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506.BONE MARROW MICROENVIRONMENT

Erythropoietin Treatment in Mice Enriches Bone Marrow Osteoclast Precursors, As Reflected By Increased Macrophage Colony-Stimulating Factor (MCSF) and Elevated Expression of Osteoclast Markers in Monocytes

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The impact of erythropoietin (EPO) on erythropoiesis has long been established. However, recent studies have indicated that EPO may also exert regulatory effects on other hematopoietic lineages, including the monocyte lineage. In that respect, we have previously shown that EPO treatment in mice induces bone loss. Here, we studied the effect of EPO on bone marrow (BM) monocytes and its potential implications for osteoclastogenesis. To address the dynamic changes in monocyte populations following EPO administration, we injected EPO (180U) once, or 3 times on alternating days for one week. Mice were sacrificed 16 h after EPO injection. Our results revealed a significant 20 percent increase in the monocyte population (TER119 $^{-}$, LY6G $^{-}$, CD11b $^{+}$) 16 hours after EPO injection, and a twofold increase in the levels of these cells after one week of 3 injections of EPO. Soluble macrophage colony-stimulating factor (MCSF) protein levels in the bone marrow were increased 1.5-fold 16 h after EPO injection, while MCSF mRNA expression levels remained unchanged. After 1-week of EPO administration (3 injections), although the global BM expression of MCSF was reduced, we observed a two-fold increase in MCSF expression levels in T cells (CD3 $^{+}$). To further elucidate the functional consequences of EPO-induced monocyte expansion, we isolated monocytes from mice treated with EPO for one week. We characterized expression levels of key osteoclastic markers in these cells. Indeed, we found that in BM monocytes, EPO treatment led to the upregulation of Lymphocyte function-associated antigen 1 (LFA-1) and Receptor Activator of Nuclear Factor κ B (RANK). The former is implicated in osteoclastogenesis *via* its interaction with intercellular adhesion molecule-1 (ICAM−1), while the latter is the surface receptor for RANK ligand which regulates osteoclast differentiation and activation. These data suggest that EPO not only influences BM monocyte expansion, but also contributes to the regulation of osteoclast differentiation, thus linking erythropoiesis to bone homeostasis. Furthermore, we investigated the early effects of EPO treatment on the expression of transcription factors implicated in monocyte differentiation. Remarkably, we found that EPO administration for 16 hours resulted in the downregulation of KLF2 and KLF4, transcription factors involved in monocytic lineage commitment. The rapid EPO-induced expansion of the monocytic population, coupled with the EPO-regulated expression of MSCF, osteoclastic markers, and transcription factors, suggests a role for EPO in modulating monocyte-to-osteoclast differentiation. The current study opens avenues for further investigating the crosstalk between erythropoiesis, myelopoiesis, and bone homeostasis.

Disclosures No relevant conflicts of interest to declare.

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