Cytokine Regulation of Stem Cells

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Abstract

Different types of stem cells are targeted by a number of cytokines that alter proliferation, differentiation, or other properties of stem cells. Stem cells are known to express various cytokine genes. As IL-12, IL-14, G-CSF, and GM-CSF expression is lost after the differentiation of MSCs, these factors might have major contribution to pluripotency. Several other cytokines that are produced by immune cells, frequently target stem cells. Modulation of stem cell functions by cytokines can be a cause of various diseases including cancer. Stem cells can show immunosuppressive properties by a number of mechanisms. MSC-induced immunosuppression is often mediated by IFN-γ, TNF-α, IL-1α, or IL-1β. In co-culture experiments, MSCs were able to control T cells IL-2 response, or, dendritic cells TNF-α and IL-10 secretion. MSCs are also known to cause decreased interferon γ (IFN-γ) and increased IL-4 production by immune cells. However, the outcome in most of the cases depends on the presence of various factors that might synergize or antagonize with each other.

Introduction

Cytokines are small glycoprotein messengers that facilitate efficient communication among immune cells. Immune responses depend on the orchestrated activities of various cytokines. Cytokines not only control innate and adaptive immune responses, but also affect non-immune organs and tissues [1]. Stem cells are probably the biggest breakthrough of applied medical research. These cells can not only self-renew, but differentiate into different types of cells under different conditions. Stem cell research has contributed to the understanding of fundamental

questions related to cell division, senescence, differentiation, and regeneration [2]. Potential benefits of stem cell technology are huge and new discoveries are eagerly awaited in this area. Cytokines regulate stem cell functions more than any other molecule. This review is a concise overview of all the cytokines that affect proliferation, differentiation, or other properties of stem cell(s), either alone or in combination of other cytokines. Cytokines that have not been reported to have any effect on stem cells are not included in this review.

Stem cells understand the language of cytokines

Stem cells are not only known to express various cytokine receptors, but also respond to various cytokines by activation of conventional cytokine signaling pathways [3]. Despite their pluripotent advantage, stem cells appear to be regulated by cytokines in the same manner as other immune cells [1]. The characterization of many cytokines that control hematopoiesis or neuropoiesis has led to intense investigation to find out potential use of these cytokines for ex vivo expansion of various types of stem cells [2]. Effects of various 'colony stimulating factors' (CSFs) to stimulate growth of distinct colonies in bone marrow is the hallmark of stem cell biology. In this regard, Granulocyte colony-stimulating factor (G-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF), Macrophage colony-stimulating factor (M-CSF), Interleukin-3 (IL-3), Interleukin-6 (IL-6), erythropoietin (EPO), thrombopoietin (TPO), Stem cell factor (SCF), flt-3/flk-2 Ligand (FL), and leukemia inhibitory factor (LIF) are most important [4, Table 1].

Cytokines regulate stem cell proliferation and self-renewal

SCF, being a major regulator of stem cells, has been so important for stem cell research that most of the common cytokines have been tested along with it for potential synergistic or antagonistic effects [5]. SCF signaling, through its receptor c-Kit, is not only important for hematopoiesis, but also for pigment control, male fertility, and various aspects of nervous system development. LIF prevents apoptosis, and promotes cell proliferation during embryonic stem (ES) cell differentiation. IL-3 is crucial for proliferation and survival of Hematopoietic Stem Cells (HSCs), and in absence of IL-3, HSCs may remain quiescent [6]. Because of its crucial role, IL-3 is

routinely used during proliferation and differentiation of HSCs. Similarly, IL-3 withdrawal has been very useful for depletion of HSCs [7]. IL-3, SCF, and IL-6 have become the key cytokines for retroviral gene transfer into hematopoietic cells [8]. Most HSCs remain quiescent during homeostasis. However, in response to irradiation or other types of hematopoietic cell stress, HSCs get activated and generate all types of progenitor cells so that mature blood cells can be produced. Signals that regulate this transition in HSCs are a matter of intense research. One clearly identified factor that control this transition is interferon-alpha (IFN-α) [9]. Mice treated with IFN-α, quickly exit dormant phase and enter into active cell cycle. These events are associated with increased phosphorylation of STAT1 and AKT1, and, higher expression of stem cell antigens [9]. Interleukin-1 (IL-1) is associated with accelerated growth of HSCs specifically increasing the production of the cells of myeloid and the granulocyte–macrophage (GM) lineage [4]. These effects are mediated by the rapid activation of a transcription factor Pu.1, the master regulator of GM lineage commitment [4]. Furthermore, IL-1 receptor-deficient mice showed poor recovery of GM-lineage following fluorouracil-mediated myeloablation [10]. Although, HSCs from interleukin-2 (IL-2) knock-out mice were able to proliferate normally, they were defective for reconstitution after lethal irradiation [11]. Furthermore, IL-2 knock-out mice, despite having normal numbers of bone marrow cells (BMCs), had increased numbers of Lin (-) Kit(+)Sca1(+)CD34(-) and Lin(-)Kit(+)Sca1(+)CD34(+) cells [11]. IL-9 induces the proliferation of very primitive human erythroid cells, and synergize with SCF, c-kit, and other cytokines to promote growth of hematopoietic progenitors [12]. When tested in a hematopoietic stem cell line, both IL-4 and IL-9 stimulated growth promoting tyrosine phosphorylation of SHP-2, whereas IL-9 additionally phophorylated STAT3 [13]. IL-10 disrupted mice show reduced primitive hematopoietic cell populations, and, HSCs from fluorouracil treated bone marrows showed enhanced repopulating ability in presence of IL-10 [14]. Stroma-free cultures of Lin−Sca-1+c-kit+ cells yield 3-4 fold more HSCs upon addition of IL-10, and this effect of IL-10 was direct, as, TNF-α or interferon-γ (IFN-γ) secretion was not changed in this case [15]. IL-11 or IL-6, when combined with SCF caused the expansion of murine hematopoietic progenitors that were derived from fluorouracil-treated bone marrow cells [16]. Furthermore, IL-6 and IL-11 were also found to be important for proliferation of megakaryocyte progenitor cells [16]. IL-13, like IL-4, can be very important during early myelopoiesis. In fact, IL-13 enhanced SCF-induced proliferation of Lin-Sca-1+ progenitor cells more efficiently than IL-4, although, IL-13 alone was not able to stimulate

colony formation in this case [17]. IL-13, but not IL-4, synergized with GM-CSF for enhanced colony formation of Lin-Sca-1+ progenitors, however, in case of granulocyte colony-stimulating factor (G-CSF)-induced colony formations, both IL-4 and IL-13 were able to synergize and promote colony formation [17]. Interleukin-32 (IL-32) induced the proliferation of hematopoietic progenitors, and decreased chemotherapy-induced bone marrow toxicities [18]. Interestingly, human cytomegalovirus has been reported to activate cellular IL-32 expression, which means that certain viruses can also directly or indirectly modulate stem cell functions [19]. Interleukin-33 is a cytokine that is secreted, when epithelial cells are exposed to pathogens, allergens, or injury. Other than targeting various immune cells during inflammation, IL-33 also targets hematopoietic stem and progenitor cells to promote myelopoiesis and myeloid cell migration [20].

While several cytokines promote growth of stem cells, some inhibit it. TNF-α is a potent suppressor of normal HSC activity, and its overexpression leads to bone marrow failure syndrome [21]. By downregulating c-kit receptor, TNF-α not only inhibits the SCF-stimulated proliferation of CD34+ hematopoietic progenitor cells, but also completely blocks the colony formations that is caused by combination of SCF and GM-CSF or SCF and IL-3 [22]. Most of these effects are through p55 TNF, not by p75 TNF, receptor. TNF-α also synergized with IFN-γ to abrogate NF-κB and SMAD7 mediated self-renewal and differentiation of mesenchymal stem cells (MSCs) [21]. TGF-β is known to regulate embryonic stem cell heterogeneity [4]

Cytokines regulate stem cell differentiation

IL-1α is known to enhance neurogenesis from human MSCs [23]. When cultured with IL-1β, human bone marrow-derived MSCs differentiated into osteoblast like cells that expressed bone sialoprotein, and deposited abundant mineral. IL-1β, in this case, phosphorylated multiple mitogen-activated protein kinases (MAPKs) and activated nuclear factor-κB (NF-κB) [24]. Interleukin-4 (IL-4) has been reported to cause differentiation of human embryonic stem cells into fibroblast-like cells [25]. In case of mesenchymal stem cells, IL-4 mediated signaling has been reported to activate the expression of genes that are characteristic of cardiac and skeletal muscle cells. However, differentiation was incomplete in this case, as, these cells lacked certain properties of functional muscle cells including lack of contractile activity [26]. Interleukin-6 (IL-6), the

principal proinflammatory cytokine, has recently gained attention as a neuromodulatory cytokine [27]. Maternal administration of IL-6 caused expanded adult forebrain neural precursors and altered olfactory neurogenesis in offsprings, months after fetal exposure [28]. This established the role of IL-6 as an important regulator of neural precursors. Both IL-6 and LIF has been reported to synergize with bone morphogenetic protein (BMP) 7 for neuroepithelial to astrocyte transition [29]. IL-6 inhibits the differentiation of bone marrow-derived MSCs into chondrocytes [B]. Interleukin-7 (IL-7) is indispensible for differentiation of T and B cells during haematopoesis, and, common lymphoid progenitors are known to upregulate IL-7 receptor before producing other type of lineages [30]. Interleukin-8 (IL-8) is a potent mobilization factor for hematopoietic progenitor cells, and is also known to be upregulated in the ischemic brain, henceforth, like IL-6, it is important for both hematopoesis and neuropoiesis [31]. IL-8 induced PI3K/Akt and MAPK/ERK-mediated VEGF production in human MSCs, and, decreased the infarction volume by enhancing angiogenesis in a rat stroke model [32]. Interestingly, SCF+G-CSF stimulation of Lin-Sca-1+ progenitors that normally results into the formation of 90% granulocytes, shifted towards the production of macrophages upon addition of IL-13 or IL-4 [17]. Interleukin-15 (IL-15) instructs the generation of human memory stem T cells from naive precursors [33]. Interleukin-16 (IL-16) also is reported to cause proliferation and differentiation of CD34 (+) hematopoietic cells into mature dendritic cells [4]. Interleukin-27 (IL-27) directly induces differentiation in hematopoietic stem cells. IL-27 transgenic mice exhibited greater myelopoiesis and defective B lymphopoiesis [35]. IL-27 has also been reported to synergize with SCF to induce differentiation of HSCs [35]. IL-27 can be of greater importance, as, significant proportion of HSCs are known to express IL-27 receptor. Interleukin-34 (IL-34) is an alternative ligand for colony stimulating factor 1 (Csf-1) receptor in both mice and humans. Mice lacking IL-34 displayed reduced Langerhans cells and diminished microglial cells. However, no effect was seen on monocytes, macrophages, and dendritic cells [36]. IL-34 appears to be indispensible for the development of Langerhans cells not only during embryogenesis but also during normal homeostasis in the adult skin [36]. Though, repopulation of Langerhans cells during inflammation appears to be dependent on Csf-1, post-inflammation survival of Langerhans cells is IL-34 dependent. IL-34 expression is generally high in brain tissues, and along with its receptor, it appears to be crucial for the development of microglial cells and their yolk sac precursors [37, 38]. Interestingly, a new receptor of IL-34 namely receptor-type protein-tyrosine phosphatase has been discovered that expresses on neural

progenitors, glial cells, and glioblastomas [39]. LIF promote differentiation of ES cells into neuronal cells, but inhibits the differentiation of ES cells to both mesodermal and extraembryonic endodermal lineages [40]. Interestingly, inhibition of LIF-induced STAT3 signaling abrogated the neuronal differentiation of ES cells, but inhibition of LIF-induced MEK signaling blocked the glial differentiation [40]. IL-6 and ciliary neurotrophic factor are also neuropoietic cytokines that control neural stem cell renewal, progenitor cell division, and differentiation. JAK/STAT pathway appears to be crucial for these effects [41]. However, the effects of cytokines on neural stem cells are more complex, and, these effects not only vary with the type of cytokine (s) but also with the concentration and tissue-specific localization of these molecules. TNF-α has also been shown to cause premature neural phenotype in human MSCs with the concurrent expression of LIF, BMP2, SRY box 2 protein, and glial fibrillary acidic protein [42]. Inhibition of ERK1/2 signaling abolished the TNF-α-mediated regulation of neural genes in this case. Furthermore, TNF-α enhanced the expression of CXCR4 on human MSCs that caused these cells to respond to stromal cell-derived factor 1 (SDF-1) [42].

Cytokines regulate stem cell-mediated immunosuppression

MSCs and their immunosuppressive properties are subject of intense investigation, and MSC-mediated down-modulation of proinflammatory cytokines appears to be very important in this regard. MSCs produce multiple cytokines that not only affect their own functions, but also affect immune cells in the neighborhood. Phosphoinositide 3-kinase (PI3 kinase), serine/threonine protein kinases, and NF-κB are important for cytokine induced migration of mesenchymal stem cells [43]. MSC-derived matrix metalloproteinases (MMPs) caused downregulation of IL-2 signaling by cleavage of IL-2 receptor α (CD25) from the surface of activated T cells. During MSC co-culture experiment with PHA activated T cells; IFN-γ, TNF-α, IL-1β, IL-2, IL-12p70, and IL-17A were found to inhibit MSC-mediated immunosuppression of T cells [44]. Conditioned media from MSC culture that had elevated levels of VEGF, monocyte chemoattractant Protein-1 (MCP-1), macrophage inflammatory protein-1 (MIP-1), and monokine induced by IFN-γ (MIG), induced angiogenesis in vascular endothelial cells [45]. In this case, MCP-1 and MIP-1α increased cell migration of MSCs while VEGF reduced it. Furthermore, this conditioned media lead to reduced caspase-3 activity in hypoxic H9c2 cells, and this effect was reversed by PI3-kinase inhibitors.

MSCs conditioned media inhibited phosphorylation at Ser112 of BAD and Ser473 of AKT, but increased AKT's phosphorylation at Thr308 [45]. Long-term culture-initiating cells (LTC-IC) proliferated 30 fold more in combination of Flt3-1igand, Steel factor, and IL-3. Although, each one of the three factors were able to induce proliferation alone, the most potent single factor, in this case, was IL-3 [46].

Cytokines regulate cancer stem cells (CSCs)

CSCs are often resistant to chemotherapy and some reports suggests that IL-4 might be contributing to this phenomenon ,as, abrogation of IL-4 signaling causes apoptosis in CSCs, and, IL-4 mediated STAT-6 expression enhances cancer-promoting survivin expression [47]. IL-8 is often found upregulated in certain types of cancers and has been suspected to promote CSC's growth. Inhibition of IL-8 or SNAIL signaling appears to be beneficial for controlling colon and breast cancers [48]. Carcinopromoting role of M-CSF was confirmed, when disruption of M-CSF gene was found to cause diminished tumour growth and metastasis as a result of defective angiogenesis [49]. Defective c-Kit kinase activity has been found in a number of diseases including cancer and allergy [40]. Interestingly, sustained elevated levels of IFN-γ and TNF-α also potentiated NF-κB, c-Fos and c-Myc mediated malignant transformation in MSCs, and depletion of either IFN-γ or TNF-α in this case, abolished the MSCs impairment and malignant transformation [50]. Aspirin, which is known to reduce the levels of IFN-γ and TNF-α, also corrected MSC deficiency and tumorigenesis in this case. These effects were mediated by inhibition of NF-κB/SMAD7, NF-κB/c-FOS, and c-MYC pathways. Interestingly, MSCs can both suppress or promote cancer development under different conditions. Cancer cells can stimulate MSCs to produce RANTES (regulated on activation, normal T cell expressed and secreted) that in turn enhances cancer cell motility, invasion and metastasis [51]. On the other hand, TNF-α upregulates TRAIL from human bone marrow MSCs, which results into cancer cell apoptosis. MSCs that were preactivated with TNF-α, controlled the progression of lung and breast tumors, and induced apoptosis in various TRAIL-sensitive cancer cell lines [52]. IL34, like M-CSF, can increase vascular endothelial growth factor (VEGF) production and promote angiogenesis and vascularisation both in vitro and in vivo. Unfortunately, by promoting angiogenesis and extravasation of immune cells, IL34 can enhance tumour development too [53]. TNF-α has also

been reported to activate MSCs for IL-6 or IL-8 mediated angiogenesis, and, intramuscular injection of conditioned media derived from TNF-α-treated MSCs stimulated blood perfusion and angiogenesis in the ischemic limb [54]. Immunodepletion of IL-6 and IL-8, in this case, resulted into attenuated blood perfusion and angiogenesis. Furthermore, Intramuscular injection of TNF-α-treated MSCs into the ischemic limb caused increased homing of tail vein-injected endothelial progenitor cells (EPCs) in IL-6 and IL-8 dependent manner [54].

Conclusion

In summary, several cytokines target stem cells to alter pluripotency, differentiation, growth and proliferation, or other properties. However, the outcome in such cases depends on the presence of several other factors that might synergize or antagonize with each other. Presence of various soluble factors along with different types of cells in the proximity might reprogram stem cells. At the same time, stem cell can also produce different types of cytokines that can target various immune cells or the producer itself, in an autocrine manner.

Table 1.

Cytokine	Main Effect(s) on Stem Cells	Type of Stem Cell Affected	Mechanism of Regulation
SCF	Proliferation and self-renewal.	Most types	c-Kit Signaling
LIF	Promotes cell proliferation, promotes differentiation to neuronal cells.	Most types	Activation of STAT3 and MEK
IL-1	Accelerated growth.	HSCs	Activation of transcription factor Pu.1
IL-1α	Enhanced neurogenesis.	Neural stem cells (NSCc), MSCs	Not reported
IL-1β	MSCs differentiate into osteoblast.	MSCs	Activation of MAPKs and NF-κB
IL-2	Might be important for reconstitution ability.		Not reported
IL-3	Proliferation and survival.	Most types	IL-3 Signaling
IL-4	Very important during early myelopoiesis, Promote differentiation to cardiac and skeletal muscle cells.	Most types	Activation of STAT3
IL-6	Regulator of neural precursors. When combined with SCF, caused the	Most types	JAK/STAT pathway

	expansion of hematopoietic progenitors.		
IL-7	Differentiation of T and B cells.	HSCs, ESCs	IL-7 Signaling
IL-8	Important for both hematopoesis and neuropoiesis.	HSCs, NSCs	Induced PI3K/Akt and MAPK/ERK-mediated VEGF production.
IL-9	Proliferation of very primitive human erythroid cells.	HSCs	Phophorylation of STAT3
IL-10	Enhanced repopulating ability.	HSCs	Not reported
IL-11	When combined with SCF caused the expansion of murine hematopoietic progenitors.	HSCs	Not reported
IL-13	Very important during early myelopoiesis.	HSCs	IL-13 Signaling
IL-15	Generation of human memory stem T cells from naive precursors.	HSCs	IL-15 Signaling
IL-16	Proliferation and differentiation of CD34 (+) hematopoietic cells into mature dendritic cells.	HSCs	IL-16 Signaling
IL-27	Induces differentiation in hematopoietic stem cells.	HSCs	IL-27 Signaling
IL-32	Proliferation of hematopoietic progenitors.	HSCs	IL-32 Signaling
IL-34	Indispensible for the development of Langerhans cells.	HSCs	IL-34 Signaling
TNF-α	Potent suppressor of normal HSC activity.	HSCs	Signaling through p55 TNF receptor
IFN-α	Activation of HSCs, NSCs.	HSCs, NSCs	Increased phosphorylation of STAT1 and AKT1
TGF-β	Regulates embryonic stem cell heterogeneity	ESCs	Nodal signaling

HSCs: Hematopoietic Stem Cells, **MSCs:** Mesenchymal Stem Cells, **ESCs**: Embryonic Stem Cells

Competing interests

No competing interests were disclosed.

References

1. Stem Cells Int. 2014;2014:516278. Stem cells: innovations in clinical applications. Sutton MT, Bonfield TL.

2. Int J Clin Exp Med. 2014 Nov 15;7(11):3843-52.Stem cell-based therapies for age-related macular degeneration: current status and prospects. Mu Y, Zhao M, Su G.
3. Arterioscler Thromb Vasc Biol. 2014 Jun;34(6):1114-9. Stem/Progenitor cells in vascular regeneration. Zhang L, Xu Q.
4. Exp Cell Res. 2014 Jul 18. S0014-4827(14)00291-2. Instruction of hematopoietic lineage choice by cytokine signaling. Endele M, Etzrodt M, Schroeder T.
5. Physiol Rev. 2012 Oct;92(4):1619-49. Stem cell factor receptor/c-Kit: from basic science to clinical implications. Lennartsson J1, Rönnstrand L.
6. Dev Cell. 2006 Aug;11(2):171-80. An unexpected role for IL-3 in the embryonic development of hematopoietic stem cells. Robin C1, Ottersbach K, Durand C, Peeters M, Vanes L, Tybulewicz V, Dzierzak E.
7. Stem Cells. 2003;21(2):236-44. Interleukin-3 promotes proliferation and differentiation of human hematopoietic stem cells but reduces their repopulation potential in NOD/SCID mice. Nitsche A1, Junghahn I, Thulke S, Aumann J, Radonić A, Fichtner I, Siegert W.
8. Blood. 1992 Jul 15;80(2):396-402. Stem cell factor, interleukin-3, and interleukin-6 promote retroviral-mediated gene transfer into murine hematopoietic stem cells. Luskey BD1, Rosenblatt M, Zsebo K, Williams DA.
9. Nature. 2009 Apr 16;458(7240):904-8. IFNalpha activates dormant haematopoietic stem cells in vivo. Essers MA1, Offner S, Blanco-Bose WE, Waibler Z, Kalinke U, Duchosal MA, Trumpp A.
10. Ann N Y Acad Sci. 1993 Jun 23;685:259-68. Experimental modulation of IL-1 production and cell surface molecule expression by levamisole. Kimball ES.
11. Hematother Stem Cell Res. 2002 Dec;11(6):905-12. Hematopoietic stem cell functional failure in interleukin-2-deficient mice. Chen J1, Astle CM, Harrison DE.
12. J Immunol. 2003 Apr 1;170(7):3461-7. IL-9 enhances the growth of human mast cell progenitors under stimulation with stem cell factor. Matsuzawa S1, Sakashita K, Kinoshita T, Ito S, Yamashita T, Koike K.
13. Exp Hematol. 1999 Jan;27(1):139-46. Distinct actions of interleukin-9 and interleukin-4 on a hematopoietic stem cell line, EMLC1. Wang XY1, Gelfanov V, Sun HB, Tsai S, Yang YC.

14. Stem Cells. 2007 Jul;25(7):1814-22. A novel function of interleukin-10 promoting self-renewal of hematopoietic stem cells. Kang YJ1, Yang SJ, Park G, Cho B, Min CK, Kim TY, Lee JS, Oh IH.
15. Stem Cells Int. 2011;2011:276193. Cord blood-derived hematopoietic stem/progenitor cells: current challenges in engraftment, infection, and ex vivo expansion. Kita K1, Lee JO, Finnerty CC, Herndon DN.
16. Stem Cells. 1995 Jul;13(4):404-13. Synergistic effects of stem cell factor and interleukin 6 or interleukin 11 on the expansion of murine hematopoietic progenitors in liquid suspension culture. Ariyama Y1, Misawa S, Sonoda Y.
17. J Exp Med. 1994 Jul 1;180(1):75-82.Interleukin 13: novel role in direct regulation of proliferation and differentiation of primitive hematopoietic progenitor cells. Jacobsen SE1, Okkenhaug C, Veiby OP, Caput D, Ferrara P, Minty A.
18. Eur J Immunol. 2011 Jun;41(6):1774-86. Interleukin 32 promotes hematopoietic progenitor expansion and attenuates bone marrow cytotoxicity. Moldenhauer A1, Futschik M, Lu H, Helmig M, Götze P, Bal G, Zenke M, Han W, Salama A.
19. Virol J. 2013 Feb 12;10:51. The expression of interleukin-32 is activated by human cytomegalovirus infection and down regulated by hcmv-miR-UL112-1. Huang Y1, Qi Y, Ma Y, He R, Ji Y, Sun Z, Ruan Q.
20. J Immunol. 2014 Oct 1;193(7):3792-802. IL-33-Induced Hematopoietic Stem and Progenitor Cell Mobilization Depends upon CCR2. Kim J1, Kim W1, Le HT2, Moon UJ2, Tran VG2, Kim HJ2, Jung S2, Nguyen QT2, Kim BS2, Jun JB3, Cho HR4, Kwon B5.
21. Blood. 2003 Sep 15;102(6):2053-9. TNF-alpha and IFN-gamma are overexpressed in the bone marrow of Fanconi anemia patients and TNF-alpha suppresses erythropoiesis in vitro. Dufour C1, Corcione A, Svahn J, Haupt R, Poggi V, Béka'ssy AN, Scimè R, Pistorio A, Pistoia V.
22. J Clin Invest. 1994 Jul;94(1):165-72.Tumor necrosis factor-alpha inhibits stem cell factor-induced proliferation of human bone marrow progenitor cells in vitro. Role of p55 and p75 tumor necrosis factor receptors. Rusten LS1, Smeland EB, Jacobsen FW, Lien E, Lesslauer W, Loetscher H, Dubois CM, Jacobsen SE.

23. J Immunol. 2007 Sep 1;179(5):3342-50. Enhancing effect of IL-1alpha on neurogenesis from adult human mesenchymal stem cells: implication for inflammatory mediators in regenerative medicine. Greco SJ1, Rameshwar P.
24. J Bone Metab. 2014 Feb;21 (1):55-60. Mouse models for the evaluation of osteocyte functions. Komori T. J
25. J Allergy Clin Immunol. 2011 Jun;127(6):1595-603. IL-4 induces differentiation of human embryonic stem cells into fibrogenic fibroblast-like cells. Sato T1, Liu X, Basma H, Togo S, Sugiura H, Nelson A, Nakanishi M, Kanaji N, Wang X, Kim M, Li Y, Michalski J, Farid M, Sharp JG, Rennard SI.
26. Genes Dev. 2005 Aug 1;19(15):1787-98. Mesenchymal stem cells are recruited to striated muscle by NFAT/IL-4-mediated cell fusion. Schulze M1, Belema-Bedada F, Technau A, Braun T.
27. Clin Rev Allergy Immunol. 2005 Jun;28(3):249-56. Role of IL-6 in the neural stem cell differentiation. Taga T1, Fukuda S.
28. Cell Stem Cell. 2013 Nov 7;13(5):564-76. Transient maternal IL-6 mediates long-lasting changes in neural stem cell pools by deregulating an endogenous self-renewal pathway. Gallagher D1, Norman AA, Woodard CL, Yang G, Gauthier-Fisher A, Fujitani M, Vessey JP, Cancino GI, Sachewsky N, Woltjen K, Fatt MP, Morshead CM, Kaplan DR, Miller FD.
29. J. Cell Adh Migr. 2009 Jan-Mar;3(1):107-17. Dynamic signaling for neural stem cell fate determination. Wen S, Li H, Liu
30. Immunol Rev. 1998 Oct;165:13-28. Role of interleukin-7 in T-cell development from hematopoietic stem cells. Akashi K1, Kondo M, Weissman IL.
31. Stem cells: insights into the secretome. Makridakis M, Roubelakis MG, Vlahou A. Biochim Biophys Acta. 2013 Nov;1834(11):2380-4.
32. Cell Biol Int. 2014 Sep;38(9):1050-9. IL-8 enhances the angiogenic potential of human bone marrow mesenchymal stem cells by increasing vascular endothelial growth factor. Hou Y1, Ryu CH, Jun JA, Kim SM, Jeong CH, Jeun SS.
33. Blood. 2013 Jan 24;121(4):573-84. IL-7 and IL-15 instruct the generation of human memory stem T cells from naive precursors. Cieri N, Camisa B, Cocchiarella F, Forcato M, Oliveira G, Provasi E, Bondanza A, Bordignon C, Peccatori J, Ciceri F, Lupo-Stanghellini MT, Mavilio F, Mondino A, Bicciato S, Recchia A, Bonini C.

34. Stem Cells Dev. 2009 May;18(4):671-82. IL-16 can synergize with early acting cytokines to expand ex vivo CD34+ isolated from cord blood. Rofani C1, Luchetti L, Testa G, Lasorella R, Isacchi G, Bottazzo GF, Berardi AC.
35. Blood. 2008 Feb 15;111(4):1903-12. Interleukin-27 directly induces differentiation in hematopoietic stem cells. Seita J, Asakawa M, Ooehara J, Takayanagi S, Morita Y, Watanabe N, Fujita K, Kudo M, Mizuguchi J, Ema H, Nakauchi H, Yoshimoto T.
36. Dev Biol. 2012 Jul 15;367(2):100-13. The CSF-1 receptor ligands IL-34 and CSF-1 exhibit distinct developmental brain expression patterns and regulate neural progenitor cell maintenance and maturation. Nandi S1, Gokhan S, Dai XM, Wei S, Enikolopov G, Lin H, Mehler MF, Stanley ER.
37. Immunity. 2012 Dec 14;37(6):1050-60. Stroma-derived interleukin-34 controls the development and maintenance of Langerhans cells and the maintenance of microglia. Greter M1, Lelios I, Pelczar P, Hoeffel G, Price J, Leboeuf M, Kündig TM, Frei K, Ginhoux F, Merad M, Becher B.
38. Immunity. 2012 Dec 14;37(6):1050-60. Stroma-derived interleukin-34 controls the development and maintenance of langerhans cells and the maintenance of microglia. Greter M1, Lelios I, Pelczar P, Hoeffel G, Price J, Leboeuf M, Kündig TM, Frei K, Ginhoux F, Merad M, Becher B.
39. J Biol Chem. 2013 Jul 26;288(30):21972-86. Receptor-type protein-tyrosine phosphatase ζ is a functional receptor for interleukin-34. Nandi S1, Cioce M, Yeung YG, Nieves E, Tesfa L, Lin H, Hsu AW, Halenbeck R, Cheng HY, Gokhan S, Mehler MF, Stanley ER.
40. Acta Pharmacol Sin. 2006 Jan;27(1):80-90. Effect of leukemia inhibitory factor on embryonic stem cell differentiation: implications for supporting neuronal differentiation. He Z1, Li JJ, Zhen CH, Feng LY, Ding XY.
41. Ann N Y Acad Sci. 2009 Feb;1153:48-56. Cytokine control of adult neural stem cells. Bauer S.
42. Cell Death Differ. 2011 May;18(5):853-63.TNF-α respecifies human mesenchymal stem cells to a neural fate and promotes migration toward experimental glioma. Egea V1, von Baumgarten L, Schichor C, Berninger B, Popp T, Neth P, Goldbrunner R, Kienast Y, Winkler F, Jochum M, Ries C.

43. Histol Histopathol. 2013 Nov;28(11):1427-38. Signaling molecules and pathways involved in MSC tumor tropism. Ho IA, Lam PY.
44. J. Curr Mol Med. 2013 Jun;13(5):856-67. Mechanisms of immune modulation by mesenchymal stromal cells and clinical translation. Stagg J, Galipeau.
45. PLoS One. 2012;7(4):e35685. Mesenchymal stem cells secrete multiple cytokines that promote angiogenesis and have contrasting effects on chemotaxis and apoptosis. Boomsma RA1, Geenen DL.
46. Proc Natl Acad Sci U S A. Feb 20, 1996; 93(4): 1470–1474. Self-renewal of primitive human hematopoietic cells (long-term-culture-initiating cells) in vitro and their expansion in defined medium. A L Petzer, D E Hogge, P M Landsdorp, D S Reid, and C J Eaves.
47. Cell Cycle. 2008 Feb 1;7(3):309-13. IL-4-mediated drug resistance in colon cancer stem cells. Todaro M1, Perez Alea M, Scopelliti A, Medema JP, Stassi G.
48. Gastroenterology. 2011 Jul;141(1):279-91. SNAIL regulates interleukin-8 expression, stem cell-like activity, and tumorigenicity of human colorectal carcinoma cells. Hwang WL1, Yang MH, Tsai ML, Lan HY, Su SH, Chang SC, Teng HW, Yang SH, Lan YT, Chiou SH, Wang HW.
49. Leuk Res. 1990;14(1):27-37. M-CSF and M-CSF-receptor gene expression in acute myelomonocytic leukemias. Parwaresch MR1, Kreipe H, Felgner J, Heidorn K, Jaquet K, Bödewadt-Radzun S, Radzun HJ.
50. Stem Cells. 2013 Jul;31(7):1383-95. IFN-γ and TNF-α synergistically induce mesenchymal stem cell impairment and tumorigenesis via NFκB signaling. Wang L1, Zhao Y, Liu Y, Akiyama K, Chen C, Qu C, Jin Y, Shi S.
51. Nature. 2007 Oct 4;449(7162):557-63. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis.Karnoub AE1, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA.
52. Cell Stem Cell. 2012 Dec 7;11(6):825-35. Preactivation of human MSCs with TNF-α enhances tumor-suppressive activity. Lee RH1, Yoon N, Reneau JC, Prockop DJ.
53. PLoS One. 2013;8(2):e56045. IL-34 induces the differentiation of human monocytes into immunosuppressive macrophages. antagonistic effects of GM-CSF and IFNγ. Foucher ED1, Blanchard S, Preisser L, Garo E, Ifrah N, Guardiola P, Delneste Y, Jeannin P.

54. Biochim Biophys Acta. 2013 Dec;1832(12):2136-44. Tumor necrosis factor-α-activated mesenchymal stem cells promote endothelial progenitor cell homing and angiogenesis. Kwon YW1, Heo SC, Jeong GO, Yoon JW, Mo WM, Lee MJ, Jang IH, Kwon SM, Lee JS, Kim JH