HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

HemaTopics
Open Access

# Bone Marrow Niches: Nests to Treat Anti-autoimmune Disorders?

Melania Tesio

**Correspondence:** Melania Tesio, *HemaSphere* Scientific Editor (melania.tesio@inserm.fr).

Being at the crossroad of blood and immunity, the bone marrow harbors specialized niches supporting the function of hematopoietic stem cells (HSCs) and immune cells. This includes some T-cells subsets such as memory T-cells and regulatory T-cells, which cross-talk with HSCs and regulate their function.[1] Reporting in *Cell*, Shi et al[2] extended this scenario and described a novel interplay between HSCs and autoreactive T-cells, which has a pathogenic role and a clinical relevance in multiple sclerosis (MS). This autoimmune disease is characterized by demyelinating lesions in the central nervous system, which are initiated by autoreactive T-cells. Upon being activated in the periphery, these T-cells enter the central nervous system where they promote inflammation and recruit neutrophils and monocytes. These myeloid cells further exacerbate the disease as they produce inflammatory factors and reactivate autoreactive T-cells.[3]

To characterize the role of the bone marrow during MS evolution, the researchers used a murine MS model, whereby experimental autoimmune encephalomyelitis (EAE) is induced by immunizing mice with the 35-55 epitope of myelin oligodendrocyte glycoprotein ($MOG_{35-55}$). By driving the disruption of myelin sheets, this ultimately leads to the development of the disease. The EAE model was combined with a transgenic reporter model (Fgd5-CreERT/tdTomato), which enabled the authors to trace HSCs and their progeny. Using this experiment strategy, the researchers observed tdTomato+ HSCs and myeloid progenitors (granulocyte-monocyte progenitors [GMPs] and monocyte-dendritic cell progenitors [MDPs]) but not common lymphoid progenitors (CLPs) accumulating in the bone marrow of EAE mice already at early phases of disease development. This was accompanied by an accumulation of neutrophils and $Ly6C^{high}$ monocytes in the bone marrow and brain tissues, thus indicating that EAE development is associated with an increased production of mature myeloid cells and their migration to the central nervous system. HSCs accumulation was autoantigen specific as it was observed only following immunization with $MOG_{35-55}$ but not upon immunization with ovalbumin epitopes. Similarly, a higher HSCs number was observed in the bone marrow of transgenic mice harboring autoreactive CD4+ T-cells recognizing $MOG_{35-55}$, but not in mice bearing autoreactive CD4+ T-cells recognizing ovalbumin.

To understand the mechanistic basis for EAE-induced myelopoiesis, the researchers next focused on the role of autoreactive T-cells, hypothesizing that these cells could alter the hematopoiesis of EAE mice upon migrating to their bone marrow. Supporting this hypothesis, the researchers first demonstrated that $MOG_{35-55}$ specific CD4+ T-cells accumulated in the bone marrow of EAE mice from early to peak phases of the disease evolution. Subsequently, they isolated myelin-reactive T-cells from EAE mice and inject them into recombination activating gene 2 knock-out (Rag2 KO) mice (devoid of T-cells), showing that a $CD44^{+}CD62L^{-}$ and a CD69+ T-cells subsets were able to home to the bone marrow of Rag2 KO mice in a C-X-C chemokine receptor type 4 (CXCR4)-dependent manner. A proteomic profile of autoreactive T-cells recognizing $MOG_{35-55}$ next revealed that these cells significantly upregulate the cytokine chemokine (C-C motif) ligand 5 (CCL5). This mirrored an increased expression of the CCL5 receptor CCR5 (C-C chemokine receptor type 5) on HSCs isolated either from transgenic mice harboring $MOG_{35-55}$ autoreactive T-cells or from EAE mice. These data, suggesting a role for the CCL5-CCR5 in MS-induced myelopoiesis, were next confirmed by functional experiments. The injection of $MOG_{35-55}$ autoreactive T-cells into Rag2 KO mice did not drive myelopoiesis when CCL5 was genetically silenced on these cells. In a similar manner, reduced myelopoiesis, neurological deficits and central nervous system (CNS) demyelination were observed when EAE was induced in mice previously transplanted with CCR5 KO HSCs. Taken together, these data suggest a model whereby the migration of autoreactive T-cells from the CNS to the bone marrow skew the hematopoiesis toward the myeloid lineage to increase the production of myeloid progenitors and myeloid cells that exacerbate neuroinflammation and MS progression (Figure 1). This model, which identifies a previously unrecognized role of the bone marrow in MS pathology, is corroborated by interesting translational evidences. The combination of single-cell sequencing and fluorescence-activated cell sorting (FACS) analysis revealed that

*UR LIB Lymphoma Immuno-Biology, Centre International de Recherche en Infectiologie (CIRI) U111, and Institut national de la Recherche Médicale (INSERM), Lyon, France.*

*HemaSphere (2022) 6:10(e776). http://dx.doi.org/10.1097/HS9.0000000000000776.*

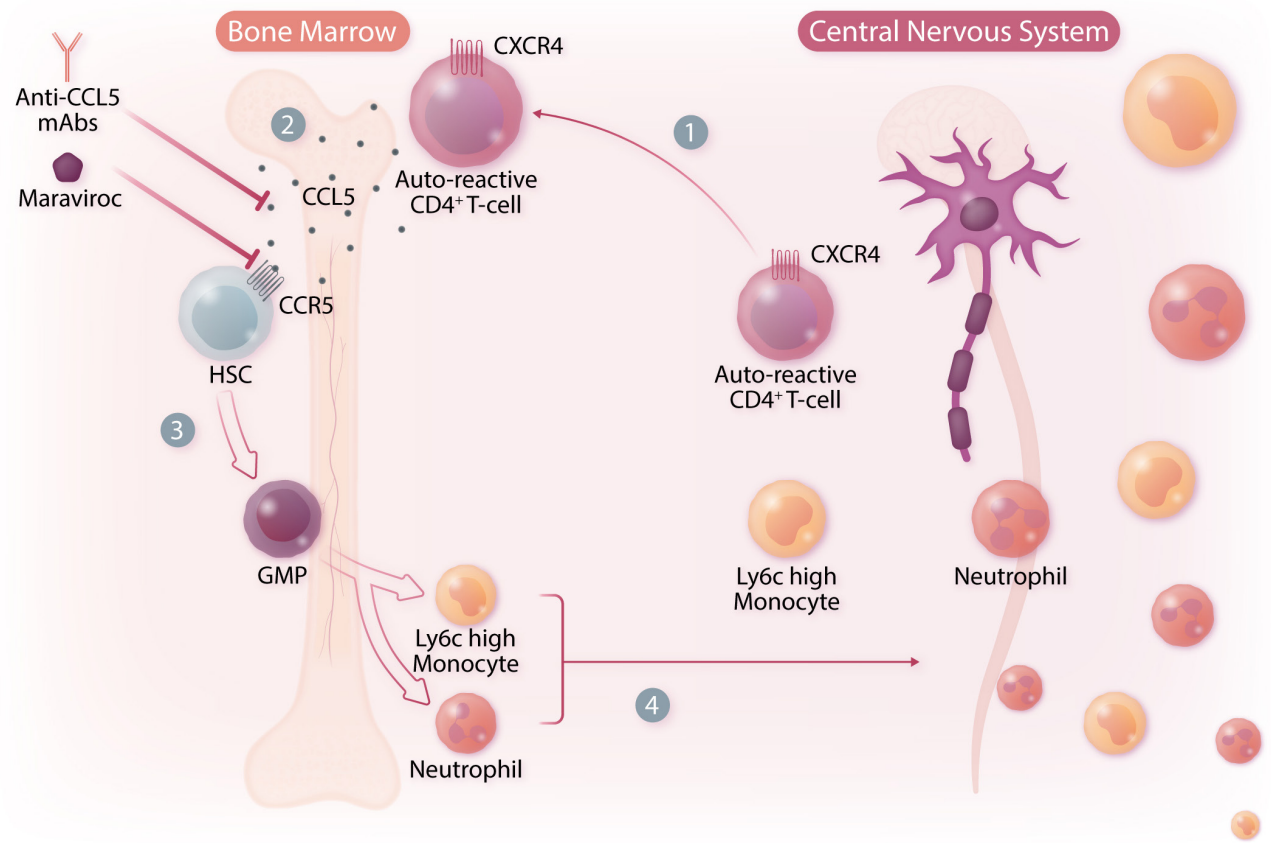


**Figure 1. Autoreactive T-cells migrating from the central nervous system to the bone marrow (1) act via the CCL5-CCR5 axis (2) to skew the hematopoiesis towards the myeloid lineage (3), thus increasing the production of myeloid cells (3) that exacerbate neuroinflammation and multiple sclerosis progression (4).** Blocking the CCL5-CCR5 axis provides clinical benefit in animal models of the disease. CCL5 = chemokine (C-C motif) ligand 5; CCR5 = C-C chemokine receptor type 5; CXCR4 = C-X-C chemokine receptor type 4; GMP = granulocyte-monocyte progenitor; HSC = hematopoietic stem cell; Ly6C = Ly6c1 lymphocyte antigen 6 complex, locus C1; mAb= monoclonal antibody.

in MS patients, the bone marrow hematopoiesis is also rewired towards the myeloid lineage and associated with an expansion of T-cell clones. An increase in CCL5 expressing T-cells and CCR5-expressing HSCs was also observed in these patients. These results are important and exciting given that research into anti-HIV already prompted the development of drugs targeting CCR5, such as the US Food and Drug Administration (FDA)-approved CCR5 antagonist maraviroc. Both this drug and anti-CCL5 monoclonal antibody (mAb) were able to reduce neurological deficits, CNS demyelination and leukocyte infiltration into spinal cord tissues when administered to EAE mice. As these treatments did not significantly alter HSCs and myeloid progenitors numbers in wild-type mice, they could open new therapeutic opportunities for MS patients. Thanks to this elegant study, the HSCs-neuroimmune interplay explored in recent years gets enriched with novel aspects, which have a clinical relevance extending beyond hematological diseases.

## DISCLOSURES

The author has no conflicts of interest to disclose.

## REFERENCES

1. Pinho S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. *Nat Rev Mol Cell Biol*. 2019;20:303–320.
2. Shi K, Li H, Chang T, et al. Bone marrow hematopoiesis drives multiple sclerosis progression. *Cell*. 2022;185:2234–2247.e17.
3. Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. *Lancet*. 2018;391:1622–1636.