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Cell Stem Cell
Article

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

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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

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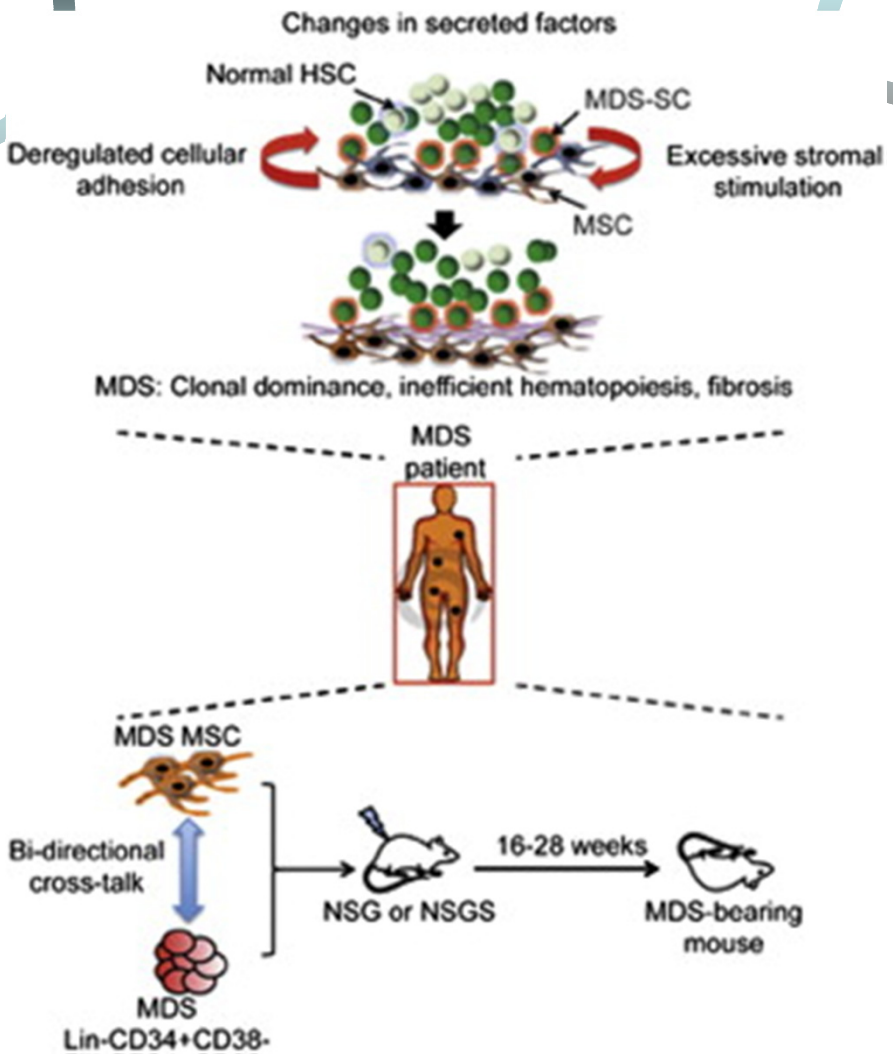

Hypothesis - disease propagating cells in lower risk patients form a functional unit with their respective stromal niche cells

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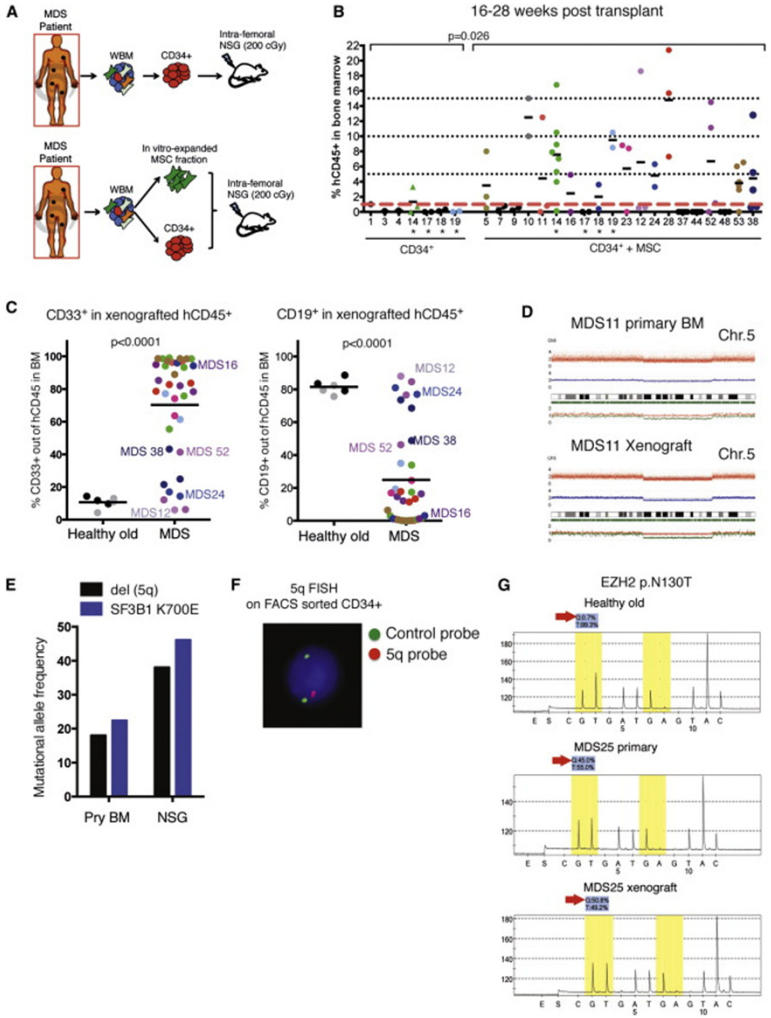
Xenograft Model using NOD-*scid* IL2Rgamma^{null} mice



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

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Gene	Amplicons	Frequency [%]
SF3B1	7	14.5
SRSF2	4	12.4
U2AF1	8	7.3
ZRSR2	12	3.1
DNMT3A	16	2.5
EZH2	17	6.4
IDH1/2	1/1	1.4/2.1
TET2	27	20.7
ASXL1	11	14.4
TP53	7	7.5
CBL	2	2.7
KRAS/NRAS	2/2	0.9/6.3
RUNX1	7	8.7
ETV6	8	2.6
NPM1	1	1.8

Genes commonly mutated in MDS and analysed in this study

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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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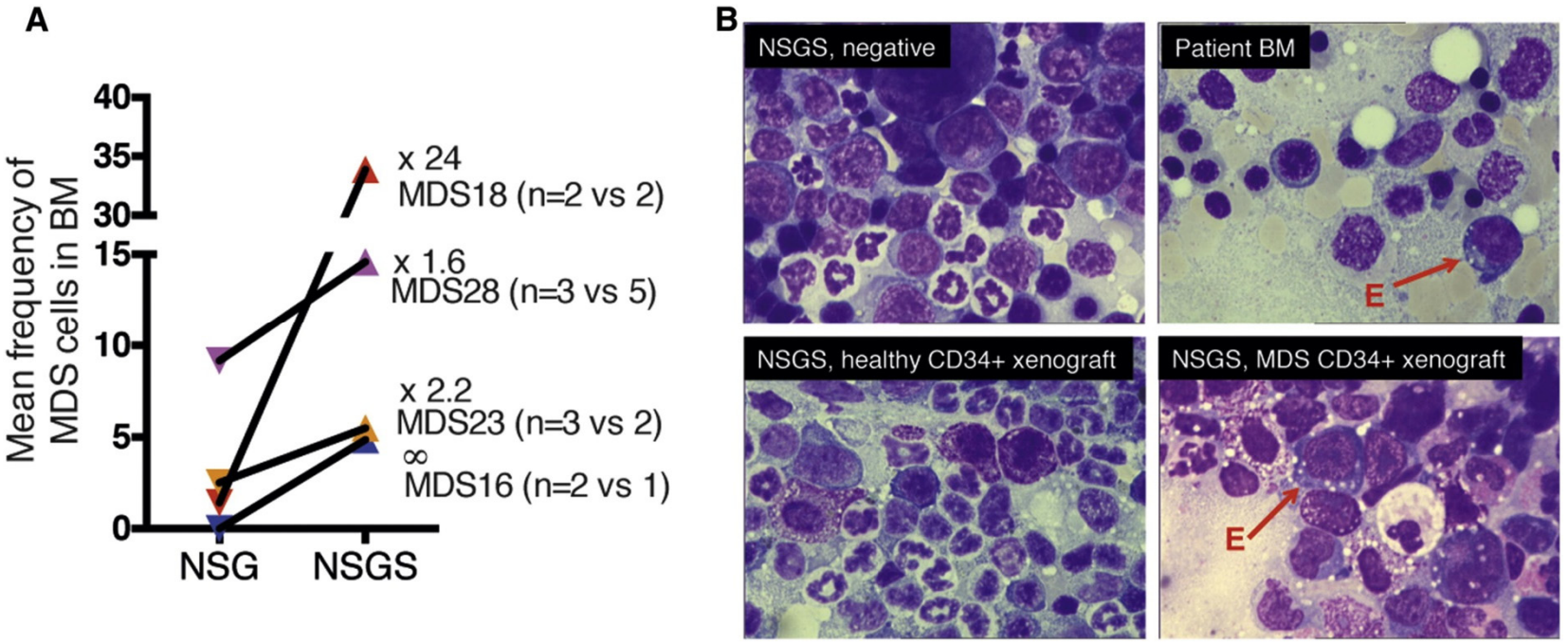

NSGS mice further enhance the engraftment of dysplastic MDS cells

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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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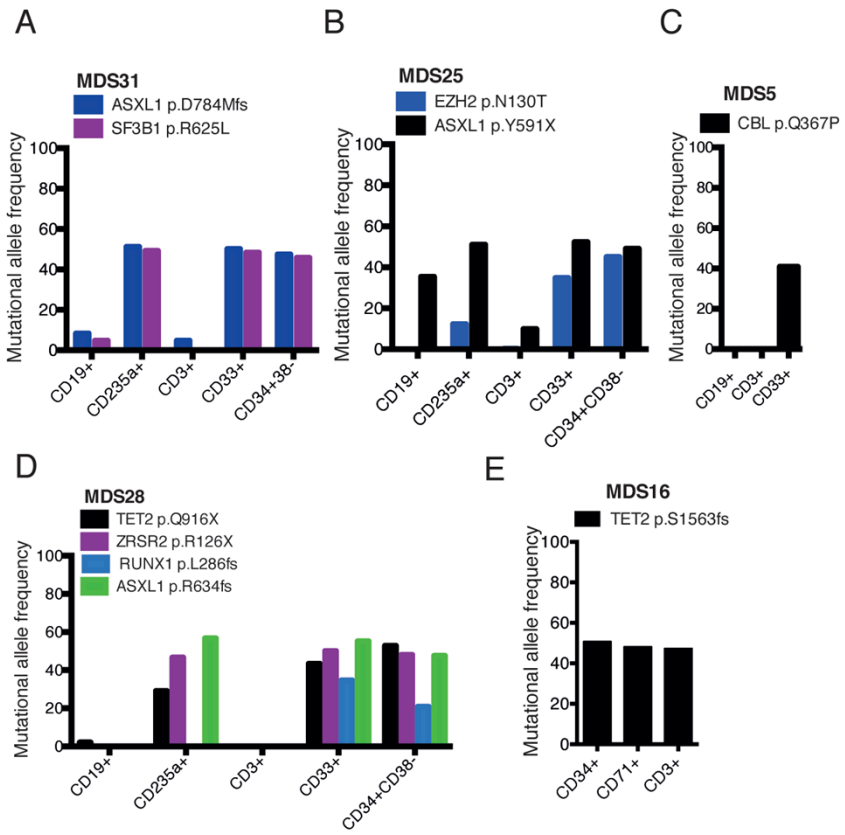
Figure S2



Myeloid and erythroid cells are consistently derived from MDS cells

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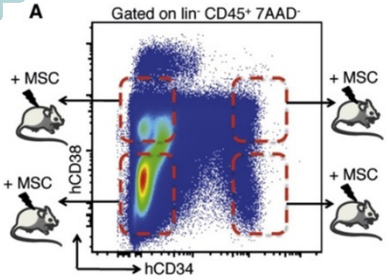
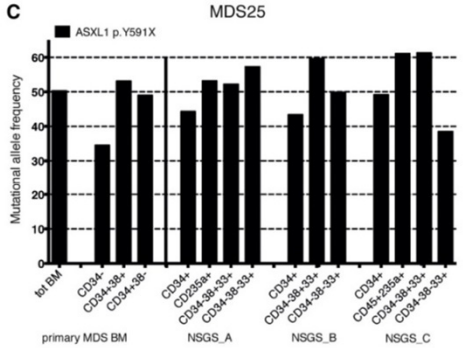
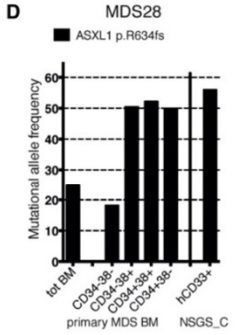
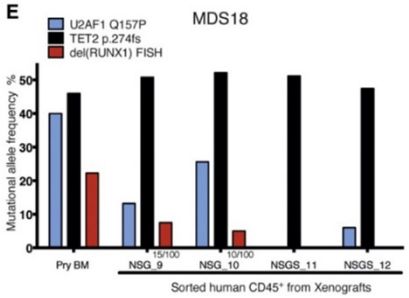


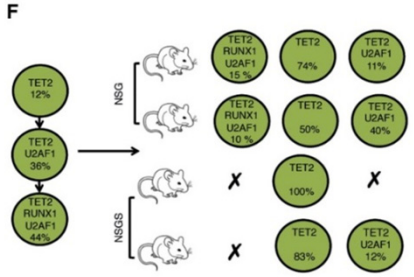
B

MDS ID	Injected cells	Nb. Cells / mouse	Mice > 1% hCD45+	% hCD45+ in BM	Weeks post-transplant
MDS25	**CD34+CD38-**	13,000	**3/3**	**6 ; 33 ; 29.6**	14
del(5q)	CD34+CD38+	13,000	0/4	0	14
	CD34-	13,000	0/3	0	14
	CD34-	2,500,000	0/2	0; 0.036	14
MDS28	**CD34+CD38-**	40,000	**1/2**	0.21 ; **35**	16
RCMD	CD34+CD38+	40,000	0/2	0	16
	CD34+CD38+	150,000	0/1	0.04	16
	CD34-CD38+	40,000	0/2	0	16
	CD34-CD38+	150,000	0/2	0	16
	CD34-CD38-	40,000	0/2	0	16
	CD34-CD38-	150,000	0/2	0	16









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

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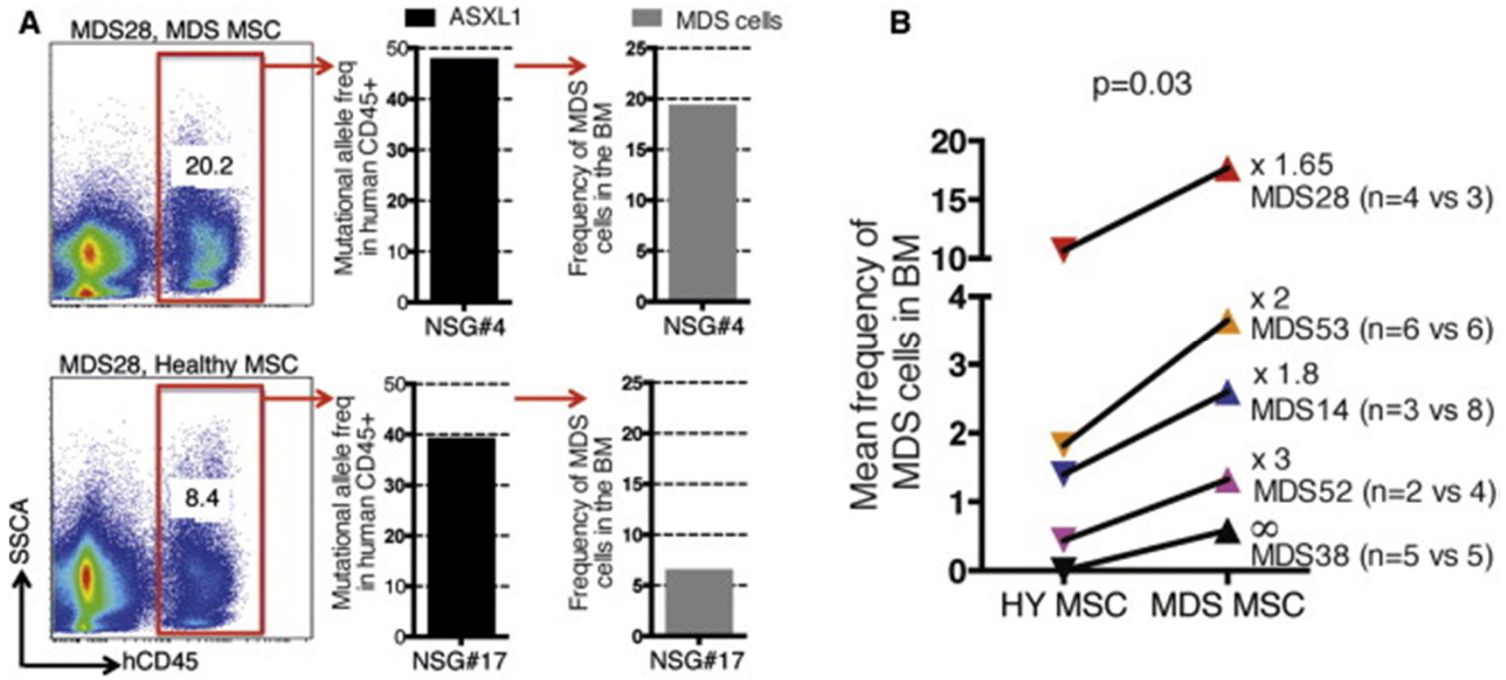
Comparison of MDS engraftment with MDS MSCs versus healthy MSCs



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

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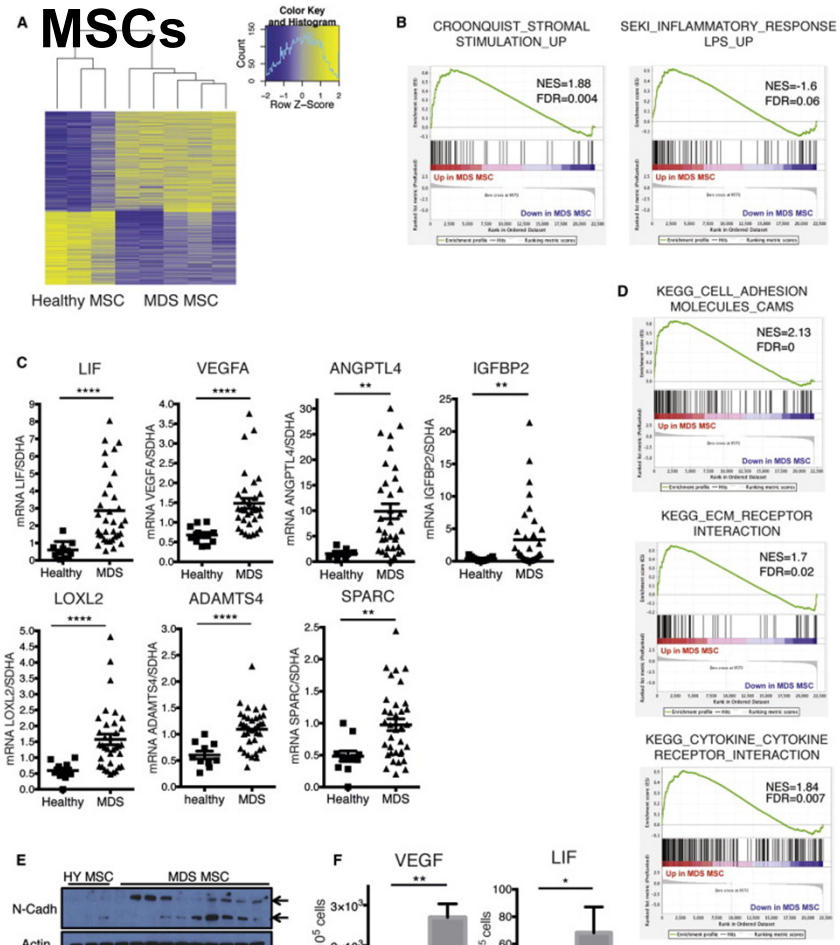
Molecular features of MDS MSCs in comparison with healthy MSCs



MDS MSC

Factors for survival and proliferation of HSPC ↑

Fibrosis-associated genes ↑

Ongoing stromal stimulation

Response to inflammatory environment

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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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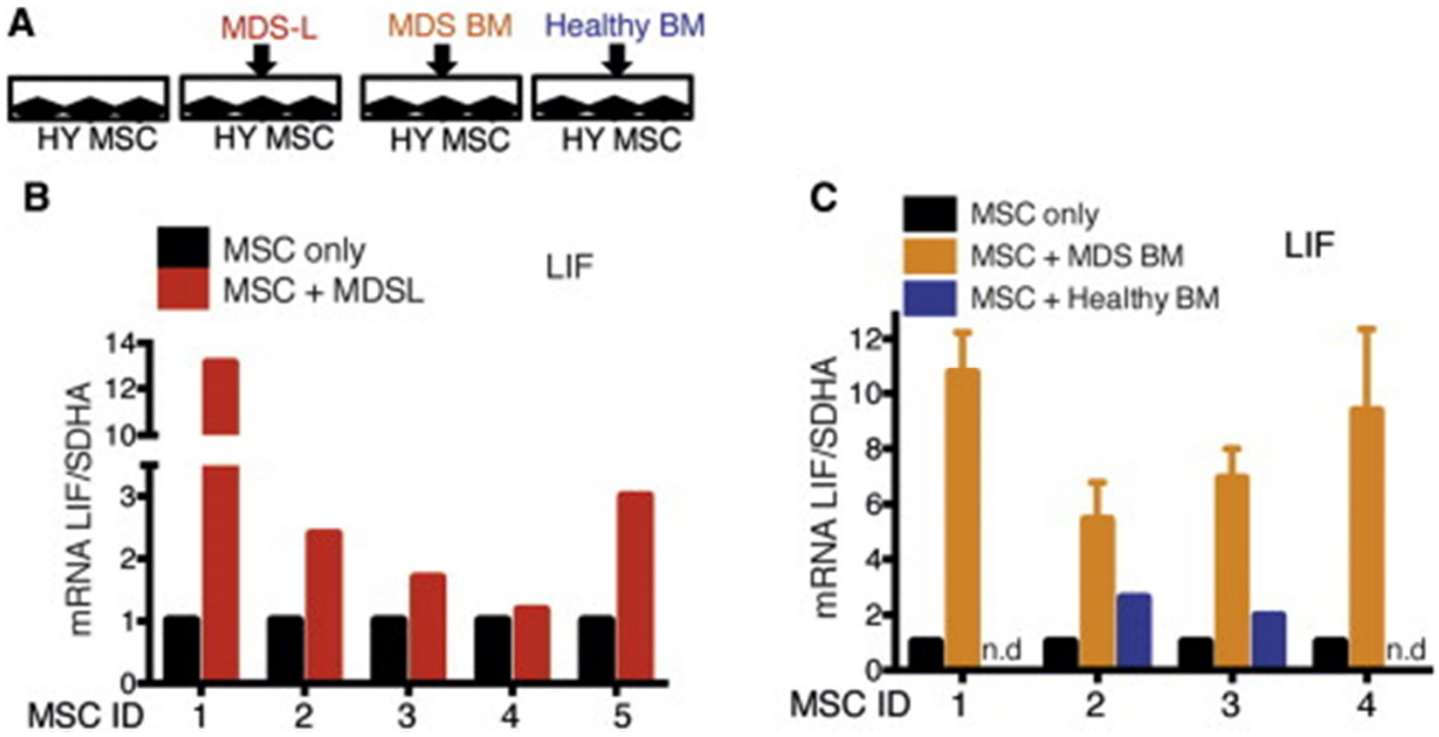

Exposure of healthy MSCs to MDS BM leads to altered gene expression in MSCs

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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

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