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Stem Cells signaling and microenviroment

BCR-ABL1 AND JAK2 V617F MUTATIONS IN MESOANGIOGENIC PROGENITOR CELLS SUGGEST A COMMON BONE MARROW PRECURSOR FOR HEMATOPOIETIC AND STROMAL CELL NICHE

I.S. Burzi[1], M. Montali[2], S. Barachini[2], E. Pardini[1], G. Sardo Infirri[1], D. Tagliafierro[1], A. Brunetti[2], A. Votto[2], L. Sijoni[2], R. Fazzi[3], S. Galimberti[2], V. Susini[1], M. Franzini[1], I. Petrini[1]

[1]Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa; [2]Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa; [3]U. O. Ematologia, A. O. U. Pisana, Italy

Introduction: Mesangiogenic progenitor cells (MPCs) can differentiate into osteoblasts, chondrocytes, and adipocytes, and, unlike mesenchymal stromal cells (MSCs), can give rise to endothelial progenitors. MPCs can be isolated ex vivo only from human Pop#8 progenitors, which share markers with monocytic precursors. Their position in the bone marrow hierarchy remains unclear. Therefore, we analyzed MPCs in chronic myeloid leukemia (CML) with *BCR-ABL1* and in Myeloproliferative Neoplasms (MPN) with V617F *JAK2* mutation. Since CML and MPN originate from hematopoietic stem cells bearing *BCR-ABL1* or V617F *JAK2* mutation, their detection in patients' MPCs indicates a common ancestor for hematopoietic and stromal lineages in the bone marrow niche.

Methods: At Pisa University Hospital, we accrued 15 patients with CML carrying the *BCR-ABL1* fusion gene (at diagnosis or within 1 year of TKI therapy) and 3 patients with MPN carrying the V617F *JAK2* mutation at diagnosis. MPCs were isolated from bone marrow aspirates by Ficoll-Paque™ gradient and cultured in DMEM with 10% PhABS. Differentiation into MSCs was induced with StemMACS™ MSC Expansion Media (Miltenyi Biotech). To avoid myeloid contamination, MPCs were sorted ($CD34^-CD31^+CD18^+CD14^-$) using a CytoFLEX SRT Cell Sorter (Beckman Coulter). DNA/RNA were extracted with the AllPrep DNA/RNA Micro Kit (Qiagen). RT-PCR detected BCR-ABL1 in MPCs and MSCs, while ARMS-PCR identified the V617F *JAK2* allele.

Results: We detected BCR-ABL1 in MPC cultures from 6 out of 8 CML bone marrows. Sorting MPCs to avoid contamination, BCR-ABL1 was confirmed in all 7 cases evaluated. CML-derived MPCs showed reduced mesengenic differentiation compared with healthy controls ($p<0.05$), yet the BCR-ABL1 transcript persisted in 3 out of 4 MSCs differentiated from MPCs. From the bone marrow of MPN patients, we isolated MPCs and, after cell sorting, all 3 samples carried the V617F *JAK2* mutation. The mutation was retained in MSC in the unique sample tested.

Conclusions: Our results show that MPCs from patients with chronic myeloproliferative neoplasms can carry disease-specific mutations. Their detection in purified MPCs and derived MSCs suggests a possible reservoir of the disease during pharmacological treatment, supporting a role of the bone marrow microenvironment in disease maintenance. Moreover, the presence of BCR-ABL1 and V617F *JAK2* mutation in MPC and MSC suggests a common precursor for hematopoietic and stromal niches, challenging the traditional separation between hematopoietic and mesenchymal lineages and positioning MPCs as a cellular bridge between these compartments.

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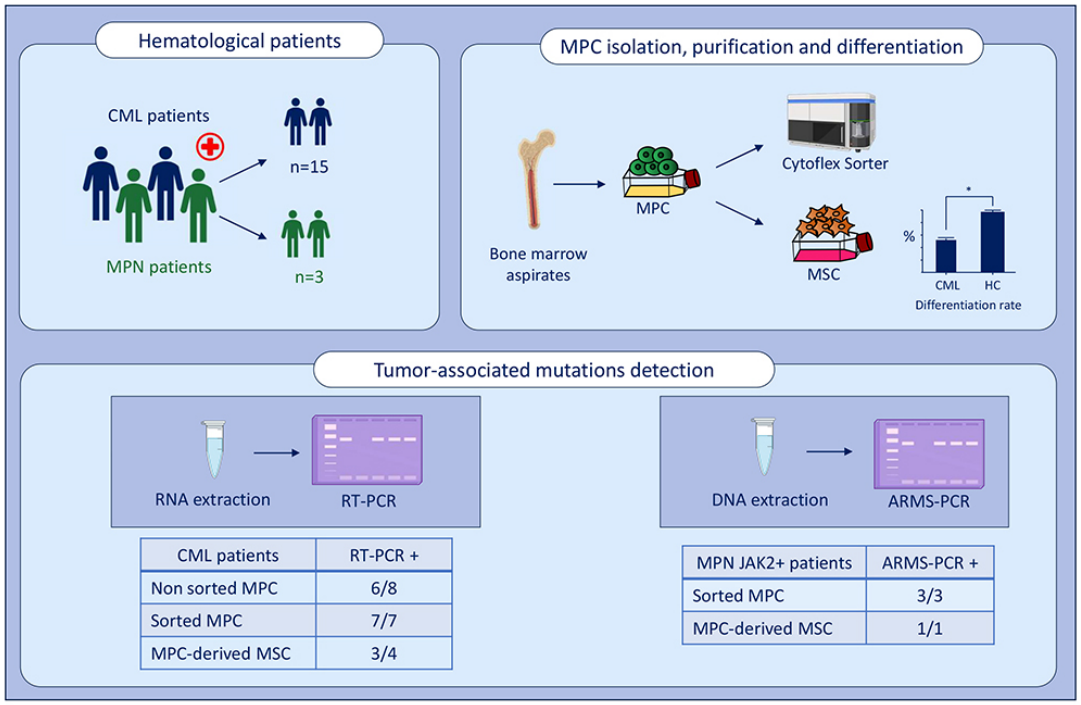

CML patients	RT-PCR +
Non sorted MPC	6/8
Sorted MPC	7/7
MPC-derived MSC	3/4

MPN JAK2+ patients	ARMS-PCR +
Sorted MPC	3/3
MPC-derived MSC	1/1