TIMP-1 signaling via CD63 triggers granulopoiesis and neutrophilia in mice.

Abstract:
The homeostasis of neutrophil granulocytes can affect the outcome of several inflammation-associated diseases including cancer. The regulation of this homeostasis is still not completely understood. We previously found that elevated systemic levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) induce an increase of neutrophils in the liver, which in turn strongly promotes liver metastasis. Here, we report that increasing systemic TIMP-1 levels were sufficient to induce neutrophilia in mice. This was not attributed to prolonged survival or direct mobilization of neutrophils. However, TIMP-1 induced enrichment of myeloid progenitors and concomitant upregulation of granulopoiesis-associated genes in the bone marrow compartment. BrdU pulse-labeling confirmed that proliferating progenitors accounted for TIMP-1-induced neutrophilia. TIMP-1 variants that dissect its protease-inhibitory from its CD63 binding function relevant for cell signaling revealed that the TIMP-1 signaling domain was necessary and sufficient to augment granulopoiesis. Consequently, ablation of the TIMP-1 receptor CD63 abolished both neutrophilia and TIMP-1-enhanced granulopoiesis in the bone marrow. Our findings reveal that elevated levels of TIMP-1 impact on neutrophil homeostasis via signaling through CD63. This may provide a link to clinical observations, where TIMP-1...
correlates with high severity and bad prognosis in inflammation-associated diseases.

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