Mesenchymal stem cells: the fibroblasts' new clothes?

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ABSTRACT

Mesenchymal stem cells are adherent stromal cells, initially isolated from the bone marrow, characterized by their ability to differentiate into mesenchymal tissues such as bone, cartilage and fat. They have also been shown to suppress immune responses *in vitro*. Because of these properties, mesenchymal stem cells have recently received a very high profile. Despite the dramatic benefits reported in early phase clinical trials, their functions remain poorly understood. Particularly, several questions remain concerning the origin of mesenchymal stem cells and their relationship to other stromal cells such as fibroblasts. Whereas clear gene expression signatures are imprinted in stromal cells of different anatomical origins, the anti-proliferative effects of mesenchymal stem cells and fibroblasts and their potential to differentiate appear to be common features between these two cell types. In this review, we summarize recent studies in the context of historical and often neglected stromal cell literature, and present the evidence that mesenchymal stem cells and fibroblasts share much more in common than previously recognized.

Key word: mesenchymal stem cells, fibroblasts, graft-versus-host disease.

Citation: Haniffa MA, Collin MP, Buckley CD, and Dazzi F. Mesenchymal stem cells: the fibroblasts' new clothes? Haematologica 2009; 94:258-263. doi:10.3324/haematol.13699

Introduction

The stem cell properties of bone marrow stroma were first described by Friedenstein in 1968[1] and subsequent experiments demonstrated their multipotent differentiation potential and immunosuppressive activity in the late nineties.[2,3] The apparently surprising immunosuppressive functions were further substantiated by reports of their activity when transfused intravenously into animal models of graft-versus-host disease (GVHD), arthritis and encephalitis[4,5,5-9] although some concerns have been raised about their immunogenicity and susceptibility to malignant transformation.[10,11] The results of early phase clinical trials with mesenchymal stem cells (MSC) in humans have been dramatic. In the first report, a nine year old boy with steroid-resistant GVHD, an invariably fatal condition, responded to intravenous infusions of haploidentical *ex vivo* expanded MSC[12] and in subsequent Phase I and II trials 6 out of 8 and 39 out of 55 patients with steroid-resistant GVHD responded to MSC treatment.[13,14] Although GVHD prevention in humans has been reported to be at the expense of the desirable graft versus leukemia (GVL) effect,[15] this was not observed in other clinical studies in which MSC infusions were exploited to reduce stem cell graft failure and GVHD.[14,16] The potency of MSC immunotherapy in humans is certainly encouraging. However, many important scientific questions remain unanswered, especially regarding the identity of these cells in relation to fibroblasts and the physiological relevance of their immunoregulatory properties.

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MSC are currently defined as plastic adherent, multipotential fibroblast-like cells expressing CD73, CD105 and negative for the hematopoietic markers CD14, CD34 and CD45[17,18] but these properties and markers are also shared by fibroblasts (Table 1). Osteoblastic, chondrogenic, adipogenic differentiation from fibroblasts has also been described.[19-21] More recently, hepatocyte differentiation potential of adult human dermal fibroblasts was demonstrated in an *in vivo* model of liver-injured immunodeficient mice.[21] The current definition sug-

Funding: MAH is supported by an Action Medical Research Training Fellowship; MPC is supported by a Leukemia Research Fund UK Bennett Senior Fellowship, Tyneside Leukemia Research Fund and Histiocytosis Association of America; CDB is supported by the Arthritis Research Campaign and Medical Research Council and FD is supported by Arthritis Research Campaign and Leukemia Research Fund.
Manuscript received July 22, 2008. Revised version arrived September 10, 2008. Manuscript accepted September 30, 2008.
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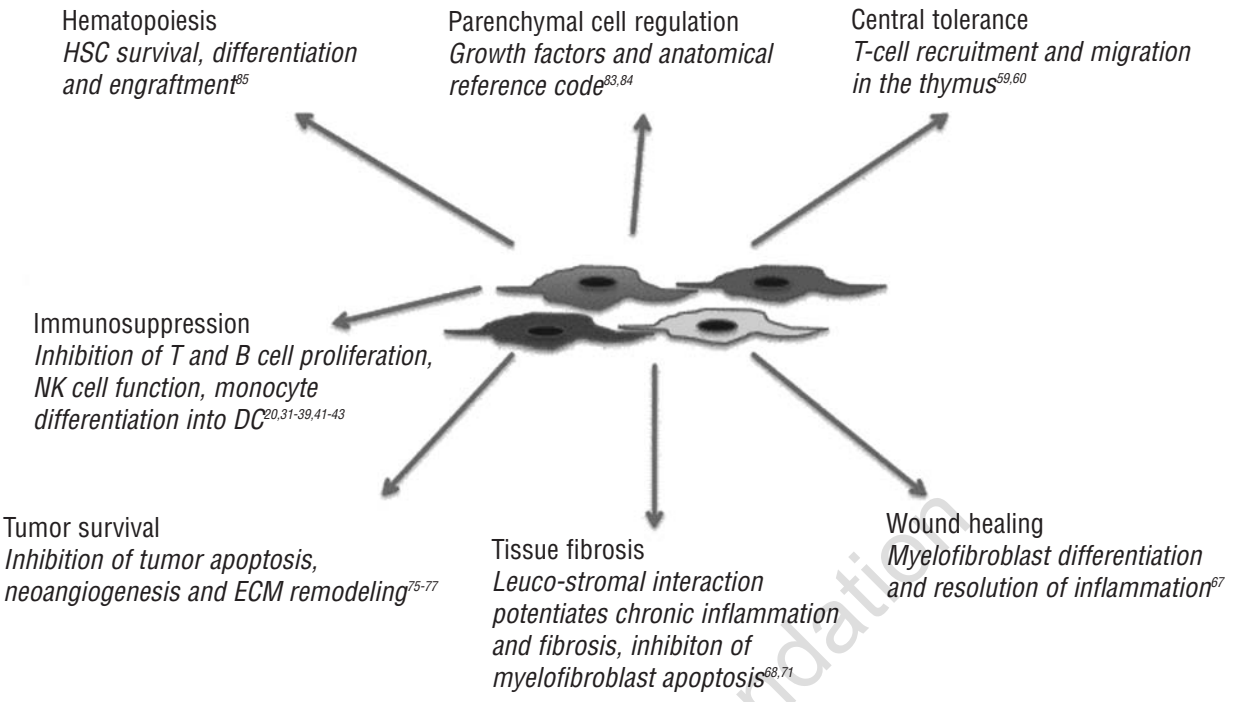

Figure 1. Stromal cells modulate diverse biological processes. Stromal cells are actively involved in all of the above processes although subsets with specialized functions within the heterogeneous site-specific population remain to be defined

gested by the International Society of Cellular Therapy (ISCT) is thus incapable of distinguishing MSC from generic fibroblasts.[17,18] More recent studies have involved markers such as SSEA-1, SSEA-4 and GD2.[22-24] These studies have established a hierarchy of mesenchymal differentiation and appear encouraging. Despite these limitations, there has been widespread speculation that MSC constitute a unique cell type distinct from fibroblasts.[25]

There is also a wealth of historical data on the immunosuppressive properties of fibroblasts. In fact, it had been comprehensively demonstrated some ten years earlier that fibroblasts from various tissue sites inhibit mitogen and allo-antigen stimulated T-cell proliferation[26-29] and IFNγ production[30] in exactly the same vein as more recent reports using MSC.[3,31,32]

MSC-mediated immunomodulation is promoted by close contact but ultimately mediated by a number of soluble factors including hepatocyte growth factor-1 (HGF-1), transforming growth factor-β (TGF-β), indoleamine 2,3-dioxygenase (IDO), prostaglandin-E2 (PGE_2) nitric oxide and insulin-like growth factor (IGF) binding proteins.[20,33-38] Similarly, PGE2 and IDO have also been implicated in fibroblast-mediated T-cell suppression.[20,26,27] Furthermore, both MSC and fibroblast suppressive effects are enhanced in the presence of inflammatory cytokines such as IFNγ and TNFα.[27,28,30-39] Pre-treatment of human fibroblasts and MSC with IFNγ and TNFα up-regulates MHC Class II molecule expression but both cell types have poor capacity to activate allo-responses.[27,40] Different culture conditions, experimental kinetics, species and cell populations used in the *in vitro* assays may account for the variety of soluble factors identified as responsible for fibroblast and MSC-mediated suppression but may also reflect a redundancy or pleiotropy in the mechanisms employed by these cells. However, nearly all studies suggest that an inflammatory microenvironment is a prerequisite for observing stromal-mediated suppressive effects.[41]

MSC-mediated inhibition of monocyte differentiation into dendritic cells[42,43] has also been previously documented using fibroblasts.[44] This effect is dependent on interleukin 6 (IL-6)[44,45] and involves cell cycle arrest.[46] More recently, direct comparison between adult fibroblasts from various tissues and bone marrow MSC showed similar *in vitro* immunosuppressive potency.[20,41,47] Both MSC and fibroblasts induce cell cycle arrest, prevent apoptosis and support the survival of T cells.[41,48] Although this could be a fundamental process to maintain memory T cells, it may have a negative effect when MSC are used in the clinical setting leading to the preservation of pathogenic memory T cells with future adverse consequences.

Both fibroblasts and MSC may be isolated using tissue culture adherence from many tissue sites including adipose tissue, placenta, skin, thymus, periosteum, muscle, synovium, synovial fluid, fetal liver and blood, and cord blood.[49-51] Bone marrow-derived MSC and fibroblasts from various anatomical sites have been shown to have distinct gene expression profiles[52] (*Collin M, unpublished data*). However, it is also well recognized that fibroblasts from different tissues possess site-specific molecular identity and topographical memory due to differential expression of homeobox (HOX) genes.[53]

Although subtle and interesting niche-specific differences may exist between stromal cells, there is no evidence that these alter the general immunosuppressive and differentiation properties that have been described for these cells.

The naked fibroblast

Fibroblasts exist in virtually every organ in the human body. They are defined as adherent cells, which are not endothelium, epithelium or hematopoietic in origin, and which have the capacity to synthesize and remodel the extracellular matrix. In addition to their presumed role as scaffolding support, fibroblasts have been directly shown to play roles in regulating self-tolerance, organ development, wound healing, inflammation and fibrosis (Figure 1).[54-57]

Central and peripheral immunological tolerance

Fibroblasts have at least two recognized supportive roles in central tolerance. Firstly, thymic fibroblasts support the proliferation of thymic epithelial cells through the release of FGF-1, FGF-7 and FGF-10.[58,59] Secondly, they are directly involved in the recruitment of early T-cell precursors[60] and migration of developing T cells through the thymic medulla and cortex.[59] Furthermore, a recent study has elegantly described a startling role for lymph node stroma in maintaining peripheral tolerance. Antigen presentation by lymph node stromal cells was shown to be functionally similar to medullary thymic epithelial cells leading to active deletion of self-reactive peripheral T cells.[61] Marrow stromal cells are crucial for B-cell development[62,63] and more recent studies have shown that MSC under particular circumstances, can promote the survival of B cells[64] and stimulate B-cell antibody production.[65,66]

Wound healing and tissue repair

Tissue injury and wounding are accompanied by changes in the extracellular matrix, mechanical stress and inflammation in the surrounding microenvironment. These changes result in the activation of fibroblasts which express contractile bundles and α-smooth muscle actin and differentiate into myofibroblasts.

Myofibroblasts participate in wound healing through migration, proliferation and contraction necessary to restore homeostasis in damaged tissue. Return to normal physiology requires resolution of the inflammation accompanying the injury,[57] a process traditionally thought to occur passively from *the fizzling out* of inflammatory signals. However, current evidence clearly demonstrates the importance of the local stromal network in mediating active inflammatory cell clearance.[67]

Tissue fibrosis

Inappropriate tissue repair and continued insult can result in chronic inflammation and eventually lead to fibrosis. At the cellular level, accumulation and persistence of myofibroblasts during tissue repair and healing has been proposed as a leading cause of fibrosis.[68] This process is associated with the transformation of granulation tissue into a hypertrophic scar with excessive production of ECM and rarification of the microvasculature. Fibrosis is modulated by a dynamic 'leuco-stromal interaction', a notion supported by the observation that carbon tetrachloride-mediated liver fibrosis is reduced in immunodeficient *rag*$^{-/-}$ mice following liver injury[69] and after selective macrophage depletion during advanced liver fibrosis.[70] Recently, myofibroblasts in fibrotic tissue have been shown to acquire resistance to Fas-induced apoptosis by T lymphocytes,[71] a process that normally accompanies tissue repair. In addition, fibrosis-related pathological myofibroblasts promote their own survival by expressing Fas molecules and killing surrounding lymphocytes.[71]

Table 1. Characteristics of fibroblasts and mesenchymal stem cells.

	Fibroblast	MSC
Distribution	Ubiquitous	
Phenotype	Identical	
Frequency	Common	Rare in BM
Growth potential	Identical	
Transdifferentiation	*Bone, fat, cartilage	
Immunoregulation (*in vitro*)	Similar potency	
Immunosuppressive clinical use	Untested	Yes

**Differentiation capacity of both cell types extends beyond the mesodermal lineage.*

Tumor survival and metastases

The protective and facilitative role of stroma in tumor growth was first described by pathologists as *desmoplasia*, a typical feature of many solid tumors.[72] Tumor stroma is predominantly comprised of myofibroblasts, often referred to as carcinoma associated fibroblasts (CAF).[73] The restrictive role of myofibroblasts in wound healing is taken over by growing tumors. Breast tumors with a *wound-response gene signature* are associated with an increased risk of progression and metastases.[74] Injection of a mixture of CAF or MSC with breast cancer cells into immunocompromised mice showed that both stromal cell types were capable of accelerating cancer growth and invasiveness.[75,76] CAF provide nutritional support by the secretion of growth factors, promoting neoangiogenesis and ECM remodeling to facilitate tumor invasion and metastasis.[77] The distribution of tumor metastases is also not random showing clear organ preferences for the various cancer types for certain *receptive* stromal environments.[78] Recently, mutations and loss of heterozygosity in the tumor suppressor gene *TP53* in the stromal compartment adjacent to breast carcinoma was found to be associated with lymph node metastases presenting a compelling case for stroma-facilitated cancer progression.[79] However, other animal studies have reported anti-tumor effects with bone marrow and skin-derived stromal cells and this may be related to the ability of the tumor to recruit and activate different stromal cell functions.[80-82]

Parenchymal and stem cell regulation

The functional diversity and positional identity of fibroblasts may act to regulate local parenchymal cells in

several ways. Firstly, fibroblasts could act as a source of growth factors such as fibroblast growth factor (FGF), keratinocyte growth factor (KGF) and leukemia inhibitory factor (LIF) for cell survival; a property that has been exploited in the laboratory with the use of fibroblast feeder layers to expand parenchymal and stem cells.[83] Secondly, fibroblasts may provide a co-ordinate system of positional reference points for site-specific epithelial-mesenchymal interactions critical for the development, differentiation, patterning and renewal of the adjacent epithelia such as in the skin, lung, gastrointestinal, genitourinary systems and the thymus.[84] In addition, stromal cells also provide the appropriate niche for stem cell maintenance and differentiation. One of the best-studied examples of stem cell-niche regulation is the orchestration of HSC survival and differentiation by bone marrow stroma.[85] However, stromal cells are heterogenous with specialized niche functions confined to particular subsets. This was recently demonstrated *in vivo* where only CD146 expressing bone marrow stromal cells were found to be capable of conferring a hematopoietic microenvironment when transplanted to heterotopic sites.[86]

Future speculation and conclusion

The plethora of recent studies on MSC has to some extent recapitulated what had been previously described over ten years ago for fibroblasts. Present definitions of MSC and fibroblasts emphasize generic properties of these cells and fail to distinguish subsets of stromal cells with specialized niche functions. The lack of appropriate markers means we are currently unable to functionally dissect the important differences within the extended fibroblast family. Are there common mesenchymal progenitors throughout the body or are these progenitors specialized and site specific? What is clear is the ubiquitous presence and functional heterogeneity of fibroblasts.

The physiological significance of stromal cell immunoregulation has also been poorly recognized despite the overwhelming evidence for their varied role in maintaining immune equilibrium and in pathology. The consequences of these findings emphasize the need to recognize the common ground between the fields of fibroblast and MSC biology in order to redefine and dissect the complex family of stromal cells.

Authorship and Disclosures

MAH, MPC, CDB and FD equally contributed to writing this review article.

The authors reported no potential conflicts of interest.

References

1. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 1968;6:230-47.
2. Pittenger MF, Mackay AM, Beck SC Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-7.
3. Tse WT BW, Pendleton JD, D'Andrea A, Guinan EC. Bone marrow derived mesenchymal stem cells suppress T cell activation without inducing allogeneic anergy. Blood 2000;96:241a.
4. Chung NG, Jeong DC, Park SJ, Choi BO, Cho B, Kim HK, et al. Cotransplantation of marrow stromal cells may prevent lethal graft-versus-host disease in major histocompatibility complex mismatched murine hematopoietic stem cell transplantation. Int J Hematol 2004; 80:370-6.
5. Tisato V, Naresh K, Girdlestone J, Navarrete C, Dazzi F. Mesenchymal stem cells of cord blood origin are effective at preventing but not treating graft-versus-host disease. Leukemia 2007;21:1992-9.
6. Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002;30:42-8.
7. Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 2005;106:1755-61.
8. Yanez R, Lamana ML, Garcia-Castro J, Colmenero I, Ramirez M, Bueren JA. Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of the graft-versus-host disease. Stem Cells 2006;24:2582-91.
9. Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. Arthritis Rheum 2007;56:1175-86.
10. Nauta AJ, Westerhuis G, Kruisselbrink AB, Lurvink EG, Willemze R, Fibbe WE. Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a non-myeloablative setting. Blood 2006;108:2114-20.
11. Tolar J, Nauta AJ, Osborn MJ, Panoskaltsis Mortari A, McElmurry RT, Bell S, et al. Sarcoma derived from cultured mesenchymal stem cells. Stem Cells 2007;25:371-9.
12. Le Blanc K, Rasmusson I, Sundberg B, Götherström C, Hassan M, Uzunel M, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 2004;363: 1439-41.
13. Ringdén O, Uzunel M, Rasmusson I, Remberger M, Sundberg B, Lönnies H, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation 2006;81:1390-7.
14. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Developmental Committee of the European Group for Blood and Marrow Transplantation. Lancet 2008;371: 1579-86.
15. Ning H, Yang F, Jiang M, Hu L, Feng K, Zhang J, et al. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. Leukemia 2008;22: 593-9.
16. Ball LM, Bernardo ME, Roelofs H, Lankester A, Cometa A, Egeler RM, et al. Cotransplantation of ex vivo expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. Blood 2007;110: 2764-7.
17. Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, et al. Clarification of the nomenclature for MSC. The International Society for Cellular Therapy position statement. Cytotherapy 2005;7:393-5.
18. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for

defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.
19. Harris J. Differentiated cells and the maintenance of tissues. In: Alberts B, Bary D, Lewis J, Raff M, Roberts K, Watson JD, editors. Molecular Biology of The Cell. New York: Garland Publishing, Inc.; 1994. p. 1139-93.
20. Haniffa MA, Wang XN, Holtick U, Rae M, Isaacs JD, Dickinson AM, et al. Adult human fibroblasts are potent immunoregulatory cells and functionally equivalent to mesenchymal stem cells. J Immunol 2007;179:1595-604.
21. Lysy PA, Smets F, Sibille C, Najimi M, Sokal EM. Human skin fibroblasts: From mesodermal to hepatocyte-like differentiation. Hepatology 2007;46:1574-85.
22. Anjos-Afonso F, Bonnet D. Non-hematopoietic/endothelial SSEA-1+ cells define the most primitive progenitors in the adult murine bone marrow mesenchymal compartment. Blood 2007;109:1298-306.
23. Gang EJ, Bosnakovski D, Figueiredo CA, Visser JW, Perlingeiro RC. SSEA-4 identifies mesenchymal stem cells from bone marrow. Blood 2007;109: 1743-51.
24. Martinez C, Hofmann TJ, Marino R, Dominici M, Horwitz EM. Human bone marrow mesenchymal stromal cells express the neural ganglioside GD2: a novel surface marker for the identification of MSCs. Blood 2007; 109:4245-8.
25. Horwitz EM, Andreef M, Frassoni F. Mesenchymal Stromal Cells. Biol Blood Marrow Transplant 2007; 13S1:53-7.
26. Korn JH. Modulation of lymphocyte mitogen responses by cocultured fibroblasts. Cell Immunol 1981;63: 374-84.
27. Shimabukuro Y, Murakami S, Okada H. Interferon-γ-dependent immunosuppressive effects of human gingival fibroblasts. Immunology 1992; 76:344-7.
28. Donnelly JJ, Xi MS, Rockey JH. A soluble product of human corneal fibroblasts inhibits lymphocyte activation. Enhancement by interferon-gamma. Exp Eye Res 1993;56:157-65.
29. Sarkhosh K, Tredget EE, Li Y, Kilani RT, Uludag H, Ghahary A. Proliferation of peripheral blood mononuclear cells is suppressed by the indoleamine 2,3-dioxygenase expression of interferon-γ-treated skin cells in a co-culture system. Wound Repair Regen 2003;11:337-45.
30. Le JM, Vilcek J. Accessory function of human fibroblasts in mitogen-stimulated interferon-γ production by T lymphocytes. Inhibition by interleukin 1 and tumor necrosis factor. J Immunol 1987;139:3330-7.
31. Klyushnenkova EN, McIntosh KR. Human mesenchymal stem cells suppress allogeneic T cell responses in vitro: Implications for allogeneic transplantation. Blood 1998;92:642a.
32. Krampera M, Glennie S, Dyson J, Scott D, Laylor R, Simpson E, et al. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 2003; 101:3722-9.
33. Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99:3838-43.
34. Meisel R, Zibert A, Laryea M, Gobel U, Daubener W, Dilloo D. Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. Blood 2004;103:4619-21.
35. Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 2005;105:2821-7.
36. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815-22.
37. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 2007; 109:228-34.
38. Gieseke F, Schütt B, Viebahn S, Koscielniak E, Friedrich W, Handgretinger R, et al. Human multipotent mesenchymal stromal cells inhibit proliferation of PBMCs independently of IFNγR1 signaling and IDO expression. Blood 2007;110: 2197-200.
39. Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, et al. Role for interferon-γ in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells 2006;24:386-98.
40. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringden O. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003;31:890-6.
41. Jones S, Horwood N, Cope A, Dazzi F. The antiproliferative effect of mesenchymal stem cells is a fundamental property shared by all stromal cells. J Immunol 2007;179:2824-31.
42. Jiang XX, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, et al. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 2005; 105:4120-6.
43. Nauta AJ, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE. Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells. J Immunol 2006;177: 2080-7.
44. Chomarat P, Banchereau J, Davoust J, Palucka AK. IL-6 switches the differentiation of monocytes from dendritic cells to macrophages. Nat Immunol 2000;1:510-4.
45. Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, Apparailly F, et al. Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells 2007;25: 2025-32.
46. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 2007;83:71-6.
47. Bocelli-Tyndall C, Barbero A, Candrian C, Ceredig R, Tyndall A, Martin I. Human articular chondrocytes suppress in vitro proliferation of anti-CD3 activated peripheral blood mononuclear cells. J Cell Physiol 2006;209:732-34.
48. Filer A, Parsonage G, Smith E, Osborne C, Thomas AM, Curnow SJ, et al. Differential survival of leukocyte subsets mediated by synovial, bone marrow, and skin fibroblasts: site-specific versus activation-dependent survival of T cells and neutrophils. Arthritis Rheum 2006; 54:2096-108.
49. da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci 2006; 119:2204-13.
50. Bieback K, Kluter H. Mesenchymal stromal cells from umbilical cord blood. Curr Stem Cell Res Ther 2007;2:310-23.
51. He Q, Wan C, Li G. Concise review: multipotent mesenchymal stromal cells in blood. Stem Cells 2007;25:69-77.
52. Ishii M, Koike C, Igarashi A, Yamanaka K, Pan H, Higashi Y, et al. Molecular markers distinguish bone marrow mesenchymal stem cells from fibroblasts. Biochem Biophys Res Commun 2005;332:297-303.
53. Chang HY, Chi JT, Dudoit S, Bondre C, van de Rijn M, Botstein D, et al. Diversity, topographic differentiation, and positional memory in human fibroblasts. Proc Natl Acad Sci USA 2002;99:12877-82.
54. Fries KM, Blieden T, Looney RJ, Sempowski GD, Silvera MR, Willis RA, et al. Evidence of fibroblast heterogeneity and the role of fibroblast subpopulations in fibrosis. Clin Immunol Immunopathol 1994;72: 283-92.
55. Mebius RE. Organogenesis of lymphoid tissues. Nat Rev Immunol 2003;3:292-303.
56. Parsonage G, Filer AD, Haworth O, Nash GB, Rainger GE, Salmon M, et al. A stromal address code defined by fibroblasts. Trends Immunol 2005;26:150-6.
57. Serhan CN, Brain SD, Buckley CD Gilroy DW, Haslett C, O'Neill LA, et al. Resolution of inflammation: state of the art, definitions and terms. Faseb J 2007;21:325-32.
58. Jenkinson WE, Jenkinson EJ, Anderson G. Differential requirement for mesenchyme in the proliferation and maturation of thymic epithelial progenitors. J Exp Med 2003;198:325-32.
59. Gray DH, Tull D, Ueno T, Seach N, Classon BJ, Chidgey A, et al. A unique thymic fibroblast population

revealed by the monoclonal antibody MTS-15. J Immunol 2007;178: 4956-65.
60. Liu C, Ueno T, Kuse S, Saito F, Nitta T, Piali L, et al. The role of CCL21 in recruitment of T-precursor cells to fetal thymi. Blood 2005;105:31-9.
61. Lee JW, Epardaud M, Sun J, Becker JE, Cheng AC, Yonekura AR, et al. Peripheral antigen display by lymph node stroma promotes T cell tolerance to intestinal self. Nat Immunol 2007;8:181-90.
62. Ryan DH, Tang J. Regulation of human B cell lymphopoiesis by adhesion molecules and cytokines. Leuk Lymphoma. 1995;17:375-89.
63. von Boehmer H KP, Nemazee D, Owen J, Shatz D. The development and survival of lymphocytes. In: Janeway CA Jr, Walport M, Shlomchik MJ, eds. Immunobiology. New York and London: Garland Science & Churchill Livingstone; 2005. p. 241-316.
64. Tabera S, Pérez-Simón JA, Díez-Campelo M, Sánchez-Abarca LI, Blanco B, López A, et al. The effect of mesenchymal stem cells on the viability, proliferation and differentiation of B-lymphocytes. Haematologica 2008;93:1301-9.
65. Rasmusson I, Le Blanc K, Sundberg B, Ringden O. Mesenchymal stem cells stimulate antibody secretion in human B cells. Scand J Immunol 2007;65:336-43.
66. Traggiai E, Volpi S, Schena F, Gattorno M, Ferlito F, Moretta L, et al. Bone marrow-derived mesenchymal stem cells induce both polyclonal expansion and differentiation of B cells isolated from healthy donors and systemic lupus erythematosus patients. Stem Cells 2008;26:562-9.
67. Ariel A, Serhan CN. Resolvins and protectins in the termination program of acute inflammation. Trends Immunol 2007;28:176-83.
68. Desmouliere A, Darby IA, Gabbiani G. Normal and pathologic soft tissue remodeling: role of the myofibroblast, with special emphasis on liver and kidney fibrosis. Lab Invest 2003;83:1689-707.
69. Novobrantseva TI, Majeau GR, Amatucci A, Kogan S, Brenner I, Casola S, et al. Attenuated liver fibrosis in the absence of B cells. J Clin Invest 2005;115:3072-82.
70. Duffield JS, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S, et al. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin Invest 2005;115:56-65.
71. Wallach-Dayan SB, Golan-Gerstl R, Breuer R. Evasion of myofibroblasts from immune surveillance: a mechanism for tissue fibrosis. Proc Natl Acad Sci USA 2007;104:20460-5.
72. Willis R. Pathology of Tumours. London: Butterworth and Company. 1967.
73. Barsky SH, Green WR, Grotendorst GR, Liotta LA. Desmoplastic breast carcinoma as a source of human myofibroblasts. Am J Pathol 1984; 115:329-33.
74. Chang HY, Sneddon JB, Alizadeh AA, Sood R, West RB, Montgomery K, et al. Gene expression signature of fibroblast serum response predicts human cancer progression: similarities between tumors and wounds. PLoS Biol 2004;2:E7.
75. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 2005; 121:335-48.
76. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 2007;449: 557-63.
77. Kalluri R, Zeisberg M. Fibroblasts in cancer. Nat Rev Cancer 2006;6:392-401.
78. Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature 2001;410:50-6.
79. Patocs A, Zhang L, Xu Y, Weber F, Caldes T, Mutter GL, et al. Breast-cancer stromal cells with TP53 mutations and nodal metastases. N Engl J Med 2007;357:2543-51.
80. Maestroni GJ, Hertens E, Galli P. Factor(s) from nonmacrophage bone marrow stromal cells inhibit Lewis lung carcinoma and B16 melanoma growth in mice. Cell Mol Life Sci 1999;55:663-7.
81. Ohlsson LB, Varas L, Kjellman C, Edvardsen K, Lindvall M. Mesenchymal progenitor cell-mediated inhibition of tumor growth in vivo and in vitro in gelatin matrix. Exp Mol Pathol 2003;75:248-55.
82. Khakoo AY, Pati S, Anderson SA, Reid W, Elshal MF, Rovira II, et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma. J Exp Med 2006;203:1235-47.
83. Rheinwald JG, Green H. Epidermal growth factor and the multiplication of cultured human epidermal keratinocytes. Nature 1977;265:421-4.
84. Blanpain C, Horsley V, Fuchs E. Epithelial stem cells: turning over new leaves. Cell 2007;128:445-58.
85. Dazzi F, Ramasamy R, Glennie S, Jones SP, Roberts I. The role of mesenchymal stem cells in haemopoiesis. Blood Rev 2006;20: 161-71.
86. Sacchetti B, Funari A, Michienzi S, Di Cesare S, Piersanti S, Saggio I, et al. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. Cell 2007;131:324-36.