Pathol. Oncol. Res. (2011) 17:11–16
DOI 10.1007/s12253-010-9262-x

The Role of the Bone Marrow Derived Mesenchymal Stem Cells in Colonic Epithelial Regeneration

Gábor Valcz · Tibor Krenács · Ferenc Sipos · Katalin Leiszter · Kinga Tóth · Zsófia Balogh · Annamária Csizmadia · Györgyi Műzes · Béla Molnár · Zsolt Tulassay

Received: 2 September 2009 / Accepted: 22 March 2010 / Published online: 21 April 2010

Abstract Bone marrow derived mesenchymal stem cells (BM-MSCs) take part in the colonic mucosal regeneration. They are multipotent cells, which can be identified with both negative (i.e. CD13, CD 14, CD45, c-Kit, major histocompatibility complex /MHC class I and II) and positive (i.e. CD54 (ICAM1), CD133, CD146 (MCAM), CD166, Flk-1, Sca-1, Thy-1, stage-specific antigen I /SSEA-I and Musashi-1, HLA class I) markers. These cells can repopulate the gastrointestinal mucosa as they may differentiate into stromal- (i.e. myofi-broblast) or epithelial-like (Paneth-, epithel-, goblet or enteroendocrin) cells without proliferation. During the mesenchymal to epithelial transition (MET) stem cells enter the epithelial layer and take up epithelial cell-like properties. Rarely BM-MSCs may retain their stem cell characteristics and are capable of producing progeny. The isolated lymphoid aggregates may serve as a platform from where BM-MSCs migrate to the nearby crypts as mediated by several chemoattractant proteins, which are expressed in injured tissue. The number of BM-MSCs is influenced by the degree of inflammation. In this review we summarize the current information about the role of BM-MSCs in the repair progress of injured colonic epithelium and their potential clinical applications.

Keywords Mesenchymal stem cells · Mucosal regeneration · Mesenchymal-epithelial transition · Isolated lymphoid aggregates

G. Valcz (✉) · F. Sipos · K. Leiszter · K. Tóth · G. Műzes · B. Molnár · Z. Tulassay
2nd Department of Internal Medicine, Cell Analysis Laboratory, Semmelweis University,
Szentkiralyi Street 46,
1088 Budapest, Hungary
e-mail: valczg@yahoo.com

T. Krenács · Z. Balogh · A. Csizmadia
1st Department of Pathology and Experimental Cancer Research, Semmelweis University,
Budapest, Hungary

B. Molnár · Z. Tulassay
Molecular Medicine Research Group,
Hungarian Academy of Sciences,
Budapest, Hungary

Introduction

The primary functions of intestinal tract are digestion and absorption, but they also represent a barrier for the luminal pathogens. The intestinal lumen is lined by a simple epithelial layer, whose turnover is highly regulated by local stem cell activity [1]. During the rapid regeneration process intestinal stem cells provide daughter cells in the lower part of crypts. Daughter cells migrate upwards in the crypts to serve different functions and then undergo apoptosis. During the migration, they differentiate into absorptive (epithelial-) or secretory (globet-, Paneth-, enteroendocrine-) cells [2, 3]. In the adult gut, both the number and differentiation capacity of the local stem cells are low. In case of serious tissue injury (i.e. ulcerative colitis or Crohn's disease) the regeneration capacity of local stem cells is not enough to complete tissue repair. In this case bone marrow derived mesenchymal stem cells (BM-MSC) migrate into the gastrointestinal wall, where they may contribute to the repair progress [4–6] as differentiated mesenchymal cells (e.g. myofibroblasts) [7, 8]. Under other circumstances, they enter into the epithelial monolayer, where they keep their stem cell characteristics or differentiate to specialized epithelial-like cells [9, 10]. In this review, we briefly summarize our current knowledge about the role of BM-MSCs in colonic epithelial repair and their potential clinical use.

The Characterization of Mesenchymal Stem Cells and Their Homing

An undifferentiated stem cell is capable of several functions, such as proliferation, self-renewal, the production of a large number of differentiated and functional progenies, and possesses capacity for tissue regeneration after injury [2]. BM-MSCs have multipotency resulting in high degree of plasticity. They can give rise to cells of either mesenchymal or nonmesenchymal phenotypes (i.e. neuronal like cells) [11, 12]. The mesenchymal stem cells represent a very small fraction (0,001–0,01%) of the total population of nucleated cells in bone marrow [9]. By light microscopy, cultured BM-MSCs show homogenous population of blast-like cells [11] of 8–10 μm in diameter, which have large nucleus and little cytoplasm [13], and they form colonies in vitro [14].

The identification of BM-MSCs by FACS or immunohistochemistry needs both negative (i.e. CD13, CD 14, CD34, CD45, c-Kit, major histocompatibility complex / MHC class I and II) and positive (i.e. CD29, CD44, CD49a-f, CD51, CD54 (ICAM1), CD71, CD73, CD105, CD106, CD133, CD146 (MCAM), CD166, Flk-1, Sca-1, Thy-1, stage-specific antigen I /SSEA-I and Musashi-1, HLA class I) markers [13–21]. The multi-lineage differentiation and self-proliferation of BM-MSC are regulated by several different signaling pathways (i.e. Wnt, BMP/Smad, Nocht) [3, 4, 22, 23]. With the help of these pathways, MSCs are able to differentiate into several cell types, such as osteocytes, adipocytes, chondrocytes, tenocytes, and skeletal myocytes under controlled in vitro condition [24].

The homing of BM-MSCs to colonic mucosa has been poorly revealed yet. BM-MSCs migrate via the blood stream to the sites of colonic mucosal damage, which were certified in several in vivo experiments [3, 6, 25]. Regulation of BM-MSCs migration may happen as an effect of chemical signals, which get upregulated during injury. Wei et al. (2009) demonstrated that the allogenic stem cells could not repopulate the bowel wall without damage in bone marrow transplanted rats. Conversely, the increased number of donor stem cells was detected in 2, 4, 6-trinitrobenzenesulfonic acid (TNBS) induced colitis [6]. In liver fibrosis the sphingosine 1-phosphate plays a role in homing of mesenchymal stem cells [26] but it has not been published in case of colon inflammation. BM-MSCs express several cell surface chemokine receptors, such as CCR1,−2,−7,−8,−9, CXCR1,−2,−4,−5,−6 [24, 27]. These receptors have potential role of BM-MSC migration and make them capable of tissue repair. First phase of extravasation process happens with the help of adhesion molecules such as VCAMs, ICAMs and selectins [24]. Upregulation of VCAM1 and ICAM expression in MSCs is caused by chemical mediators, such as the TNF-α and IL-8, which are overexpressed under inflammatory circumstances [28, 29]. After the endothelial transmigration on blood vessel endothelium they migrate to optimal stromal compartment, so called niche. This specific microenvironment is formed by mesenchymal cells, which are localized adjacent to the epithelial basal membrane. Stem cell- and epithelial cell functions are regulated by several paracrine mediators i.e. growth factors, cytokines produced by the niche cells [4, 11].

The Role of Mesenchymal Stem Cells in Regeneration of Colonic Epithelium

BM-MSCs may give rise to myofibroblast, epithelial- and endothelial cells in the gastrointestinal tract [30]. Transplanted bone marrow cells have been shown to aggregate in experimental colon inflammation during the healing processes [31] as localized in the stroma or epithelium monolayer. The stromal cells partially are intestinal subepithelial myofibroblasts (ISEMFs), which may differentiate from BM-MSCs [8]. The differentiation of ISEMFs may take place directly from BM-MSCs [32] and from fibroblast [33]. Both processes are regulated by transforming growth β-1 (TGF-β1), which plays an important role in intestinal mucosal healing [34]. After differentiation ISEMFs form pericryptal fibroblast sheet (PCFS) outside but adjacent to of the basal lamina of cryptal epithelium in the lamina propria [1, 5, 35]. The ISEMFs exhibit ultrastructural features both of the fibroblasts and the smooth muscle cells and show immunopostivity for α-smooth muscle actin (α-SMA) and vimentin, but negative for desmin [36]. As they are localized close to the epithelium layer they may provide important microenvironment for both mesenchymal- and intestinal stem cells [23, 37]. They secrete several factors, like cytokines (IL-1, -6, -10, TNF-α), growth factors (i.e. TGF-α, GM-CSF, PDGF-AA, -BB, bFGF, KGF, HGF), chemokines (i.e IL-8, MCP1, MIP-1α, -2) and inflammatory mediators (i.e. PGE2, prostacyclin, PAF) [38]. These regulatory ligands play an important role in physiological and pathological regeneration processes. In vivo and in vitro experiments show that the ISEMFs play a crucial role in epithelial- mesenchymal interactions, epithelial cell differentiation [8] and migration [39]. Presumably, the BM-MSCs origin ISEMFs may create a local microenvironment to proliferating bone marrow derived stem cells. Myofibroblasts contribute to the coordination of tissue regeneration by producing TGF-β, EGF, bFGF, pro-inflammatory cytokines and the formation of new basement membrane [36]. The number of myofibroblast originating from the bone marrow significantly increased in lamina propria compared to the colitis with the healthy colon [4, 8], this homing process is driven by chemokines [24].

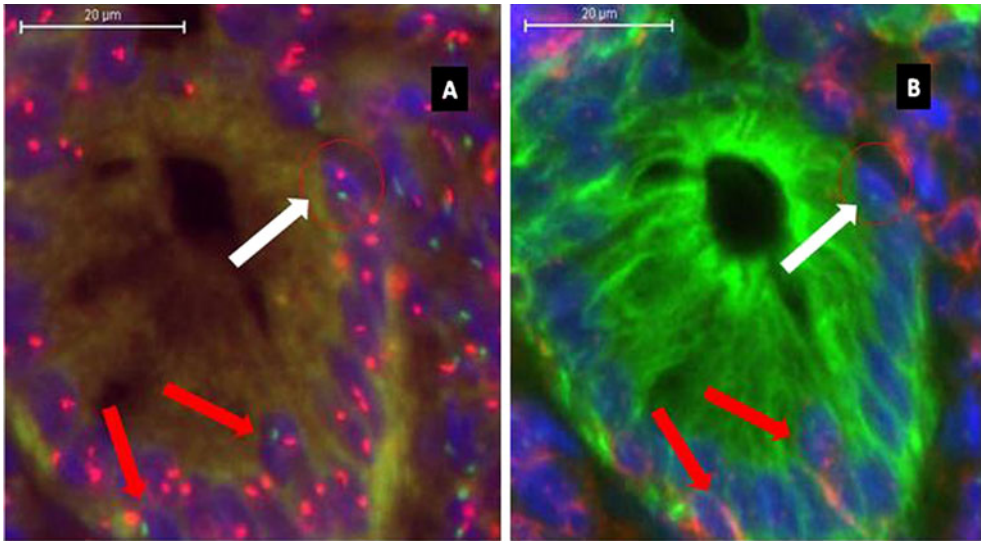

Fig. 1 Y-FISH+, CD45-, potential BM-MSC in glandular epithelium. In our study, first we used fluorescent in situ hybridization (FISH) for chromosome detection (**a**), after the digitalization, we made double stained immunohystochemistry detection of cytokeratin and CD45 (**b**) on the same slide and digitalized again. With the help of CD45 lymphocyte cytoplasmatic marker, we discriminated between the CD45+ (*red* cytoplasmatic stain), Y-FISH + (*green dots*) IELs (*red arrows*) and CD45- Y-FISH + potential BM-MSCs (*white arrows*)

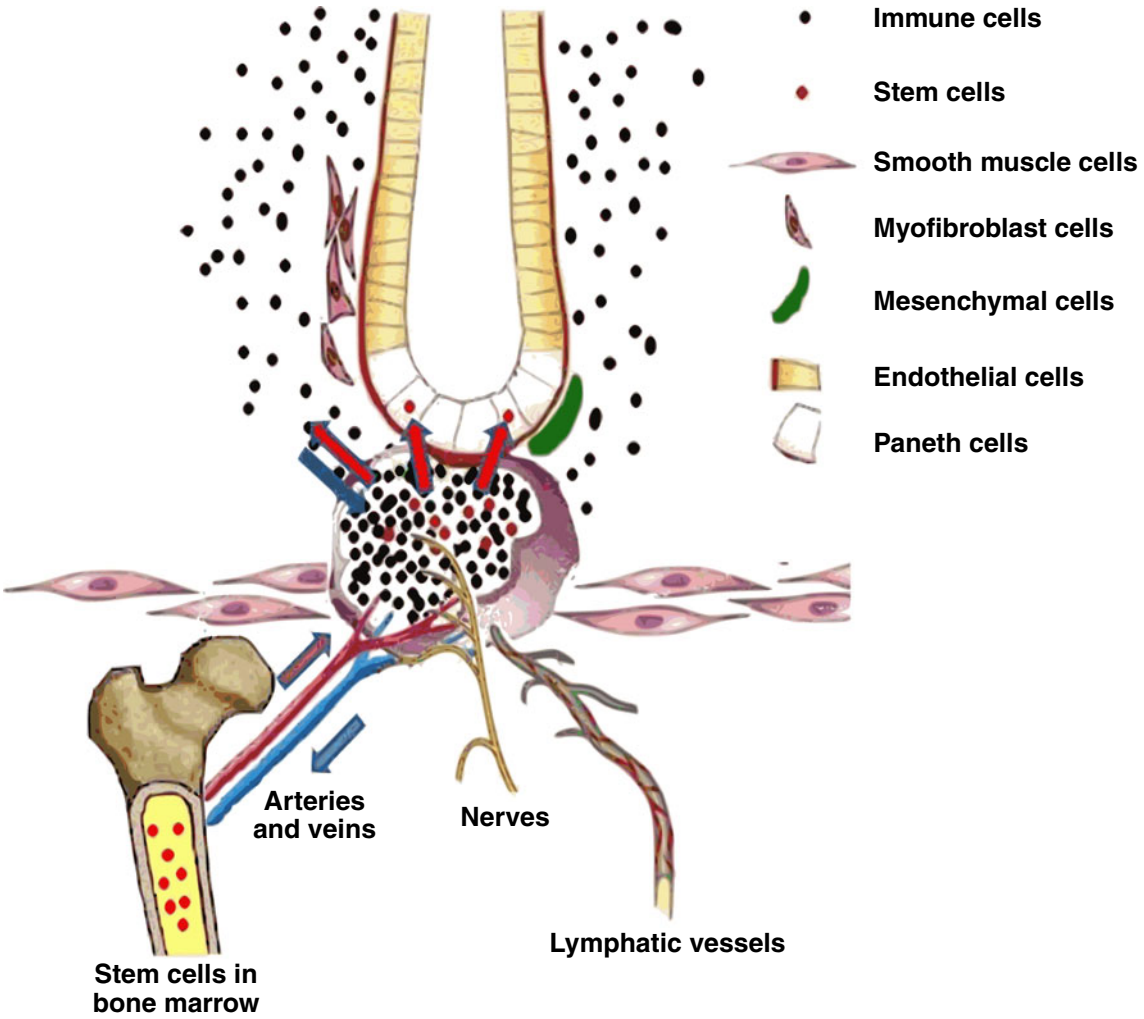

Fig. 2 In our hypothesis lymphoid aggregates serve as the transit place of BM-MSCs. After leaving the lymphoid aggregates, they migrate to the stroma or the epithelial layer. The BM-MSCs can differentiate into stromal cells such as the myofibroblast, or they enter into epithelial layer, where they produce their progeny cells or differentiate into epithelial-like cell

Another way of colonic epithelial regeneration involves the bone marrow derived stem cells and their migration into epithelium layer. The high percentages of intraepithelial cells of bone marrow origin are immune cells, such as CD45+ lymphocytes (IEL). In bone marrow transplanted (BMT) patients the numbers of CD45+, Y-FISH + (male donor origin) double positive cells (IEL) were significantly higher number in regenerating colonic epithelium than in the normal samples [25].

In other cases BM-MSCs within the epithelium layer can differentiate into functional epithelial cells or retain stem cell property. Matsumoto T et al. (2005) described, that the BM-MSCs rarely give rise to intestinal stem cell, only a very low percentage (0,08%) of Musashi-1 (a stem cell specific, mRNA binding protein) positive cells showed Y-FISH (male donor origin) coexpression. So the BM-MSCs rarely produce progeny cells, it is more typical that the intraepithelial bone marrow derived cells undergo terminal epithelial differentiation in case of strong regenerative pressure [3]. In this case the mesenchymal cells become polarized in the epithelium. This process is called mesenchymal to epithelial transition (MET) [40]. Eventually, the BM-MSCs may perform lineage specific functions, such as nutrition, absorption, production of mucin, cytokeratin and chromogranin.

Saxena SK et al. (1997) proved it experimentally that the Payer-plaques participate in the proliferation and migration processes of the epithelial cells. In their study they compared the regeneration of the epithelial layer of the healthy to the Payer-plaque extracted rats. In this latter case the development of crypts neighboring the dissected regions in the early phase of repair proved to be abnormal, the wound repair processes were slower and the proliferation of the epithelial cells decreased [41]. We also demonstrated that transplanted cells of bone marrow origin (CD45 negative, Y-FISH positive) (Fig. 1) were significantly higher number in the crypt epithelium near the lymphoid aggregates than at other regions in the samples [unpublished data]. It may be possible that isolated lymphoid aggregates serve as important transit place of BM-MSCs (Fig. 2). These cells may leave the lymphoid aggregates under the influence of tissue microenvironment. Stem cells migrate to the epithelium layer and may become committed to epithelial cell, or form further stem cell progeny.

Therapy Potential of BM-MSCs

The BM-MSCs are of primary importance as a new tool in regenerative medicine and tissue engineering. They can migrate through the circulation to the injured tissue and may contribute to local regeneration by differentiating into several cell types including vascular smooth muscle cells, hepatocytes, biliary epithelial cells, skeletal muscle fibres, cardiomyocytes, neural cells, renal tubular epithelial cells, endothelial cells, pericytes, myofibroblasts or intestinal epithelial cells [5, 8]. So these cells may be a source for regeneration in many tissues [10, 17]. Several successful clinical and preclinical studies have used bone marrow derived cells to repair myocardium [42], nervous- [43] and respiratory system [44]. But the usage of BM-MSCs in regenerative medicine requires high care. We do not know exactly what the influence of the exogenously administered BM-MSCs is on the epithelial proliferation as stem- or as niche cell. In fact the clinical experience with epithelial

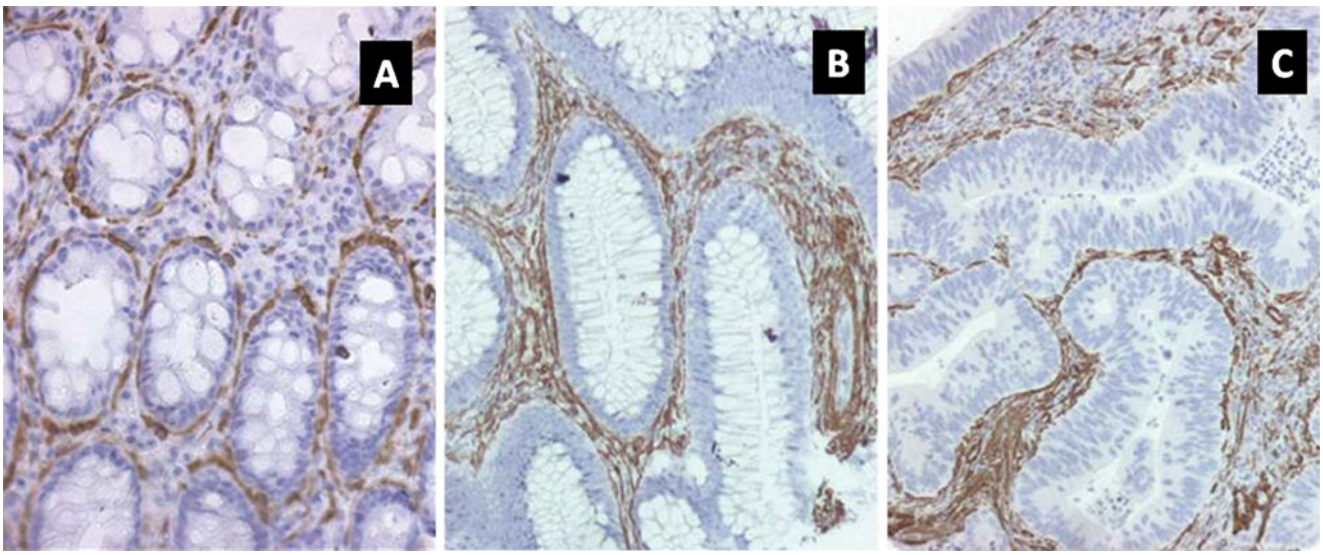

Fig. 3 The number of alfa-smooth muscle actin (α-SMA) positive myofibroblasts (*brown* cytoplasmatic staining) cells got increased compared to the adenoma- (**b**) and tumor -(**c**) with normal tissue sample (**a**)

proliferation show increased numbers of ISEMFs [45] (Fig. 3) which indicate that they have potential role in neoplastic processes in case of abnormal epithelial proliferation. Therapeutic application of BM-MSCs for epithelial regeneration requires the mesenchymal to epithelial transition (MET). During this process mesenchymal cells repress the mesenchymal proteins (i.e. vimentin) and shift to produce epithelial proteins, such as cytokeratin. The result of MET is that BM-MSCs will take up the damaged cell phenotype [10], but this cross-differentiation process may also be critical in tumor development [46]. According to the theory of Houghton and Wang (2005) bone marrow derived mesenchymal stem cells may be a source of cancer stem cells. They demonstrated that chronic *Helicobacter pylori* induction produces a new proliferation zone, which give rise to a metastatic cell line in gastric mucosa [47]. Even so, BM-MSCs are a potential source in regenerative medicine, to cure for instance intestinal bowel diseases and graft-versus-host disease (GVHD) [48]. As a result of exogenously administered stem cells the regeneration became faster [6], the inflamed area was reduced, the local inflammatory cell number and the crypt damage were decreased compared to the control group in DSS-induced colitis in rats [5]. Khalil et al. (2007) examined the repair process in DSS-inducted colitis using mice in by administering mesenchymal stem cells in infusion to the animals. In the treated animals activity of inflammation, the rectal bleeding and loss of weight decreased compared to the untreated animals [49]. The inhibition of inflammation may be related to the immunomodulatory effect on BM-MSCs by interfering with cytotoxic and interferon γ (INFγ) T cell, antigen-dependent regulatory (suppressor) T (Treg) cells, dendritic cells (DCs) and natural killer (NK) cells [5, 48]. BM-MSCs may suppress the inflammatory stress through interfering with chemokine receptor expression, migration and terminal differentiaton of B cells [12, 50]. BM-MSCs may suppress lymphocyte proliferation and formation of NK and cytotoxic T-cells. They are not targets for NK cells and cytotoxic lymphocytes [51]. Exogenous BM-MSC inhibited inflammatory shrinkage and shortening of colon in DSS-treated rats [5]. These findings indicate, that the perfect and quick regeneration of epithelial layer requires the activity of bone marrow derived stem cells. Easy isolation and high ex vivo expansive potential lend BM-MSCs a great potential in cell- and gene therapy [11].

Conclusions

Clinical application of allogenic BM-MSC may become a new milestone in regenerative medicine, but we need additional information concerning the mechanisms of their proliferation, migration and differentiation. The exclusive therapeutic importance of BM-MSCs lies in their inhibitory effects on multiple immune cells resulting in protection against rejection in the recipient and limited risk for autoimmunity. Base on their ability for mesenchymal to epithelial transition allogenic BM-MSCs may serve as a universal source for replacement of tissue deficiency as described in several animal and clinical studies. Therefore, revealing fine details of mesenchymal to epithelial transition as a basic process in tissue regeneration can be an important task in regenerative medicine. Clarifying the molecular mechanisms and safe applications of BM-MSC therapy may have a great potential in complementing of substituting those efforts testing for therapeutic uses of embryonic stem cells of restricted availability.

References

1. Grove JE, Bruscia E, Krause DS (2004) Plasticity of bone marrow-derived stem cells. Stem Cells 22:487–500
2. Potten CS, Loeffler M (1990) Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. Development 110:1001–1020
3. Matsumoto T, Okamoto R, Yajima T et al (2005) Increase of bone marrow-derived secretory lineage epithelial cells during regeneration in the human intestine. Gastroenterology 128:1851–1867
4. Brittan M, Wright NA (2004) Stem cell in gastrointestinal structure and neoplastic development. Gut 53:899–910
5. Tanaka F, Tominaga K, Ochi M et al (2008) Exogenous administration of mesenchymal stem cells ameliorates dextran sulfate sodium-induced colitis via anti-inflammatory action in damaged tissue in rats. Life Sci 83:771–779
6. Wei Y, Nie Y, Lai J et al (2009) Comparison of the population capacity of hematopoietic and mesenchymal stem cells in experimental colitis rat model. Transplantation 88:42–48
7. De Wever O, Demetter P, Mareel M et al (2008) Stromal myofibroblasts are drivers of invasive cancer growth. Int J Cancer 123:2229–2238
8. Brittan M, Hunt T, Jeffery R et al (2002) Bone marrow derivation of pericryptal myofibroblasts in the mouse and human small intestine and colon. Gut 50:752–757
9. Barry FP, Murphy JM (2004) Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol 36:568–584
10. Spees JL, Olson SD, Ylostalo J et al (2003) Differentiation, cell fusion, and nuclear fusion during ex vivo repair of epithelium by human adult stem cells from bone marrow stroma. Proc Natl Acad Sci U S A 100:2397–2402
11. Minguell JJ, Erices A, Conget P (2001) Mesenchymal stem cells. Exp Biol Med (Maywood) 226:507–520
12. Patel SA, Sherman L, Munoz J et al (2008) Immunological properties of mesenchymal stem cells and clinical implications. Arch Immunol Ther Exp (Warsz) 56:1–8
13. Jiang Y, Jahagirdar BN, Reinhardt RL et al (2002) Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 418:41–49
14. Kassem M, Kristiansen M, Abdallah BM (2004) Mesenchymal stem cells: cell biology and potential use in therapy. Basic Clin Pharmacol Toxicol 95:209–214

15. Matsumoto T, Okamoto R, Yajima T et al (2005) Increase of bone marrow-derived secretory lineage epithelial cells during regeneration in the human intestine. Gastroenterology 128:1851–1867
16. Phinney DG, Prockop DJ (2007) Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair current views. Stem Cells 25:2896–2902
17. Pittenger MF, Mackay AM, Beck SC et al (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284:143–147
18. Baksh D, Yao R, Tuan RS (2007) Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells 25:1384–1392
19. Haasters F, Prall WC, Anz D et al (2009) Morphological and immunocytochemical characteristics indicate the yield of early progenitors and represent a quality control for human mesenchymal stem cell culturing. J Anat 214:759–767
20. Mansilla E, Marín GH, Drago H et al (2006) Bloodstream cells phenotypically identical to human mesenchymal bone marrow stem cells circulate in large amounts under the influence of acute large skin damage: new evidence for their use in regenerative medicine. Transplant Proc 38:967–969
21. Gargett CE, Schwab KE, Zillwood RM et al (2009) Isolation and culture of epithelial progenitors and mesenchymal stem cells from human endometrium. Biol Reprod 80:1136–1145
22. Satija NK, Gurudutta GU, Sharma S et al (2007) Mesenchymal stem cells: molecular targets for tissue engineering. Stem Cells Dev 16:7–23
23. Leedham SJ, Brittan M, McDonald SA et al (2005) Intestinal stem cells. J Cell Mol Med 9:11–24
24. Chamberlain G, Fox J, Ashton B et al (2007) Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells 25:2739–2749
25. Okamoto R, Yajima T, Yamazaki M et al (2002) Damaged epithelia regenerated by bone marrow-derived cells in the human gastrointestinal tract. Nat Med 8:1011–1017
26. Li C, Kong Y, Wang H et al (2009) Homing of bone marrow mesenchymal stem cells mediated by sphingosine 1-phosphate contributes to liver fibrosis. J Hepatol 50:1174–1183
27. Liu ZJ, Zhuge Y, Velazquez OC (2009) Trafficking and differentiation of mesenchymal stem cells. J Cell Biochem 106:984–991
28. Liu N, Chen R, Du H et al (2009) Expression of IL-10 and TNF-alpha in rats with cerebral infarction after transplantation with mesenchymal stem cells. Cell Mol Immunol 6:207–213
29. Kim YS, Park HJ, Hong MH et al (2009) TNF-alpha enhances engraftment of mesenchymal stem cells into infarcted myocardium. Front Biosci 14:2845–2856
30. Yabana T, Arimura Y, Tanaka H et al (2009) Enhancing epithelial engraftment of rat mesenchymal stem cells restores epithelial barrier integrity. J Pathol 218:350–359
31. Komori M, Tsuji S, Tsujii M et al (2005) Involvement of bone marrow-derived cells in healing of experimental colitis in rats. Wound Repair Regen 13:109–118
32. Emura M, Ochiai A, Horino M et al (2000) Development of myofibroblasts from human bone marrow mesenchymal stem cells cocultured with human colon carcinoma cells and TGF beta 1. In Vitro Cell Dev Biol Anim 36:77–80
33. Brenmoehl J, Miller SN, Hofmann C et al (2009) Transforming growth factor-beta 1 induces intestinal myofibroblast differentiation and modulates their migration. World J Gastroenterol 15:1431–1442
34. Beck PL, Rosenberg IM, Xavier RJ et al (2003) Transforming growth factor-beta mediates intestinal healing and susceptibility to injury in vitro and in vivo through epithelial cells. Am J Pathol 162:597–608
35. Roufosse CA, Direkze NC, Otto WR et al (2004) Circulating mesenchymal stem cells. Int J Biochem Cell Biol 36:585–597
36. Andoh A, Bamba S, Fujiyama Y et al (2005) Colonic subepithelial myofibroblasts in mucosal inflammation and repair: contribution of bone marrow-derived stem cells to the gut regenerative response. J Gastroenterol 40:1089–1099
37. Brittan M, Chance V, Elia G et al (2005) A regenerative role for bone marrow following experimental colitis: contribution to neovasculogenesis and myofibroblasts. Gastroenterology 128:1984–1995
38. Powell DW, Mifflin RC, Valentich JD et al (1999) Myofibroblasts. I. Paracrine cells important in health and disease. Am J Physiol 277:1–9
39. Powell DW, Mifflin RC, Valentich JD et al (1999) Myofibroblasts. II. Intestinal subepithelial myofibroblasts. Am J Physiol 277:183–201
40. Baum B, Settleman J, Quinlan MP (2008) Transitions between epithelial and mesenchymal states in development and disease. Semin Cell Dev Biol 19:294–308
41. Saxena SK, Thompson JS, Sharp JG (1997) Role of organized intestinal lymphoid aggregates in intestinal regeneration. J Invest Surg 10:97–103
42. Chugh AR, Zuba-Surma EK, Dawn B (2009) Bone marrow-derived mesenchymal stems cells and cardiac repair. Minerva Cardioangiol 57:185–202
43. Sugaya K, Merchant S (2008) How to approach Alzheimer's disease therapy using stem cell technologies. J Alzheimers Dis 15:241–254
44. Le Visage C, Dunham B, Flint P et al (2004) Coculture of mesenchymal stem cells and respiratory epithelial cells to engineer a human composite respiratory mucosa. Tissue Eng 10:1426–1435
45. Powell DW, Adegboyega PA, Di Mari JF et al (2005) Epithelial cells and their neighbors I. Role of intestinal myofibroblasts in development, repair, and cancer. Am J Physiol Gastrointest Liver Physiol 289:2–7
46. Rubio D, Garcia S, De la Cueva T et al (2008) Human mesenchymal stem cell transformation is associated with a mesenchymal-epithelial transition. Exp Cell Res 314:691–698
47. Houghton J, Wang TC (2005) Helicobacter pylori and gastric cancer: a new paradigm for inflammation-associated epithelial cancers. Gastroenterology 128:1567–1578
48. Panés J, Salas A (2009) Mechanisms underlying the beneficial effects of stem cell therapies for inflammatory bowel diseases. Gut 58:898–900
49. Khalil PN, Weiler V, Nelson PJ et al (2007) Nonmyeloablative stem cell therapy enhances microcirculation and tissue regeneration in murine inflammatory bowel disease. Gastroenterology 132:944–954
50. Asari S, Itakura S, Ferreri K et al (2009) Mesenchymal stem cells suppress B-cell terminal differentiation. Exp Hematol 37:604–615
51. Ringdén O, Uzunel M, Rasmusson I et al (2006) Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation 81:1390–1397