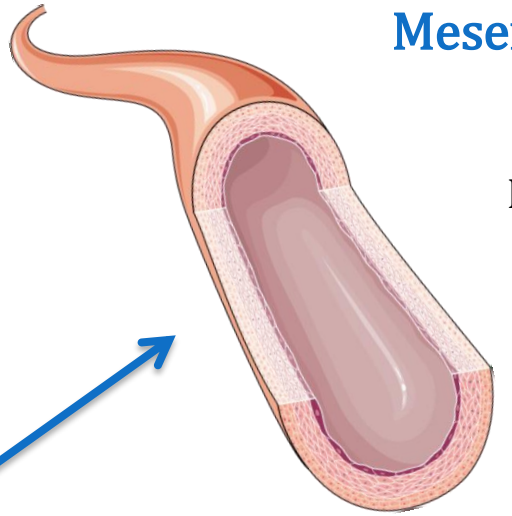
Mechanisms of action of MSCs and EPCs: How do stem cells work?

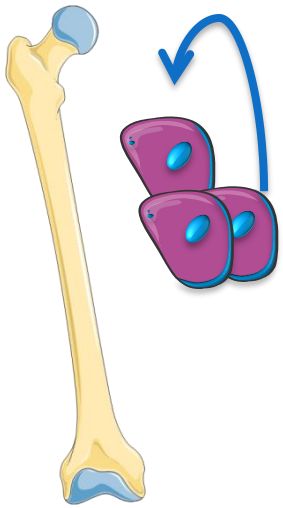
Raquel Guillamat-Prats

Mesenchymal stem/stromal cells

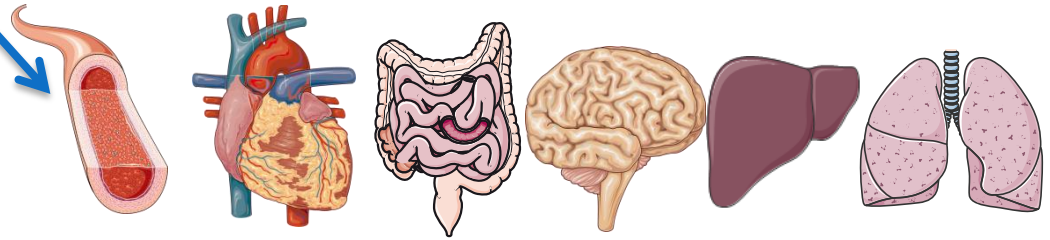


Migrate to different tissues
in case of necessity

Self-renewal factors:
FGF-4, EGF, PDGF, TGF-β, VEGF

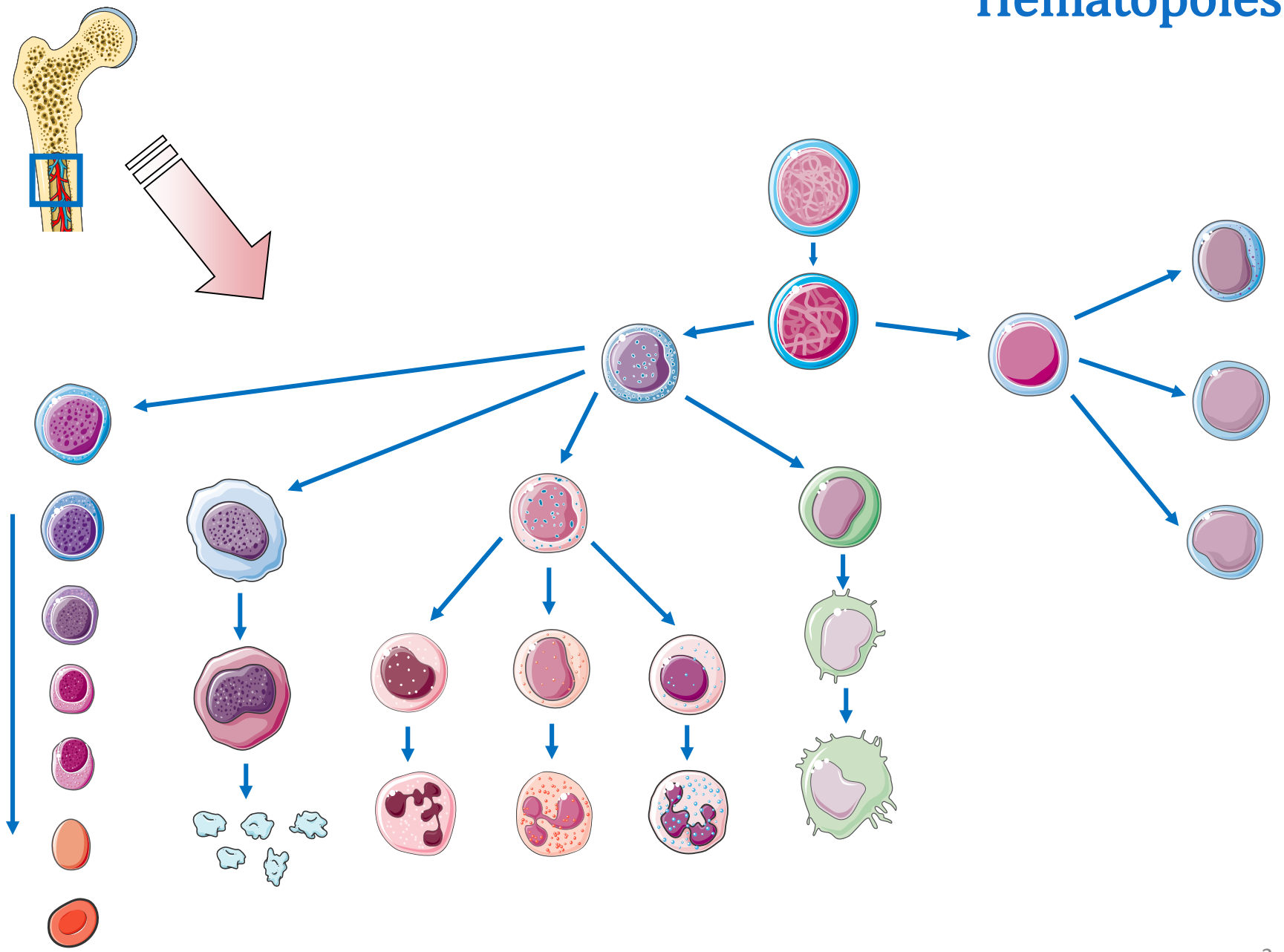


Differentiate to any type of cell

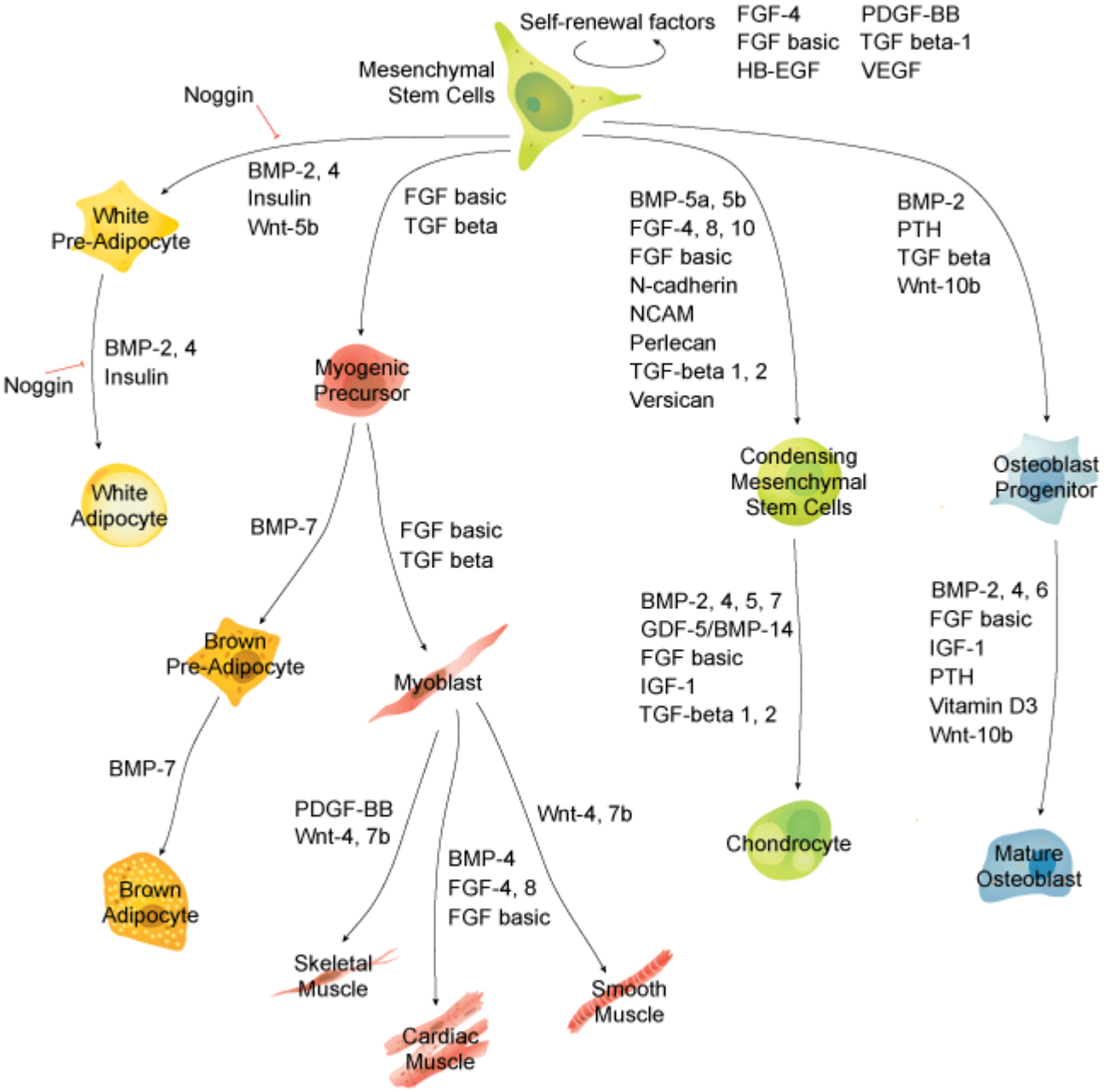


Endothelial progenitor cells
(EPCs)

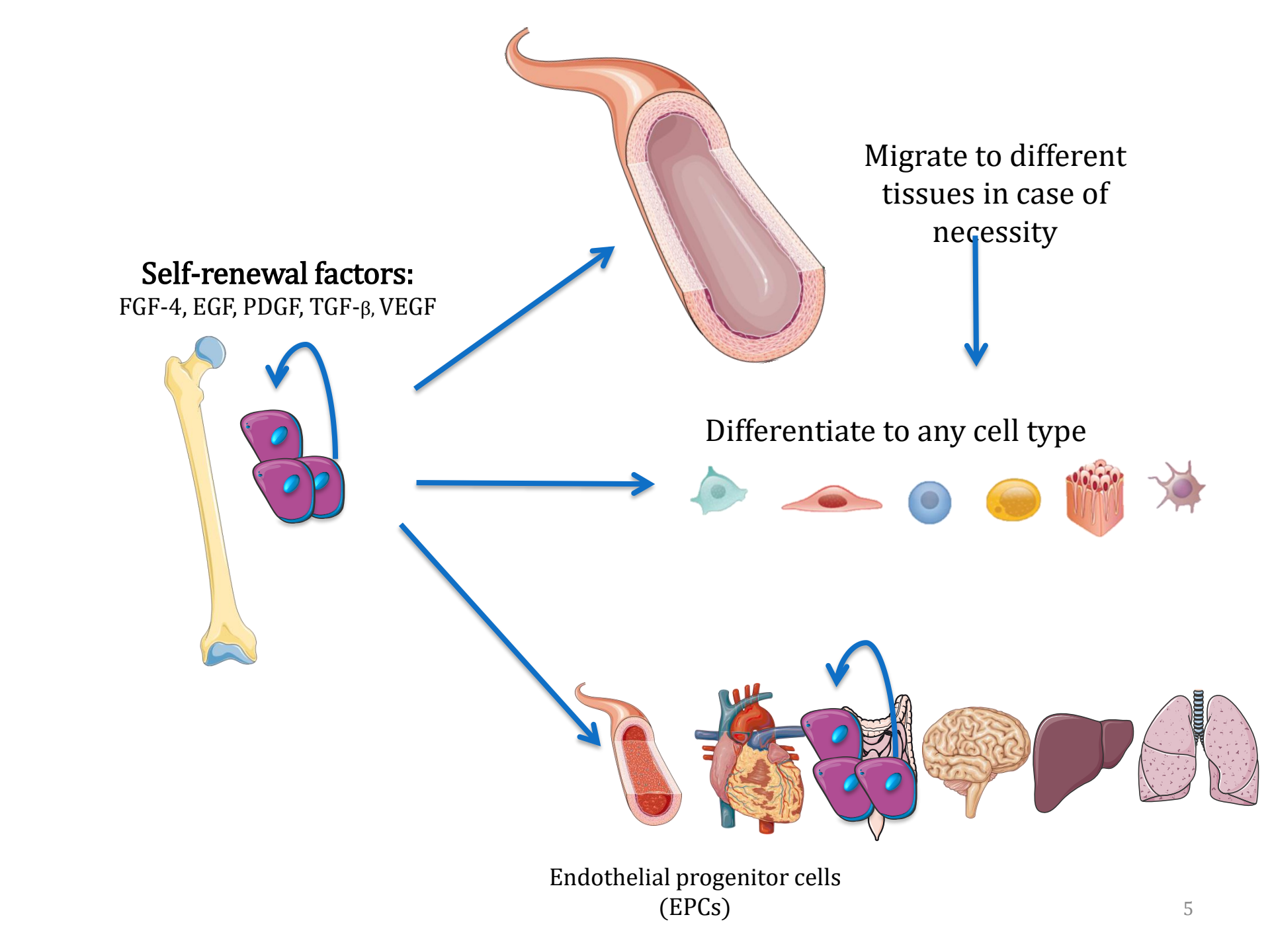
Hematopoiesis



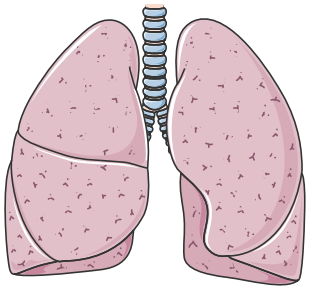
Hematopoiesis in detail



© 2014 R&D Systems, Inc.

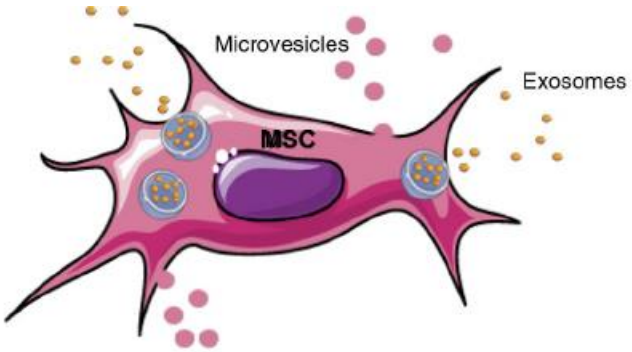

Migrate to different tissues in case of necessity
Self-renewal factors:
FGF-4, EGF, PDGF, TGF-β, VEGF
Differentiate to any cell type
Endothelial progenitor cells (EPCs)

Function of MSCs in disease



- Pulmonary Hypertension (PH)
- Acute Lung Injury (ALI)
- Pulmonary fibrosis (PF)
- Chronic Obstructive Pulmonary Disease (COPD)
- Lung cancer

Function of MSCs in disease



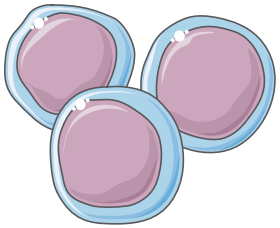
5737 identifiable unique mRNAs

- Angiogenesis
- Cell motility
- Communictaion between cells
- Hematopoiesis
- Neural activity
- Immunity
- Defense

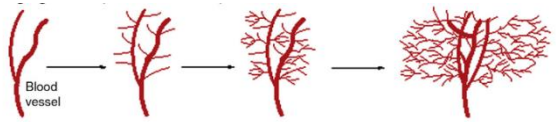
Adaptative immunity

Function of MSCs/EPCs

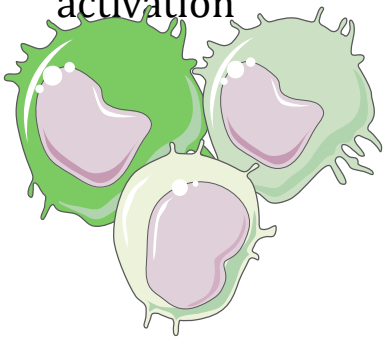
Reduce T-lymphocyte activation

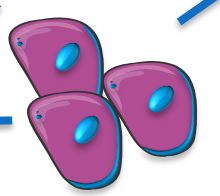


Increase angiogenesis



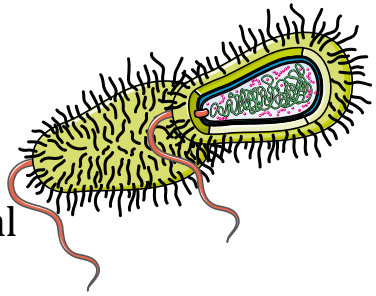
Reduce macrophage infiltration & activation



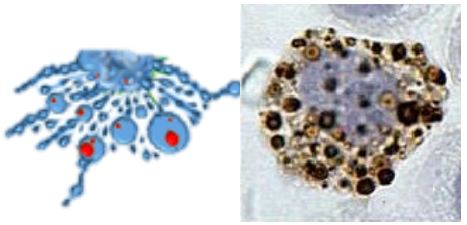


Secretion and release of throphic factors and microvesicles

Anti-bacterial properties

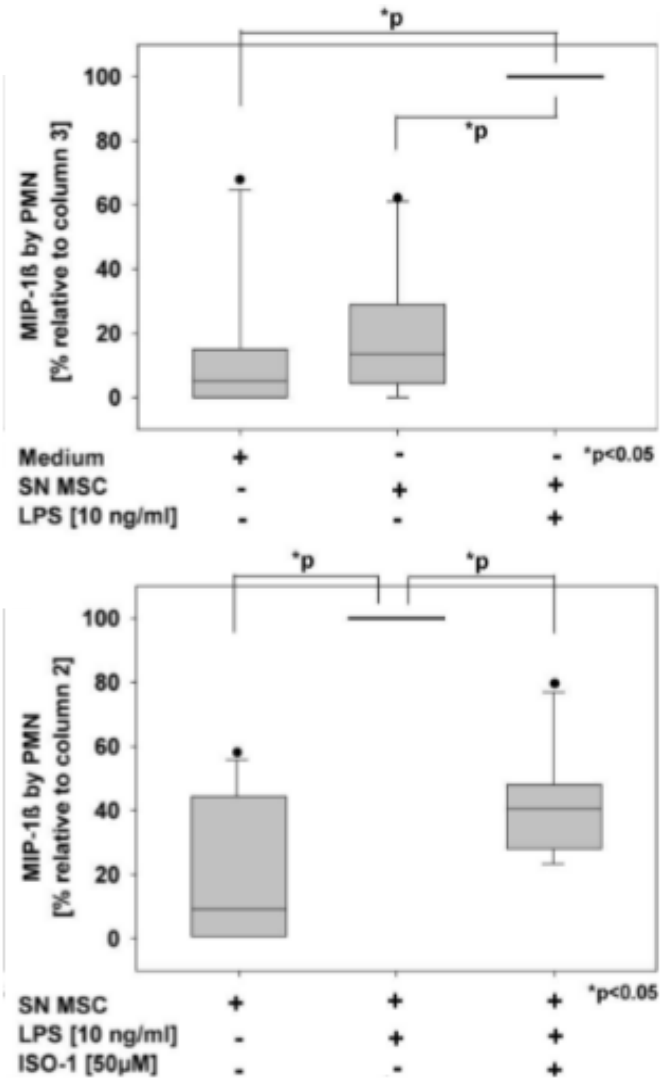


Reduce apoptosis



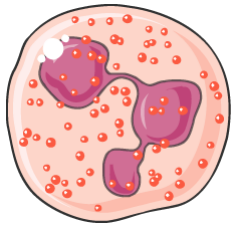
Innate immunity

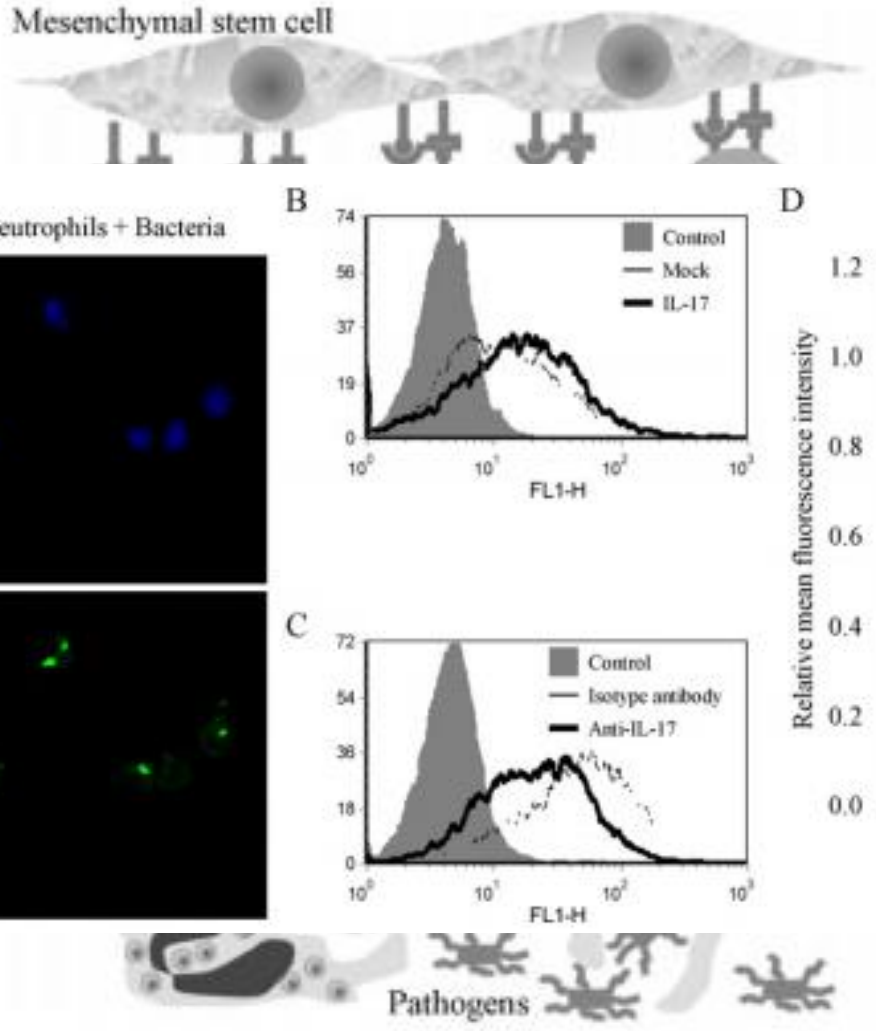
Innate immunity: Modulation of neutrophil function by MSCs



Salami F et al. Immunobiology. 2018 .

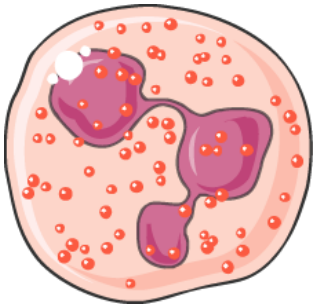
Innate immunity: MSCs activate phagocytic capacity of neutrophils

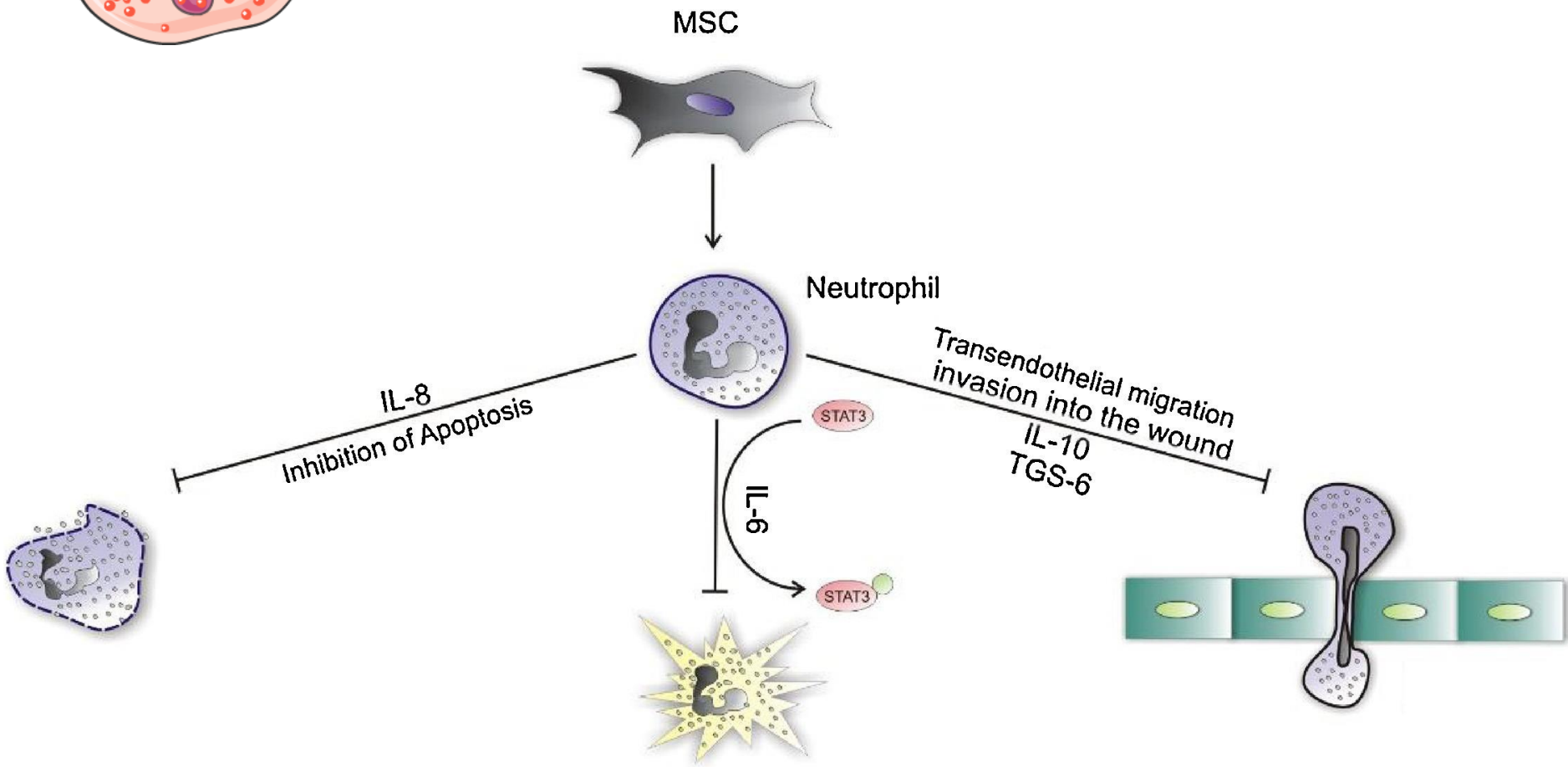




Shu-Ching Hsu et al. Immunobiology. 2013

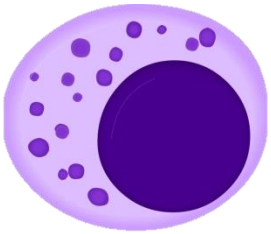
Innate immunity: MSC and neutrophils

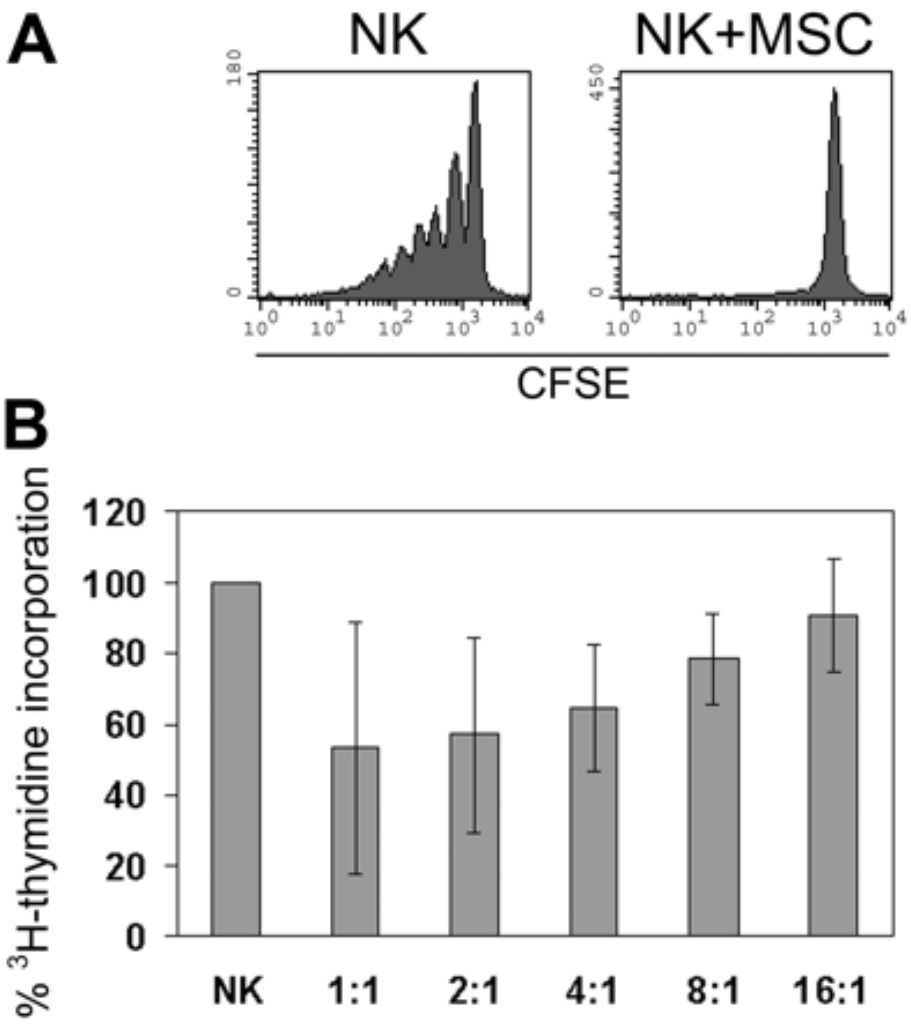




Salami et al. Immunobiology. 2018.

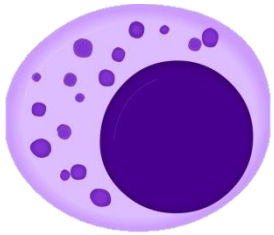
Innate immunity: MSC-induced inhibition of NK-cell proliferation

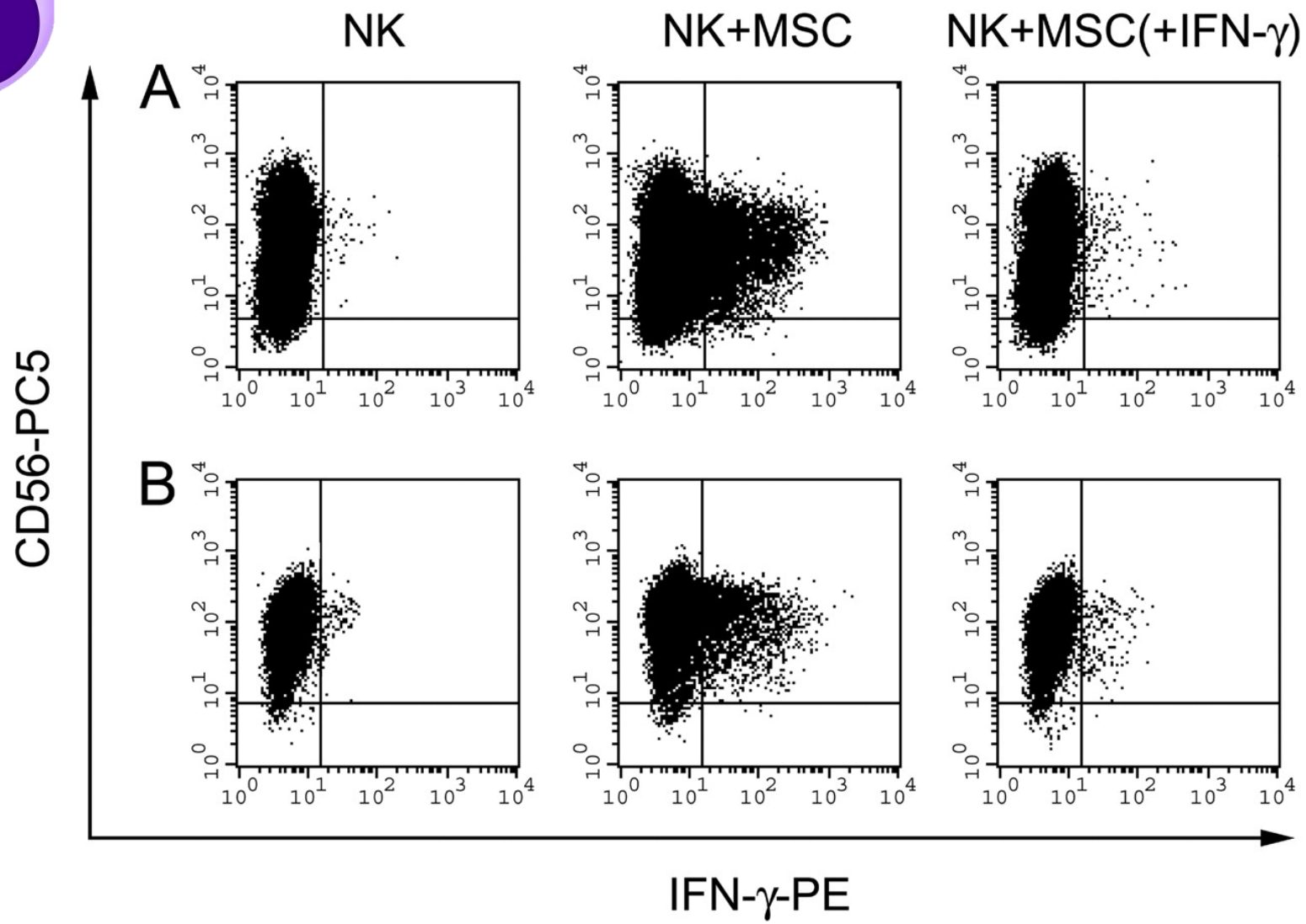




Spaggiari et al. Blood. 2006

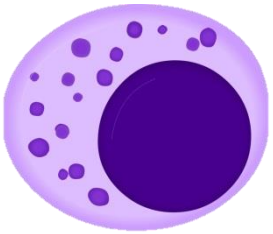
Innate immunity: MSC regulate NK production of IFN-γ

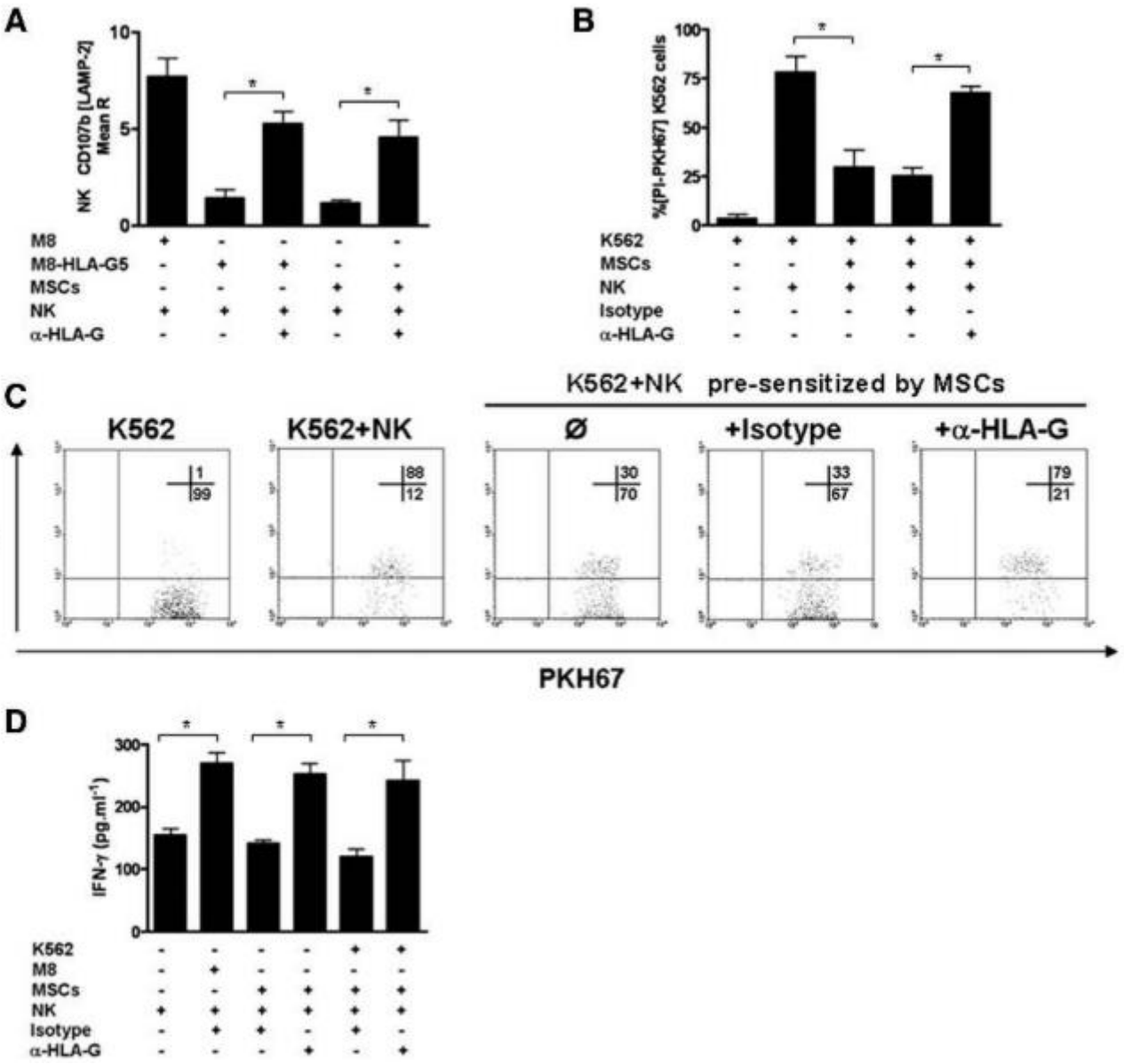




Spaggiari et al. Blood. 2006

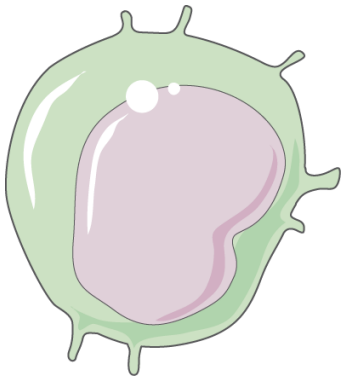
Innate immunity: Inhibition of NK functions by MSCs through HLA-G5 (NK cell lytic activity).

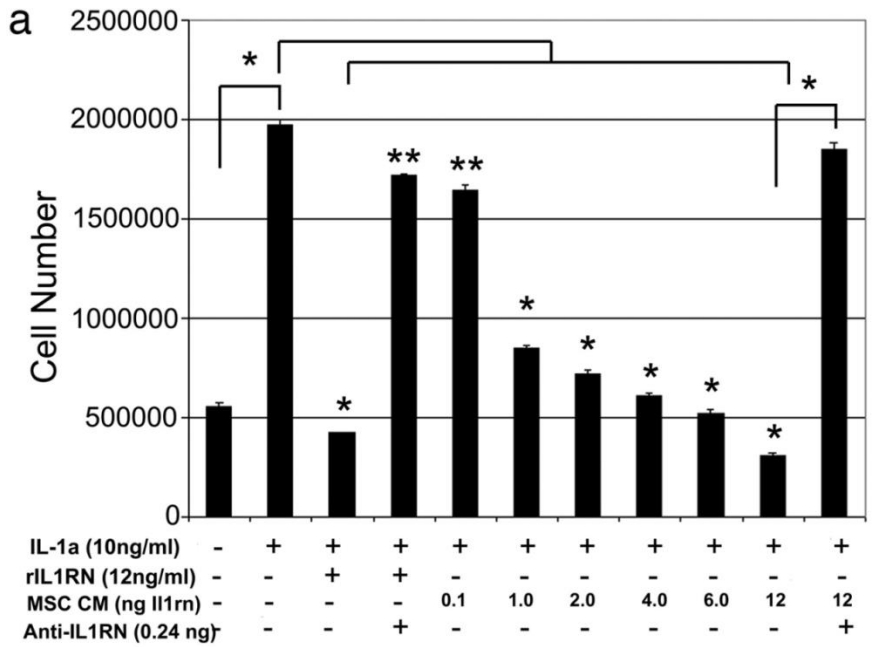


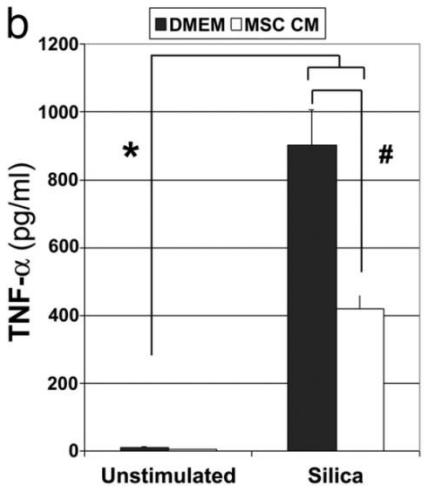


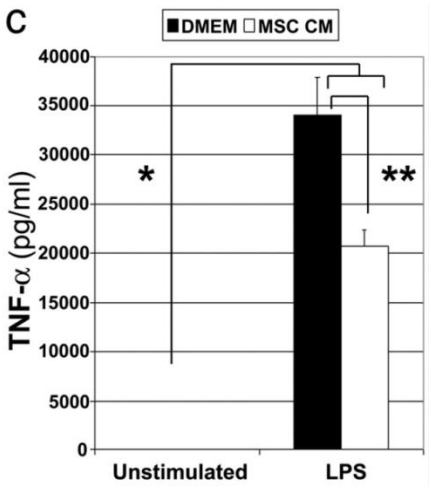
Selmani Z. et al. Stem cells. 2008

Innate immunity: IL1RN secreted by MSCs antagonizes IL-1α activity and blocks release of TNF-α from activated macrophages



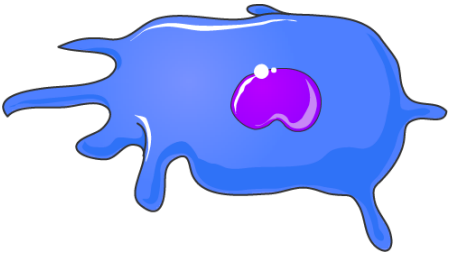


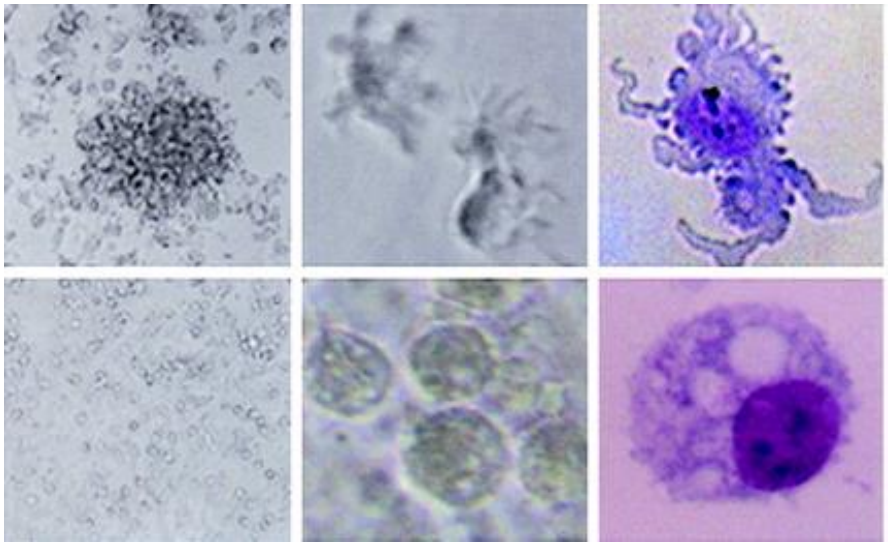


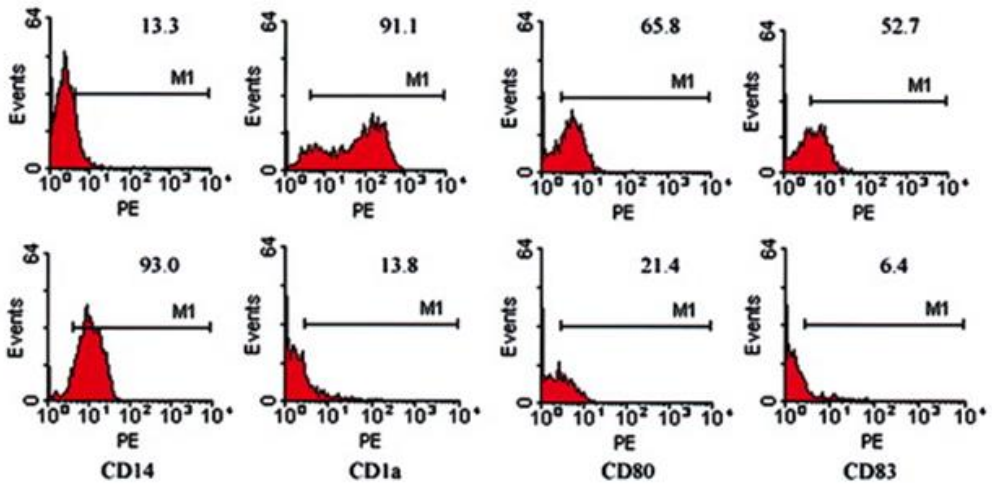


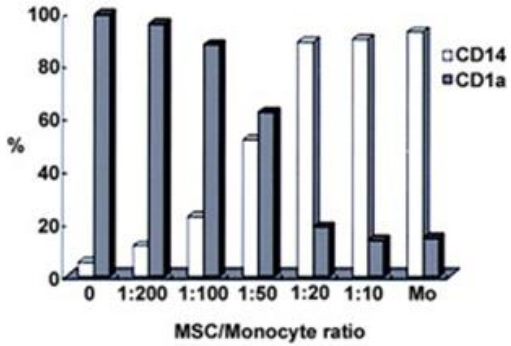
Ortiz et al. PNAS. 2007.

Innate immunity: MSCs could suppress monocyte differentiation into DCs



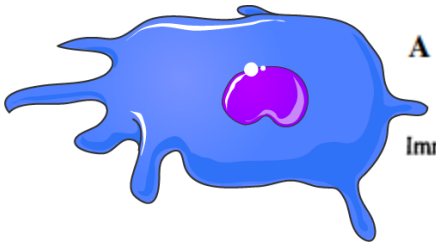


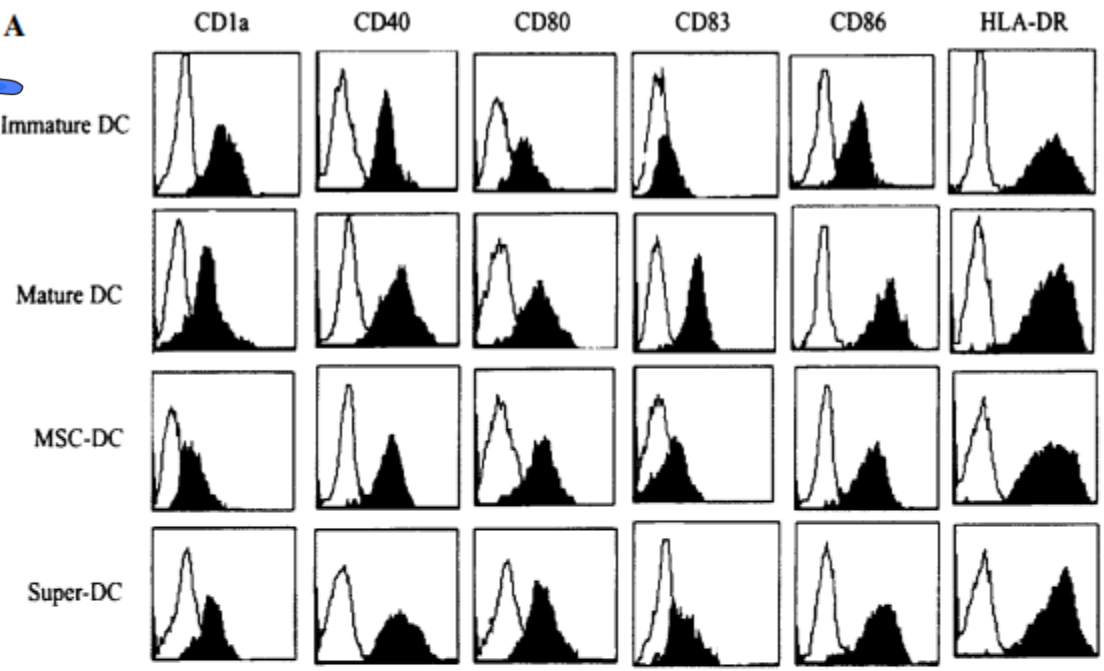


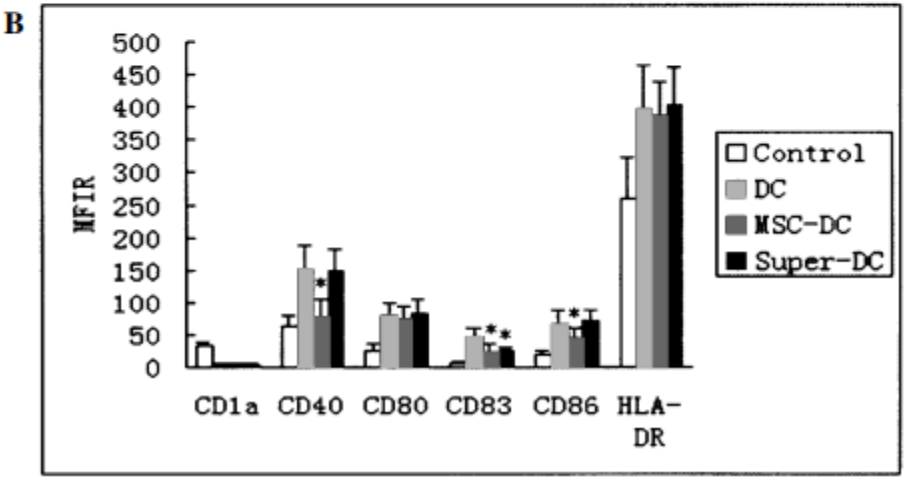


Jiang et al. Blood. 2005 PMID: 15692068.

Innate immunity: MSCs and MSCs supernatants suppress maturation of monocyte-derived DCs

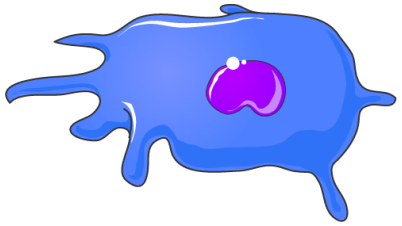


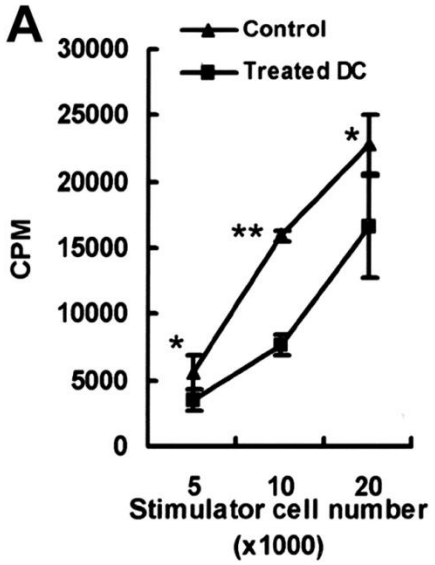


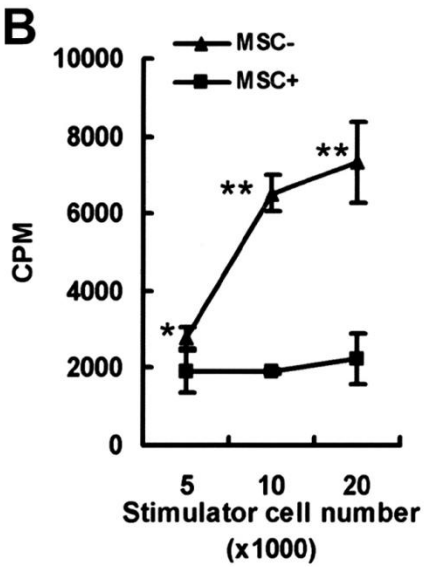


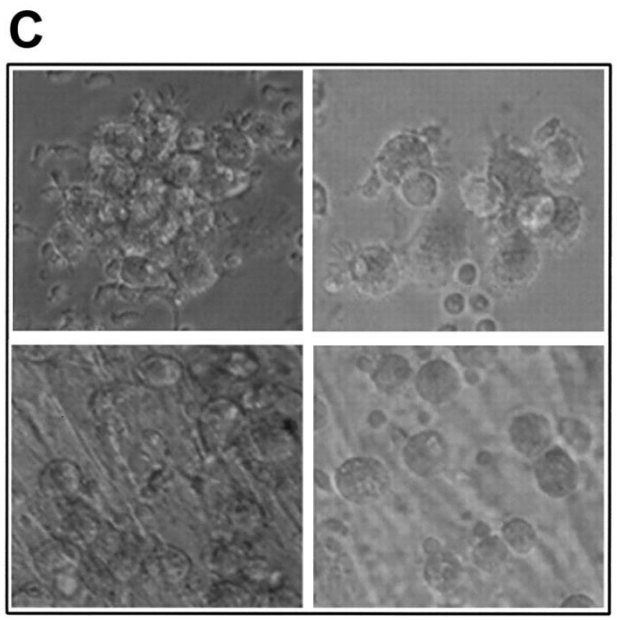
Zhang W et al. Stem cells and development. 2004

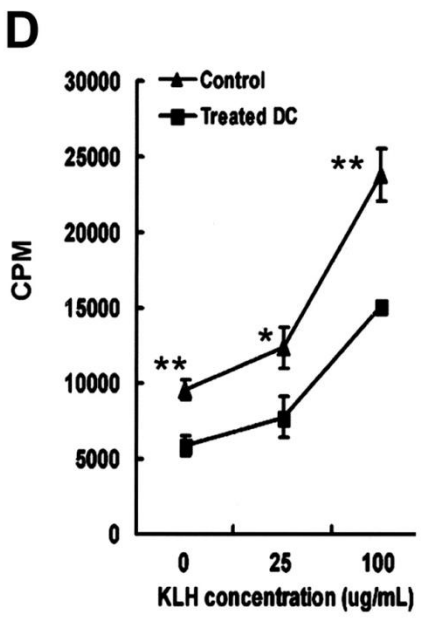
Innate/Adaptative immunity: Immunostimulation of allogeneic T-cell proliferation by mature DCs (mDCs) was impaired by MSC treatment





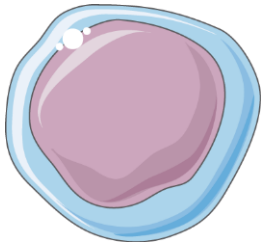


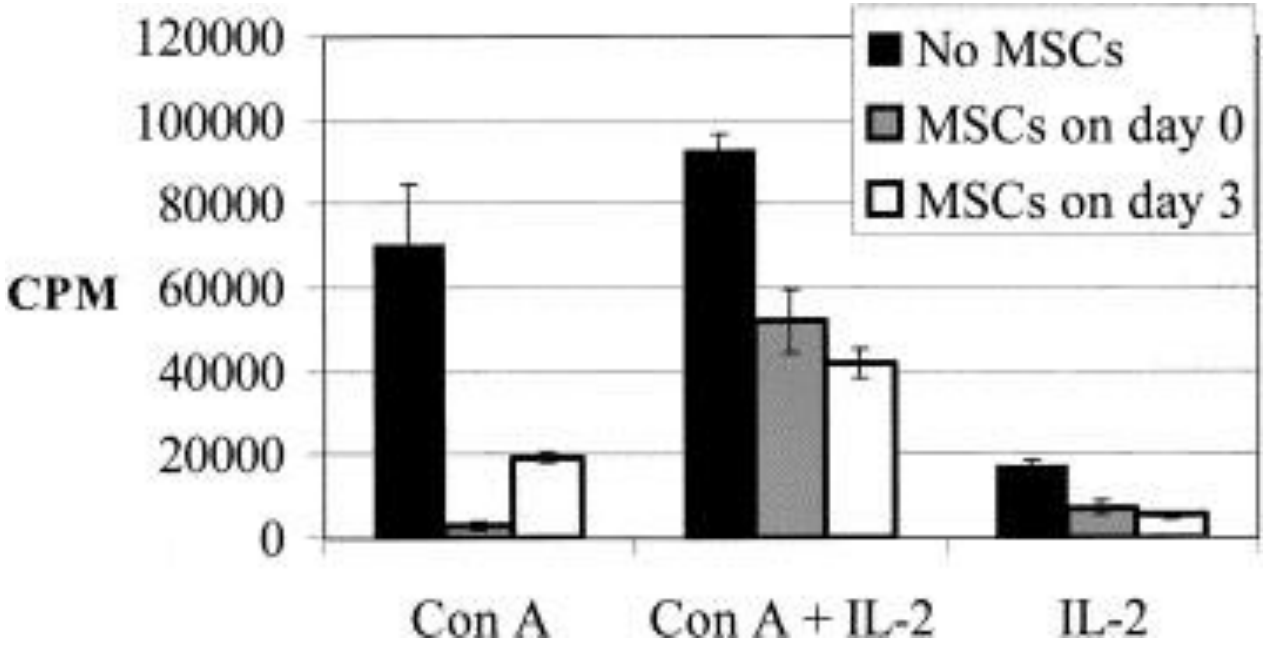




Jiang XX et al. Blood. 2005
PMID: 15692068.

Adaptative immunity: Mesenchymal stem cells suppress lymphocyte proliferation



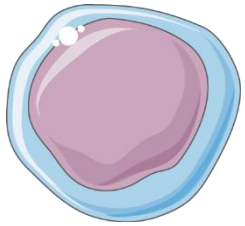


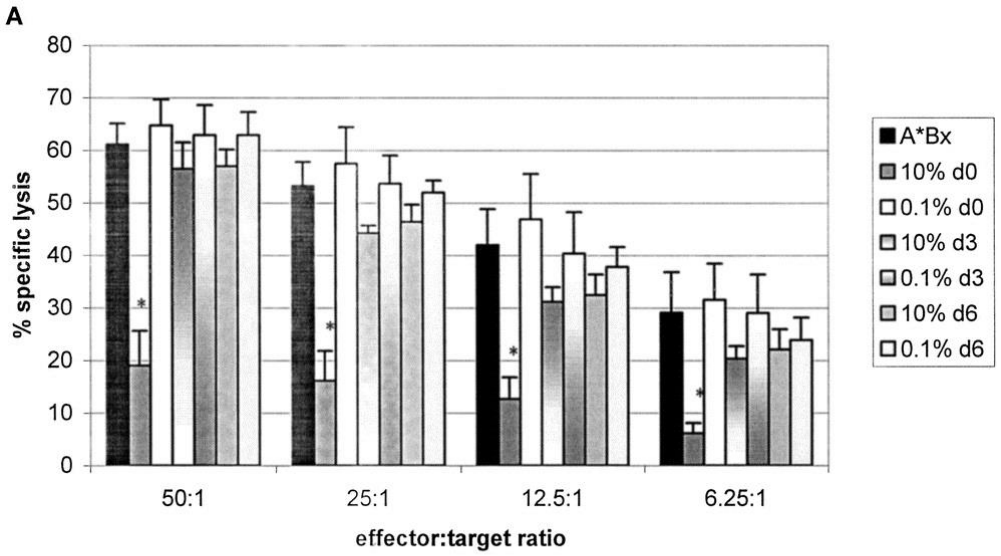
-MSC suppress the proliferative activity of allogeneic peripheral blood lymphocytes in vitro.

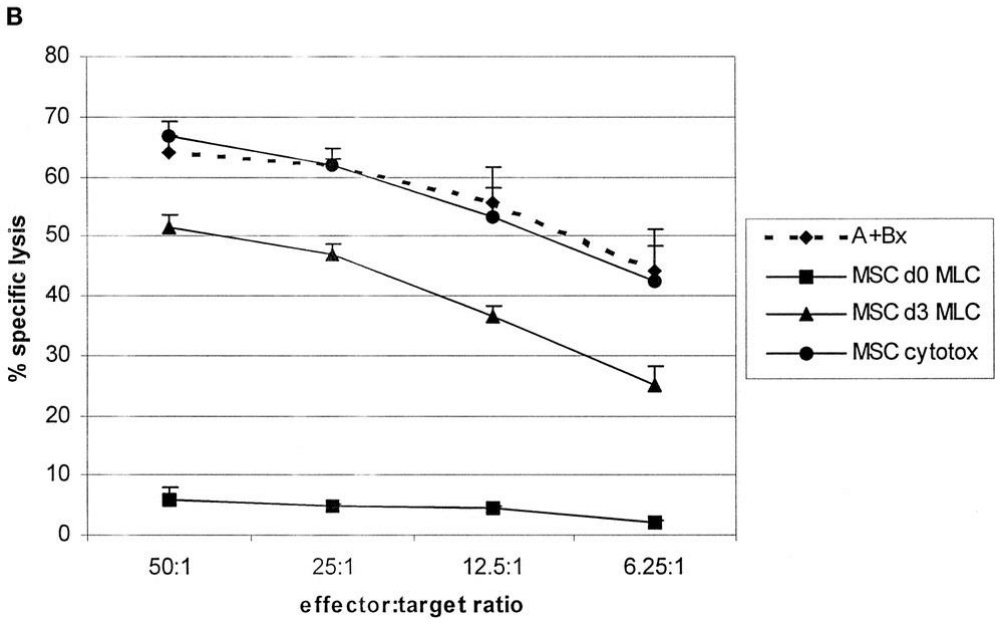
- Induced a alloproliferative response, but also suppressed activity against the mitogen ConA.

Bartholomew A, et al. Exp Hematol. 2002 . PMID: 11823036.

Adaptative immunity: Mesenchymal Stem Cells Inhibit the Formation of Cytotoxic T Lymphocytes in a Time- and Dose-Dependent Manner

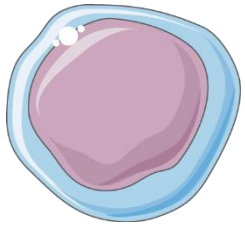


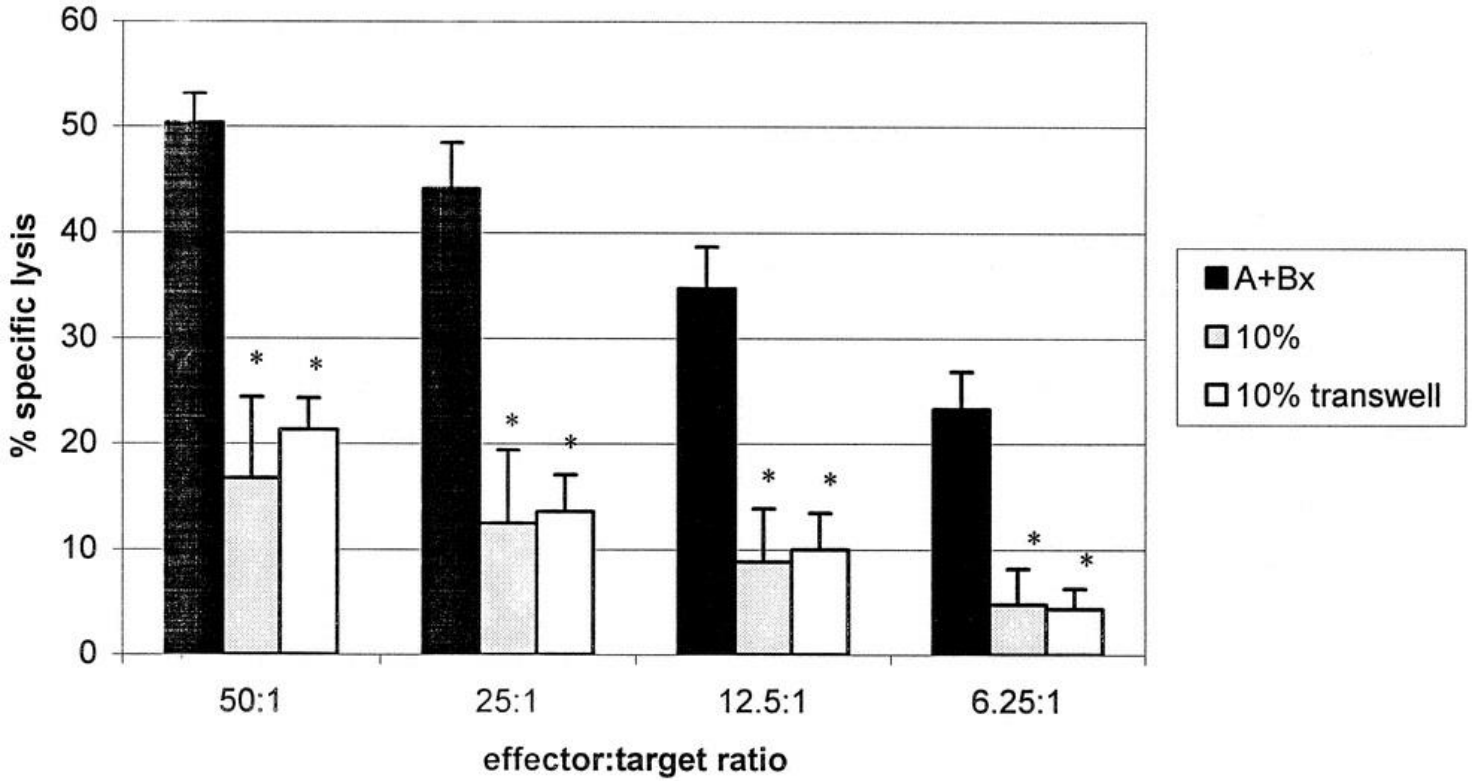




Rasmusson I, et al. Transplantion. 2003

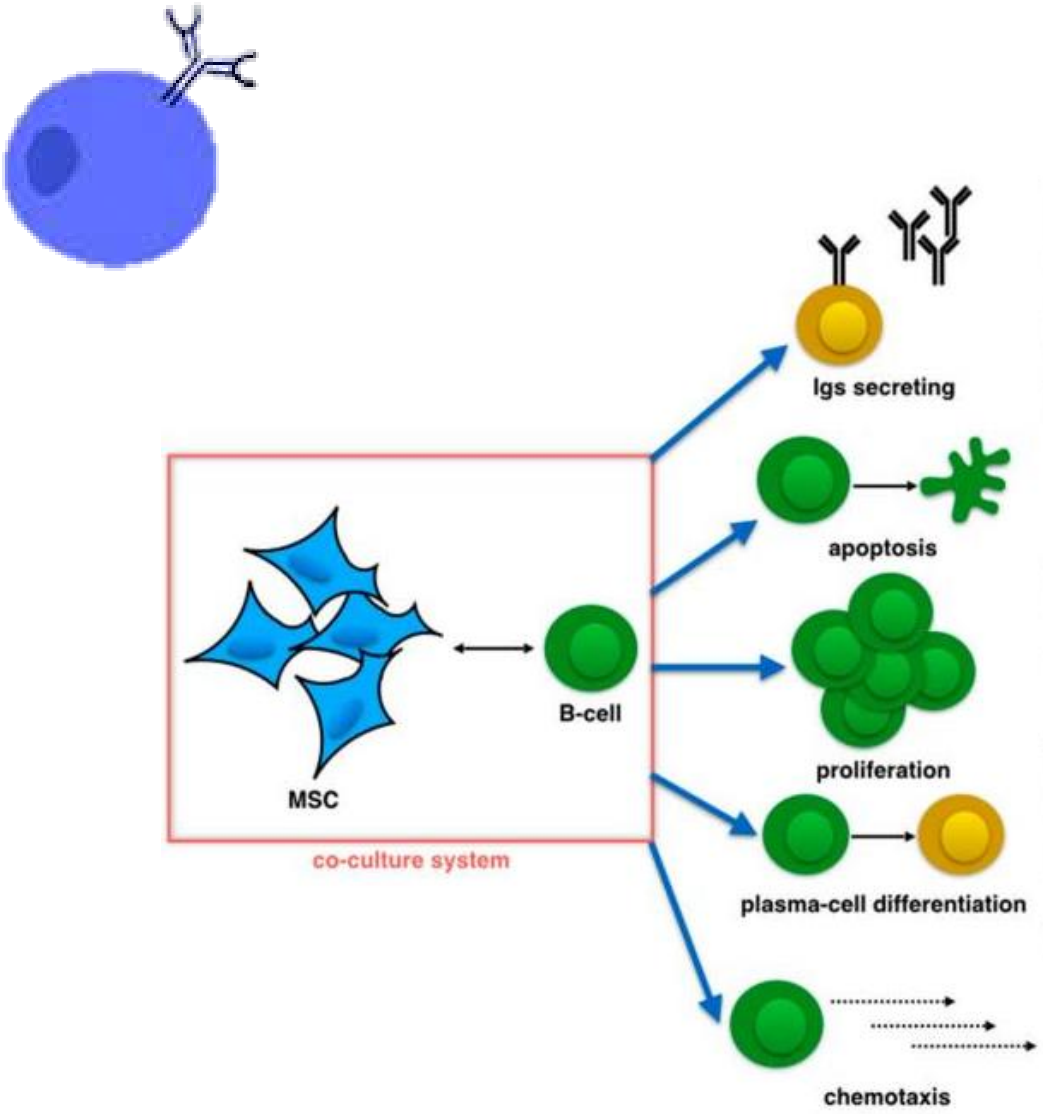
Adaptative immunity: Mesenchymal Stem Cells Inhibit Cytotoxic T Lymphocyte-Mediated Lysis Trough Soluble Factor(s)





Rasmusson I, et al. Transplantion. 2003

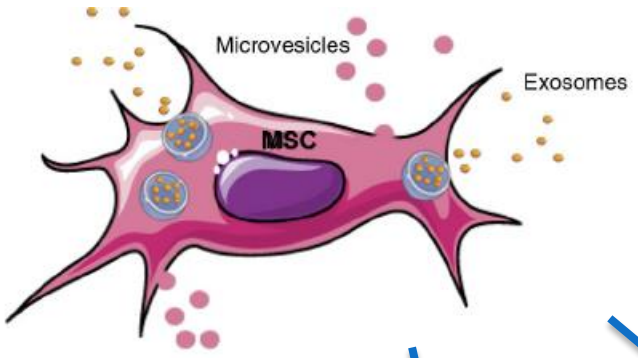
Adaptative immunity: Mesenchymal Stem Cells Inhibit antibody production in B cells



result	potential mechanism
increasing the IgG3 secreting plasma cells, decreasing the IgM secreting plasma cells.[17] down-regulation of immune globulins,including IgM,IgG and IgA[45]	mediated by an unknown soluble factors with paracrine signals of B-cells.[45]
inhibition of Caspase-3 mediated apoptosis of periphery CD19+B-cells.[43]	upregulating the expression of VEGF,phosphorylated AKT,depends on cell-cell contact[43]
inhibition of proliferation of B-cells.[17][45][30][26][34][25][60] promotion of proliferation of B-cells[16][47][72]	blocking in G0/G1 phases of cell cycle of B-cells[45] mediated by MSCs derived PGE2 and other unknown soluble cytokines[72]
inhibition of differentiation to plasma cell of B-cells[17][45][30][26][34][25][49] promotion of differentiation of plasma cell of B-cells[47][72]	down-regulation of expression of Blimp-1 mRNA in B-cells,mediated by an unknown humoral factor.[17]
promoting the chemotaxis and mobility of B-cells.[44]	mediated by an unknown soluble factor.[44]

Fan et al.vInt J Mol Sci. 2016

Summary



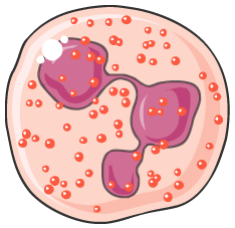
IL-6

PGE2
IDO, NO, TGF-β1, iNOS
HGF, HLA-G5

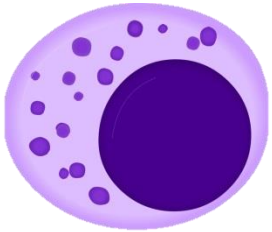
PGE2
IDO
HLA-5

PGE2

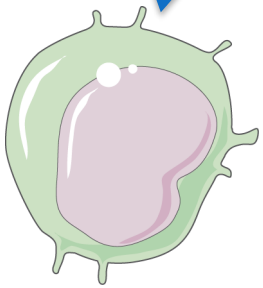
PGE2 +
unknown
factors



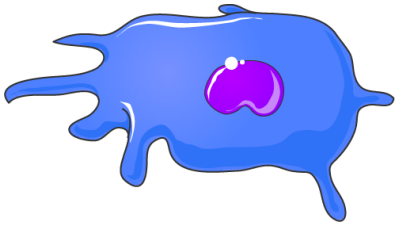
Neutrophils
Inhibiton of apoptosis, Increase phagocytic capacity and migration



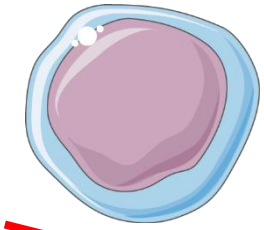
NK
Decrease of cytotoxicity and activation



Monocytes
Deactivate them and decrease the pro-inflammtory cytokines release

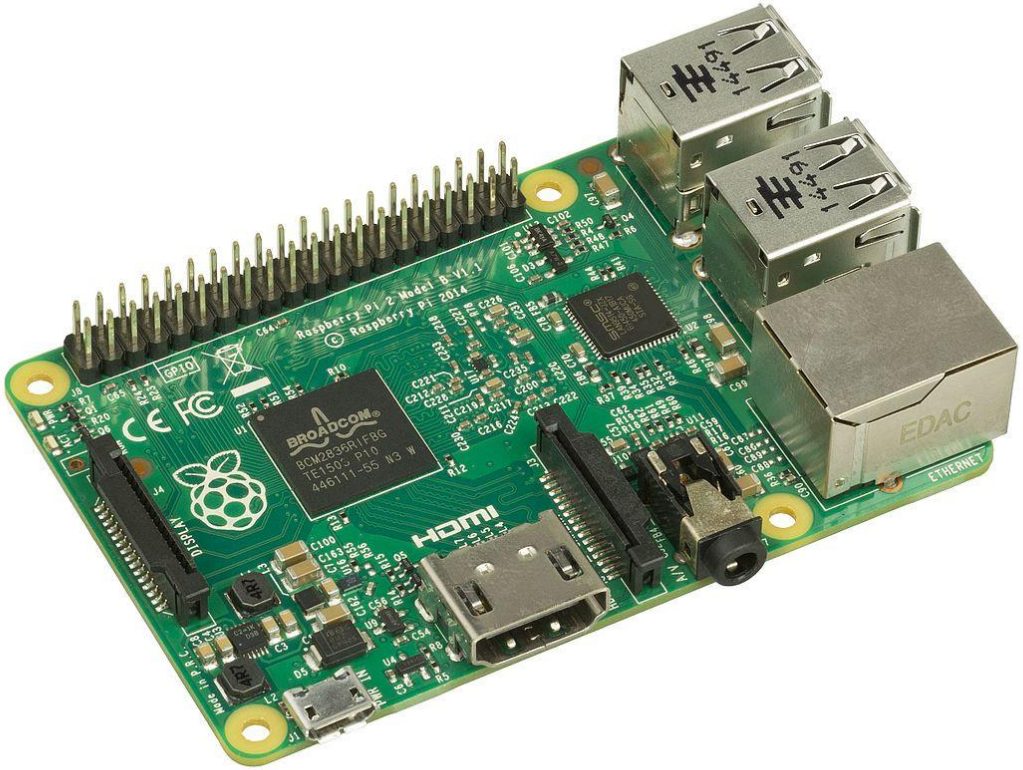


Dendritic cells
Supress their differentiation, maturation adn antigen presentation



Lymphocytes
Decrease of proliferation, cytotoxicity and cytokine secretion and inhibition of antibody production in B-cells

We know a lot about MSCs…



…but we need to further investigate all their functions

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