

REGULATION OF BLOOD-FORMING STEM CELL HOMEOSTASIS BY MENIN IN SITUATIONS OF HEMATOPOIETIC STRESS

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Introduction: Menin is the product of the *Men1* gene, a tumor suppressor gene mutated in patients with endocrine neoplasms. In addition to its endocrine effects, menin interacts with the *Mixed Lineage Leukemia (MLL)* gene product, a homologue of the fly *Trithorax* gene that regulates transcription through its H3K4 histone methyltransferase activity. Menin is required to mediate malignant transformation induced by *MLL* gene rearrangements, but its physiological functions are not well understood. Interestingly, flies with reduced menin expression develop normally, but have a markedly impaired response to several types of stress. This suggested to us that menin may also be a key regulator of the stress response in mammalian progenitors. To investigate this hypothesis, we are studying the role of menin in blood-forming stem cells in situations of hematopoietic injury.

Methods: Controlled inactivation of the *Men1* gene was achieved in mice carrying conditional *Men1^f* alleles through tamoxifen-mediated activation of a *Cre^{ERTm}* transgene. The number and function of menin-deficient hematopoietic stem cells (HSCs) was assessed in steady-state conditions and in situations of hematopoietic stress, such as after bone marrow transplantation and chemotherapy-mediated bone marrow ablation.

Results: Loss of menin led to a modest reduction in peripheral blood neutrophil, lymphocyte and platelet counts. In the absence of hematopoietic stress, numbers of bone marrow HSCs, multilineage progenitors and myelo-erythroid progenitors were well preserved, although pro-B cells and downstream B lineage progenitor subsets were decreased. In contrast, competitive transplantation revealed a profound functional defect of long-term HSCs in the absence of menin, despite normal initial homing to the bone marrow. Furthermore, menin-deficient mice had impaired hematopoietic recovery after myeloablative chemotherapy.

Conclusions: Our observations reveal an essential physiological role of menin in the homeostasis of blood-forming stem cells, specifically in situations of hematopoietic stress. While a considerable amount has been learned recently about the mechanisms regulating HSC maintenance in steady-state conditions, limited information has been available so far on the molecular pathways that control HSC homeostasis in situations of stress. Our findings provide the opportunity to gain mechanistic insights into the stress response of stem cells by studying the function of menin in hematopoietic stem cells.