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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Late B Cell-Specific Dis3-Knockout Mice Do Not Develop Plasma Cell Neoplasm

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Recent advances in next-generation sequencing have unveiled genetic abnormalities associated with multiple myeloma (MM). Of note, *DIS3* mutations have been observed in ~10% of MM patients, and 13q deletion including the *DIS3* gene locus are present in ~40% of MM patients. Furthermore, *DIS3* mutations/deletions have been shown to be associated with poorer prognosis in MM. Regardless of high incidence of *DIS3* mutations/deletions and their relation to adverse outcome, the roles of DIS3 in hematopoiesis and myelomagenesis remains incompletely understood. Here we show that Dis3 is required for normal hematopoiesis and Dis3 deficiency is not sufficient for the development of plasma cell neoplasm in mice.

We first explored DIS3 functions in hematopoiesis by generating *Dis3* conditional knockout (KO) mice (Dis3 $^{fl/fl}$;Mx-Cre). To avoid possible effects of Dis3 deficiency on nonhematopoietic cells, we transplanted bone marrow (BM) cells from Dis3 $^{fl/fl}$;Mx-Cre mice into lethally irradiated CD45.1 $^{+}$ recipient mice. Four weeks after transplantation, we knocked out *Dis3* by inducing Cre recombinase via an intraperitoneal injection of Poly(I:C). The deletion of Dis3 in BM cells was confirmed by genotyping and quantitative real time PCR. Importantly, loss of Dis3 in hematopoietic cells resulted in severe pancytopenia at 2 weeks after Dis3 deletion. Consistent with this observation, Dis3 KO mice showed reduced BM counts with relative preservation of mature lymphocytes. A flow cytometric analysis of the BM exhibited lower frequencies of Lin $^{-}$Sca-2 $^{+}$c-Kit $^{+}$ (LSK), hematopoietic stem, and multipotent progenitor cells in Dis3 KO mice compared with wild-type (WT) mice. Dis3 KO mice also exhibited lower frequencies of common myeloid progenitors, granulocyte/macrophage progenitors, and megakaryocyte/erythroid progenitors compared with WT mice. A frequency of common lymphoid progenitors (CLPs) was comparable between WT and Dis3 KO mice, whereas absolute numbers of CLPs were significantly reduced in Dis3 KO mice than in WT mice. These results indicate that Dis3 is indispensable for normal hematopoiesis, and LSK and myeloid progenitor cells are more dependent on Dis3 than lymphoid progenitor cells.

We next examined whether loss-of-function of Dis3 drives plasma cell neoplasm. To do so, we crossed Dis3 $^{fl/wt}$ or Dis3 $^{fl/fl}$ mice with Cgamma1-Cre mice and generated late B cell-specific Dis3 KO mice by activating Cre recombinase via immunizing with NP-CGG in these compound mice. However, these mice did not develop any B cell malignancies and shorten the survival compared with WT mice. In the samples of MM patients, the frequency of *DIS3* mutations is significantly higher in t(14;16) samples than in those without t(14;16) (Walker et al. Blood 2018). We therefore utilized t(14;16) model mice (c-Maf TG) (Morito et al. Cancer Res 2011) and generated c-Maf TG; Dis3 $^{fl/wt}$;Cgamma1-Cre and c-Maf TG; Dis3 ^{flfl};Cgamma1-Cre mice. As reported (Morito et al. Cancer Res 2011), a small fraction of mice with c-Maf TG developed B cell lymphoma after a long latency. However, the addition of Dis3 KO did not increase the frequency of B cell lymphoma and shorten the survival compared with c-MAF TG mice. These results indicate that only Dis3 deficiency and the combination of c-Maf overexpression and Dis3 deficiency do not develop plasma cell neoplasm and suggest that additional oncogenic events are necessary for myelomagenesis. Further investigations are required for elucidating the mechanisms of how loss-of-function of DIS3 is involved in the development of MM.

Disclosures No relevant conflicts of interest to declare.

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