Myelodysplastic Cells in Patients Reprogram Mesenchymal Stromal Cells to Establish a Transplantable Stem Cell Niche Disease Unit

Hind Medyouf,1,11,13,* Maximilian Mossner,2 Johann-Christoph Jann,2 Florian Nolte,2 Simon Raffel,3 Carl Herrmann,4,5 Amelie Lier,3 Christian Eisen,3 Verena Nowak,2 Bettina Zens,1,3 Katja Müdder,1,3 Corinna Klein,1,3 Julia Obländer,2 Stephanie Fey,2 Jovita Vogler,2 Alice Fabarius,2 Eva Riedl,6 Henning Roehl,7 Alexander Kohlmann,8 Marita Staller,8 Claudia Haferlach,8 Nadine Müller,2 Thilo John,9 Uwe Platzbecker,10 Georgia Metzgeroth,3 Wolf-Karsten Hofmann,2 Andreas Trumpp,1,5,11,15,* and Daniel Nowak5,16

1Division of Stem Cells and Cancer, Deutsches Krebsforschungszentrum (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
2Department of Hematology and Oncology, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, 68167 Mannheim, Germany
3Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM gGmbH), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
4Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, 69120 Heidelberg, Germany
5Division of Theoretical Bioinformatics, DKFZ, 69120 Heidelberg, Germany
6Department of Pathology, University Hospital Mannheim, 68167 Mannheim, Germany
7Department of Orthopedics, University Hospital Mannheim, 68167 Mannheim, Germany
8Munich Leukemia Laboratory (MLL), 81377 Munich, Germany
9Department of Traumatology, DRK Hospital Westend, 14056 Berlin, Germany
10Technical University Dresden, University Hospital ‘Carl Gustav Carus,’ Medical Clinic and Policlinic I, 01307 Dresden, Germany
11German Cancer Consortium, 69120 Heidelberg, Germany
12These authors contributed equally to this work and are co-senior authors
13Present address: Technical University Dresden, University Hospital ‘Carl Gustav Carus,’ Medical Clinic and Policlinic I, 01307 Dresden, Germany
*Correspondence: hind.medyouf@uniklinikum-dresden.de (H.M.), a.trumpp@dkfz-heidelberg.de or andreas.trumpp@hi-STEM.de (A.T.)
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Medyouf et al. (2014), Cell Stem Cell, 14, 824-837
Myelodysplastic syndromes (MDS)

Heterogeneous group of malignant clonal disorders of the myeloid lineage affecting mainly older individuals (median 68-75a)

Characteristics:
- Ineffective hematopoiesis
- Presence of dysplastic cells in the BM
- Peripheral cytopenias

Clinical presentation: Anemia
- Bleeding
- Infection

Classification according to risk-score system segregates patients according to prognosis (lower-risk, intermediate-risk, high-risk)

Several genetic lesions identified in patients with MDS

Genetic mouse models of MDS – no recapitulation of the disease heterogeneity

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Xenograft models in immunodeficient mice

- inconsistent, transient and low level engraftment especially in low-risk patients

- Engraftment only with HSC from high risk patients that are closer to AML than MDS

- Distinguishing normal and MDS HSC is difficult – no specific marker and not all MDS HSC have trackable cytogenetic lesions

- Recent studies showing that microenvironment alterations influence the development of myeloid neoplasms

Medyouf et al. (2014), Cell Stem Cell, 14, 824-837
Hypothesis - disease propagating cells in lower risk patients form a functional unit with their respective stromal niche cells

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Enhanced engraftment of lower-risk MDS by cotransplantation of patient-derived MSCs

Medyouf et al. (2014), Cell Stem Cell, 14, 824-837
Genes commonly mutated in MDS and analysed in this study

<table>
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<th>Gene</th>
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</table>

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Synergistic effect of MSC & growth factors on the expansion of HSPCs

Test the xenograft model in NSGS mice that constitutively express the human cytokines IL-3, GM-CSF and SCF

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NSGS mice further enhance the engraftment of dysplastic MDS cells

Medyouf et al. (2014), Cell Stem Cell, 14, 824-837
Identification of disease propagating cells (DPC) in MDS

-lineage restricted (myeloid) progenitor cells?

-genetic/epigenetic changes in stem cells preventing lymphoid lineage commitment?

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Myeloid and erythroid cells are consistently derived from MDS cells

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DPC in lower-risk MDS are restricted to the lin-CD34+CD38-subset and show variegated clonality

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Comparison of MDS engraftment with MDS MSCs versus healthy MSCs

MDS MSC provide MDS CD34+ cells with significantly enhanced engraftment capacity

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Molecular features of MDS MSCs in comparison with healthy MSCs

- Factors for survival and proliferation of HSPC
  - Fibrosis-associated genes
  - Ongoing stromal stimulation
  - Response to inflammatory environment

MDS MSC

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MDS MSC have an altered pattern of gene expression concerned with intercellular cross talk that might support enhanced MDS hematopoietic cell engraftment

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Exposure of healthy MSCs to MDS BM leads to altered gene expression in MSCs

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Summary

• intricate interplay between mutant hematopoietic cells and their MSCs in MDS – diseased 'hematopoietic niche unit'

• MDS hematopoietic cells instruct healthy MSCs to acquire MDS MSC-like features

• MDS MSCs produce cytokines and other factors further promoting development and expansion of diseased hematopoietic MDS stem cells and their progeny

Medyouf et al. (2014), Cell Stem Cell, 14, 824-837
Thank you!

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