

# Adult Mesenchymal Stem Cells

The hematopoietic stem cell (HSC) niche is a multi-cellular, yet complex, structure, whose identity remains to be further defined. As a newly discovered component of the bone marrow micro-environment, nestin-positive (Nes+) mesenchymal stem cells (MSCs) have been comprehensively described in this article.

This work expands our knowledge about the HSC niche and provides new insights into the mechanisms of physiologically maintaining HSCs in the bone marrow.

The authors found that green fluorescent protein (GFP)-marked Nes+ bone marrow cells were rare non-hematopoietic cells that exclusively resided in the perivascular region. The expression levels of the previously described beta3-adrenergic receptor (beta3-AR) gene, *Adrb3*, and the chemokine *Cxcl12* were much higher in CD45-Nes+ cells than in other cells, thus indicating that the Nes+ cell population is a distinct niche component of HSCs in the bone marrow. Immunohistochemistry analyses further showed a close spatial relationship between Nes+ cells and HSCs in the bone marrow.

Interestingly, Nes+ cells were able to form so-called 'mesenspheres' under appropriate conditions. Mesenspheres were self-renewing and multipotent both in vitro and in vivo. Lineage tracing studies suggested that these Nes+ MSCs had the potential to differentiate into cartilage- and bone-forming cells and were thus able to contribute to skeletal bone remodeling. Based on these results, the authors concluded that Nes+ cells are indeed a subset of MSCs.

Gene ontology and protein-protein interaction analyses further suggested that Nes+ MSCs were quiescent but metabolically active. In addition, proliferation of Nes+ MSCs increased significantly after chemical sympathectomy or parathormone administration whereas the sympathetic nervous system (SNS) and granulocyte colony-stimulating factor (G-CSF) had inhibitory effects.

Nes+ cells expressed high levels of genes that have been shown to be involved in HSC maintenance and trafficking. Consequently, the expression of these genes could be selectively down-regulated by G-CSF. In mice that were deficient in Nes+ MSCs, the homing efficiency of HSCs and HSPCs was significantly reduced.

In short, this paper clearly demonstrates that Nes+ MSCs and HSCs constitute a unique bone marrow niche, which can be regulated by hormones and the SNS. However, more work is needed to demonstrate how Nes+ MSCs actually regulate the homing process of HSCs and whether Nes+ MSCs are involved in other important functions of HSCs such as asymmetric vs. symmetric division and quiescence. Importantly, the clinical significance of Nes+ cells as opposed to Nes- cells within the complex cellular niche structure remains to be determined.

## References:

- {1} Katayama et al. Cell 2006, 124:407-21 [PMID:16439213].
- {2} Larsson and Scadden, Cell 2006, 124:253-5 [PMID:16439198].

{3} Méndez-Ferrer et al. Nature 2008, 452:442-7 [PMID:18256599].

Pang Y, Cheng T: "The hematopoietic stem cell (HSC) niche is a multi-cellular, yet complex, structure, whose identity remains..." Evaluation of: [Méndez-Ferrer S et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010 Aug 12; 466(7308):829-34; doi: 10.1038/nature09262]. Faculty of 1000, 28 Oct 2010. F1000.com/5000965

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This study defines the biological role of mesenchymal stem cells (MSCs) in the hematopoietic niche of bone marrow.

It has been previously shown that MSCs, isolated from bone marrow and other tissues, are capable of forming niches in vitro to maintain hematopoietic stem cells (HSCs) (please see reference {1}). The current study focused on nestin-positive non-hematopoietic cells in the bone marrow of mice, in which the nestin promoter drives the expression of green fluorescent protein.

These cells were shown to be similar to MSCs in that they formed colony-forming-unit fibroblasts in vitro and differentiated into bone, fat and cartilage. Nestin-positive cells were metabolically active but quiescent and co-localised with HSCs in close proximity to the vessels in bone marrow, confirming in part previous work of others {2}.

When isolated in vitro and grown in 3D culture-promoting conditions, nestin-positive MSCs were able to self-renew in serial transplantation experiments, possessed multipotentiality and supported hematopoiesis in vivo. The hypothesis that MSCs organize and regulate hematopoietic niches in bone marrow was confirmed by three main findings:

- 1) nestin-positive MSCs appeared to have strongly upregulated the expression of HSC maintenance genes;
- 2) HSCs transplanted into lethally irradiated mice were found next to nestin-positive MSCs in bone marrow;
- 3) in contrast, depletion of nestin-positive MSCs resulted in disrupted homing of HSCs and decreased number of HSCs and their progenitors.

The original concept was proposed to explain the way MSCs regulate the activity of HSCs in vivo. Both hormonal and nerve regulation were shown to be involved in niche regulation. Both chemical sympathectomy and administration of parathormone increased the proliferative activity of nestin-positive MSCs in vivo, while granulocyte colony-stimulating factor (G-CSF) treatment decreased it.

The possibility of sympathetic regulation was also confirmed by the finding that adrenergic nerve fibers were closely associated with MSCs located in perivascular regions in bone marrow.

These findings have great implications for research in both hematopoietic and MSCs, as they define for the first time the biological role of MSCs in vivo and unveil possible mechanisms of HSC regulation, although precise mechanisms are yet unknown.

References:

- {1} Prockop et al. J Cell Mol Med 2010 Aug 16, Epub ahead of print [PMID:20716123].
- {2} Sacchetti et al. Cell 2007, 131:324-36 [PMID:17956733].

Bazhanov N, Prockop D: "This study defines the biological role of mesenchymal stem cells (MSCs) in the hematopoietic niche..." Evaluation of: [Méndez-Ferrer S et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010 Aug 12; 466(7308):829-34; doi: 10.1038/nature09262]. Faculty of 1000, 15 Sep 2010. F1000.com/5000965

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This article provides solid evidence of the physical and biological interaction between mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) in the bone marrow microenvironment.

This work demonstrates that, in the mouse, the expression of nestin identifies a subset of bone marrow stromal cells that have a perivascular location, are in contact with catecholaminergic nerve fibers and are closely associated with HSCs.

In agreement with data reported previously by others (identifying bone marrow adventitial stromal cells as the 'mesenchymal' stem cells in humans), the nestin-positive cells identified in this study are shown to behave like genuine stem cells, displaying clonogenic activity, skeletal multipotency and self-renewal ability in vivo.

Data also show that nestin-positive marrow stromal cells are involved in the maintenance of HSC niches, and that neural and hormonal stimuli co-regulate the two stem cell compartments.

As a novel and interesting aspect, this work convincingly identifies perivascular marrow stromal cells (skeletal stem cells [SSCs]) as the physical entity on which different modulators of bone marrow homeostasis (neural, hormonal and probably others) may converge. Thus, it demonstrates that the association between MSCs and HSCs goes beyond the establishment and maintenance of the HSC niche; it is a dynamic event that is translated into a co-regulation of the two stem cell systems, as previously hypothesized based on human data.

Furthermore, expression of nestin in skeletal and non-skeletal mesenchymal progenitors has been previously reported in multiple works. However, in most cases, the attention was focused on the expression of this marker as a reflection of the neurogenic potential of MSCs. This work investigates the biological properties of nestin-positive bone marrow stromal cells from a skeletal perspective and in the context of bone marrow physiology.

The identification of nestin as a marker of MSCs/SSCs in the mouse improves our knowledge on the MSCs'/SSCs' phenotypic properties, and stimulates future studies to identify and define nestin-expressing cells in the human bone marrow.

Meanwhile, the Nes-GFP transgenic mouse seems to provide a very useful tool to further investigate the interaction between SSCs and HSCs in the mouse bone marrow. In sum, this work consolidates, and extends to the mouse, the notion of a microvascular niche for a dual system of stem cells in the bone marrow, and for their dynamic interaction. Of particular importance and potential for future studies is the link, originally provided by this work, between regulation of MSC function and adrenergic signaling.

References: Riminucci M, Bianco P: "This article provides solid evidence of the physical and biological interaction between mesenchymal stem cells..." Evaluation of: [Méndez-Ferrer S et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *Nature*. 2010 Aug 12; 466(7308):829-34; doi: 10.1038/nature09262]. Faculty of 1000, 15 Sep 2010. F1000.com/5000965

Short form

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Nestin(+) mesenchymal stem cells (MSCs) constitute an essential hematopoietic stem cell (HSC) niche component. The cells are spatially associated with HSCs and adrenergic nerve fibres and seem to work as a bridge between them. Many studies have identified osteoblasts, endothelial and perivascular cells as the cellular components of the HSC niche in the bone marrow (BM) {1-3}. This is a beautiful paper on the HSC niche.