cre - Casp8* $^{-/-}$ mice living in germ-free conditions. Detailed analysis suggested that *Casp8* $^{-/-}$ HSPCs are hypersensitive to polyI:C, LPS, TNFα and IFNα/γ-induced cell death. Most importantly, all these phenotypic and functional abnormalities observed in *Rosa-ERT* ^{2}*Cre- Casp8* $^{-/-}$ mice can be completely prevented by *Ripk3* deletion. In addition, serial transplantationstudy demonstrated that *Casp8* $^{-/-}$ HSCs have impaired self-renewal capacity. Interestingly, the self-renewal of *Casp8* $^{-/-}$*Ripk3* $^{-/-}$ HSCs is significantly enhanced compared to Wild-type HSCs. Our study suggests an essential role for a balance in Casp8 and Ripk3 activities in the regulation of normal hematopoiesis and the self-renewal of HSCs, the disruption of which might induce inflammation and BM failure, resulting in MDS-like disease.

Disclosures No relevant conflicts of interest to declare.

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