Open Access

SCHOLARENA

SAJ Cancer Science

RESEARCH ARTICLE

ISSN: 2375-6683

Autologous Bone Marrow Therapy to Operative Site Following Modified Radical Mastectomy to Prevent Flap Complications

Mahapatra SK[1*], LV Gouri[2] and Jha DK[3]

[1]*Professor, Department of General Surgery, Vimsar, Burla, Odisha, India*
[2]*Assistant Professor, Department of General Surgery, Vimsar, Burla, Odisha, India*
[3]*Junior Resident, Department of General Surgery, Vimsar, Burla, Odisha, India*

[*]**Corresponding author:** Mahapatra SK, Professor, Unit Head and H.O.D of General Surgery vimsar, Burla, Odisha, India, Tel: 9437025626, E-mail: drskm2010@gmail.com

Citation: Mahapatra SK (2017) Autologous Bone Marrow Therapy to Operative Site Following Modified Radical Mastectomy to Prevent Flap Complications. SAJ Cancer Sci 4:101

Abstract

Breast cancer is the second leading cause of cancer-related deaths, second to lung cancer, with approximately 40,000 deaths caused by breast cancer annually. Breast cancer is also a global health problem, with more than one million cases of breast cancer diagnosed worldwide each year [1]. Though breast-conserving surgery is more and more welcomed among female patients, modified radical mastectomy (MRM) still plays an important role in the operation for breast cancer. Postoperative complications such as wound pain, hematoma, marginal necrosis, flap necrosis, seroma, wound infection, shoulder stiffness and prolonged drainage led to a delay of adjuvant therapy after the operation [2]. In our study we have tried the autologous bone marrow therapy to operative site to prevent such complications. Two groups of patients were selected randomly containing 20 patients in each group. The patients under control group were treated by modified radical mastectomy alone whereas the patents under study group were treated by modified radical mastectomy followed by autologous bone marrow therapy to operative site. The patients were followed postoperatively and parameters like post-operative pain, seroma collection, marginal necrosis, flap necrosis, wound infection, hypertrophic scar or keloid, local recurrence of tumour was observed in both the groups of patients. After our study we found that Post operatively the patients in study group experienced less pain as compared to control group. Out of 20 patients in control group marginal necrosis was observed in 4 (20%) patients whereas in study group it was seen in 2 (10%) patients (*p value* = 0.4459). Flap necrosis was seen in 2 (10%) patients in control group whereas no such complication was observed in study group (*p value* = 0.1670). In control group 9 (45%) patients were observed to have seroma collection after removal of drain which required aspiration but in study group none of the patient had seroma collection after removal of drain (*p value* = 0.0058). In control group shoulder stiffness was observed in 8 patients (40%) whereas in in study group it was observed in 2 (10%) patients (*p value* = 0.0873). local recurrence of tumour and hypertrophic scar was only seen in 1 patient respectively in control group. No local recurrence of tumour, hypertrophic scar, keloid was seen in study group.

Keywords: Autologous Bone Marrow Therapy; Modified Radical Mastectomy; Carcinoma Breast

List of Abbreviations: HGF: Hepatic Growth Factor; MSC: Mesenchymal Stem Cell; RNS: Reactive Nitrogen Speces; ROS: Reactive Oxygen Species; LEC: Lymphatic Endothelial Cell; HRT: Hormone Replacement Therapy

Introduction

The overall incidence of breast cancer was increasing until approximately 1999 because of increases in the average life span, lifestyle changes that increase the risk for breast cancer and improved survival rates for other diseases. Breast cancer incidence decreased from 1999 to 2006 by approximately 2% per year. This decrease was attributed to a reduction in the use of HRT after the initial results of the Women's health Initiative were published but may also be the result of a reduction in use of screening mammography. During the year 2006 to 2010, the breast cancer incidence rates were stable [1]. But in our country where early diagnosis of breast cancer is not possible due to illiteracy, ignorance and social stigma many patients go into locally advanced stage or metastatic stage. Thus majority of them require modified radical mastectomy rather than breast conservative surgery. But after modified radical mastectomy they suffer from the common immediate complications like wound pain, marginal necrosis, flap necrosis, seroma, wound infection, lymphoedema, stiff shoulder and also from delayed complications like hypertrophic scar, keloid and local recurrence of tumour [2-4]. Due to these complications the duration of stay in surgery ward increases and the adjuvant therapy for such patients also gets delayed. Many studies have been done all over the world to prevent these complications like the

use of herbal medicines by the Chinese, delaying post-operative physiotherapy [5-10]. For a week, use of harmonic scalpel instead of electrocautery [6,11], use of negative suction drain and compressive dressings[11,12] etc. None of the methods alone is sufficient to prevent such problems thus a combined approach is used. Autologous bone marrow therapy is a new concept which is based on the facts that bone marrow contains mesenchymal stem cells which stimulates the local stem cells, fibroblast and macrophages for their enhanced activity. They also liberate cytokines and growth factors which helps in rapid wound healing and preventing early flap complications like wound pain, flap and marginal necrosis and seroma formation.

In this prospective study from November 2013 to November 2016 we have done a prospective analysis in the study on the effect of autologous bone marrow therapy to breast bed, axillary bed and breast flaps to prevent flap complications.

Objective

Primary Objective

"To Study The Effect of Autologous Bone Marrow Therapy to Breast Bed, Axillary Bed and Breast Flaps to Prevent Flap Complications".

Secondary Objective

"To Study The Effect of Autologous Bone Marrow Therapy to Breast Bed, Axillary Bed and Breast Flaps Following Modified Radical Mastectomy to Prevent Hypertrophic Scar, Keloid Formation and Local Recurrance of Cancer".

Methods

Institutional ethics committee clearance and informed consent of the patients was taken before the study. Then total fourty breast cancer patients with stage T1-3 N0-1 M0 in this study underwent modified radical mastectomy surgery at VSS Institute of Medical Sciences and Research Institute, Burla, Odisha, India in one surgical unit during the year 2013-16. Out of 40 patients, 20 patients were kept in study group and rest 20 in control group. Auchincloss type modified radical mastectomy was performed in all patients. In the study group, on operative table bone marrow was aspirated from the sternum of the patients using bone marrow aspiration needle under anaesthesia. Then the aspirate was kept aside after priming with heparin in a sterile syringe. Then skin flaps were raised as per standard procedure, mastectomy and axillary clearance and hemo stasis was obtained in all the cases. Bone marrow aspirate was infiltrated to under surfaces of breast flaps and breast bed and to axillary bed. Skin flaps were closed with a suction drain. Pressure garment and suction drains were used routinely in both study and control group. Post operatively the patients were followed and parameters like wound pain, marginal necrosis, flap necrosis, wound infection, seroma collection, shoulder joint stiffness, hypertrophic scar, keloid and local recurrences were studied (Figure 1 and 2).

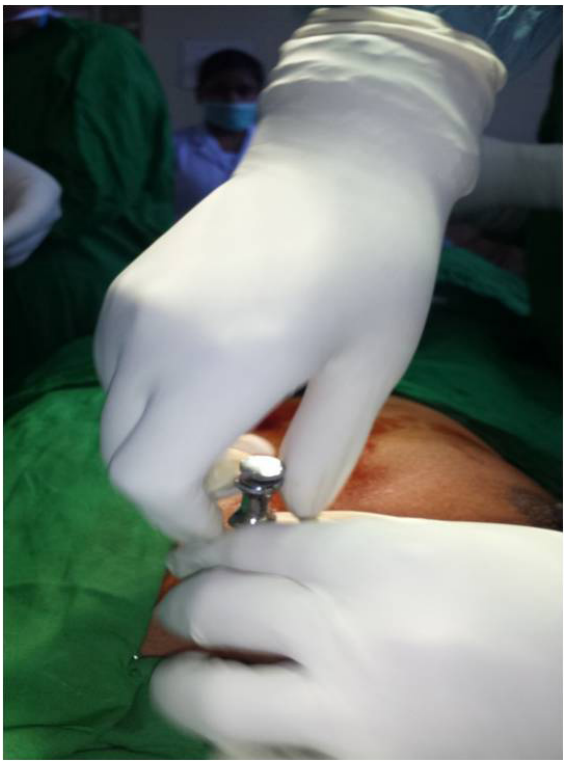

Figure 1: Picture showing bone marrow aspiration from sternum of patient of carcinoma breast

Figure 2: Showing infiltration of bone marrow after modified radical mastectomy

Results

Post operatively the patients in study group experienced less pain as compared to control group. Out of 20 patients in control group marginal necrosis was observed in 4(20%) patients whereas in study group it was seen in 2 (10%) patients (*p value* = 0.4459). Flap necrosis was seen in 2(10%) patients in control group whereas no such complication was observed in study group (*p value* = 0.1670). In control group 9(45%) patients were observed to have seroma collection after removal of drain which required aspiration but in study group none of the patient had seroma collection after removal of drain (*p value* = 0.0058). In control group shoulder stiffness was observed in 8 patients (40%) whereas in in study group it was observed in 2(10%) patients (*p value* = 0.0873). local recurrence of tumour and hypertrophic scar was only seen in 1 patient in control group. No local recurrence of tumour, hypertrophic scar and keloid was seen in study group [13-15] (Table 1, 2 and 3, Figure 3).

Post OP Days	Post OP Pains	Seroma Collection	Flap Complecations
1	Severe	130 ml	Absent
3	Mild	100 ml	Marginal2, flap1
5	Mild	70 ml	Marginal2+2, flap1+1
7	Mild	50 ml	Marginal2+2, flap1+1
10	Mild	30 ml	Marginal2+2, flap1+1

Table 1: Showing post-operative pain, seroma collection and flap complications seen in respective post-operative day of control group

Post OP Days	Post OP Pains	Seroma Collection	Flap Complecations
1	Mild	100ml	Absent
3	Mild	50ml	Absent
5	Nil	30ml	Marginal2, flap-nil
7	Nil	10ml	Marginal2, flap-nil
10	Nil	10ml	Marginal2, flap-nil

Table 2: Showing post-operative pain, seroma collection and flap complications seen in respective post-operative day of study group

	Study Group	Control Group
General well being	Good	Moderate
Seroma Collection	0/20	9/20
Shoulder stiffness	2/20	8/20
Local recurrence	0/20	1/20

Table 3: Showing comparison between study and control group with respect to general wellbeing, seroma collection after drain removal, shoulder stiffness and local recurrence

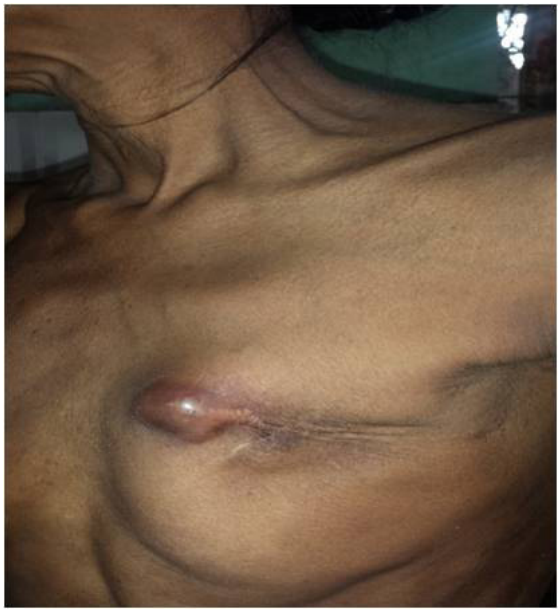

Figure 3: Showing local recurrence of a patient after modified radical mastectomy in control group

Discussion

MSCs were initially isolated from bone marrow but are now shown to reside in almost every type of connective tissue [16]. MSCs are characterized as a heterogeneous population of cells that proliferate *in vitro* as plastic adherent cells able to develop as fibroblast colony forming-units [17]. MSCs are distinguished from hematopoietic cells by being negative for the cell surface markers CD11b, CD14, CD34, CD45 and human leukocyte antigen (HLA)-DR but expressing CD73, CD90 and CD105. Importantly, the capacity to differentiate into multiple mesenchymal lineages including bone, fat and cartilage is used as a functional criterion to define MSCs [18]. MSCs are clearly capable of responding and modulating their function when exposed to the cells and biochemical factors that are characteristic of an injury environment. Human MSCs migrate preferentially to regions of inflammation [19] and express several chemokine receptors that are necessary to coordinate their homing ability [20]. Furthermore, MSCs have demonstrated chemotaxis toward a variety of wound healing cytokines *in vitro*, including platelet-derived growth factor, insulin-like growth factor-1, IL-8 and TNFα [21,22]. These data suggest that bone-marrow-derived MSCS or endogenous cells resembling MSCs, such as pericytes, are likely to migrate to and participate in the response to tissue injury. During modified radical mastectomy we iatrogenically injure the lymphatic system, blood vessels and other tissues. Injury to lymphatic system causes seroma formation and lymphoedema.

Studies have shown that mesenchymal stem cells (MSCs) derived either from bone marrow or fat can express LEC markers (prox-1, VEGF-C, VEGF-A) and that stimulation of these cells in cultured media with recombinant VEGF-C, even for brief periods of time *in vitro*, markedly increased their ability to promote lymphangiogenesis *in vivo* [23, 24]. Thus adult mesenchymal stem cells may have an important role in decreasing seroma formation and also lymphoedema after modified radical mastectomy by early healing of injured lymphatic vessels. In our study we have observed less seroma collection in study group than control group and after removal of drain 9 patients out of 20 patients in control group came for seroma collection which required aspiration by needle whereas in study group none of the patient came with complaint of seroma collection after removal of drain. Our this finding supports the above literature there by suggesting the role of autologous bone marrow therapy in early healing of injured lymphatic system resulting into decreased seroma collection.

MSCs produce basic FGF and VEGF-A, which provide powerful mitogenic cues to promote proliferation, migration and differentiation of microvascular endothelial cells [25,26]. MSCs also express paracrine factors to promote vascular stability and vasoprotection [27,28], including adrenomedullin [29]. It has been hypothesized that these functions are unique to MSCs due to their possible perivascular origin, and they are able to exploit these functions to recreate their perivascular niche as theprocess of vasculature remodeling is concluded [30]. Enhancement of vascular formation by bone-marrow derived MSCs has been demonstrated *in vitro* [31] and to facilitate the development of long-lasting functional vasculature as perivascular progenitor cells [32]. Thus autologous bone marrow therapy may facilitate neovascularisation and thereby prevent marginal necrosis and flap necrosis. Though proper surgical technique like tension free suturing, not too thin flap, less thermal injury by electro cautery have an important role in preventing marginal necrosis and flap necrosis but despite the use of all these techniques marginal necrosis and flap necrosis are very frequent in patients after modified radical mastectomy.. In our study we have seen marginal necrosis in 4 out of 20 patients in control group and 2 out of 20 patients in study group and flap necrosis in 2 out of 20 patients in control group and none of the patients in study group. Though such finding is not statistically significant still relatively we have seen less marginal necrosis and no flap necrosis in study group as compared to control group. Regarding postoperative pain , patients experienced

very less pain as compared to control group may be due to the anti- inflammatory activites of mesenchymal stem cells. MSCs have anti-inflammatory effects because they inhibit dendritic cell [DC] maturation and B and T cell proliferation and differentiation, that they attenuate natural killer [NK] cell killing, and that they also support suppressive T regulatory cells [Tregs][33-35]. MSCs also decrease the amount of IL-10 and TNF-α secreted by DC cells, and increase the amount of the anti-inflammatory IL-4 produced by T cells [33-35]. MSCs provide significant benefit during dermal wound healing, as they can,

1) Accelerate the rate of wound closure and re-epithelialization,
2) Improve the quality and strength of the regenerated tissue,
3) Recover wound healing pathologies that might otherwise result in a chronic, non-healing wound, and
4) Minimize the visual appearance of scar tissue.

In adult cutaneous wound healing, inflammatory cells are recruited to the wound and produce proinflammatory mediators such as monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These mediators can not only induce additional inflammation but also contribute to excess extracellular matrix (ECM) deposition and fibrosis. Moreover, the inflammatory cells can produce growth factors such as transforming growth factor-beta 1 (TGF-β1) and platelet-derived growth factor, which stimulate fibroblast proliferation, myofibroblast differentiation, and excess ECM deposition, leading to scar formation. We have not seen any local recurrence and it need to be studied more to prove the anti-tumour effects of mesenchymal stem cells (Figure 4). This study is purely clinical and we have only seen the effects of autologous bone marrow therapy and the rationale behind them are still being studied at molecular level. At present our sample size is small and we will continue our research in more number of patients in future.

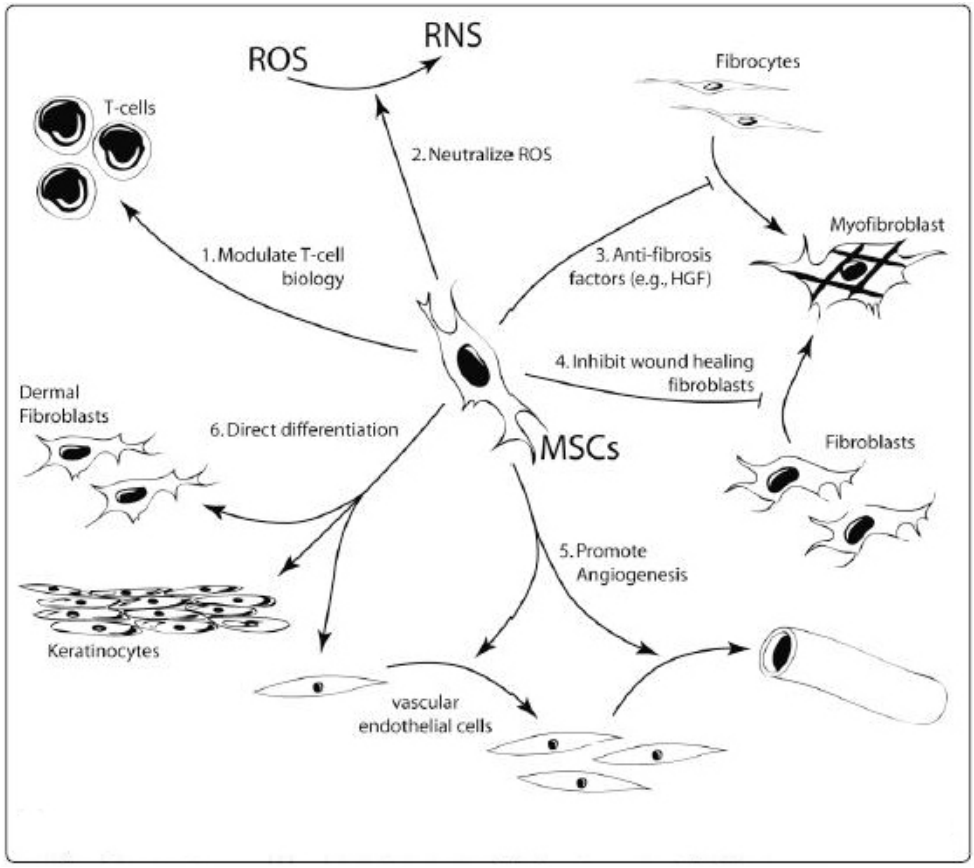

Figure 4: Mesenchymal stem cells can Influence cutaneous regeneration by multiple distinct mechanisms acting on multiple cell types [15]

Conclusion

To minimize the skin flap complications after modified radical mastectomy for breast cancer, lesser use of cautery and infiltration of autologous bone marrow, routine use of suction drains and application of pressure garments may be recommended.

References

1. Townsend, Beauchamp, Evers, Mattox (2016) Sabiston Textbook Of Surgery. First South Asia Edition Elsevier 820-60.

2. Tejler G, Aspegren K (1985) Complications and hospital stay after surgery for breast cancer:a prospective study of 385 patients. Br J Surg 72: 542-4.

3. Tadych K, Donegan WL (1987) Post mastectomy seromas and wound drainage. Surg Gynecol Obstet 165: 483-7.

4. Bryant M, Baum M (1987) Postoperative seroma following mastectomy and axillary dissection. Br J Surg 74: 1187.

5. Dawson I, Stam L, Heslinga JM, Kalsbeek HL (1989) Effect of shoulder immobilization onwound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial. Br J Surg 76: 311-2.

6. Porter KA, O'Connor S, Rim E, Lopez M (1998) Electrocautery as a factor in seroma formation following mastectomy. Am J Surg 176: 811.

7. Jeffery SS, Goodson WH, Ikeda DM, Bindwell RI, Bogetz MS (1955) Axillarylymphadenctomy for breast cancer withoutaxillary drainage. Arch Surg 130: 909-13.

8. Bonnema J, Ligtenstein DA, Wiggers T, vanGeel AN (1999) The composition of serous fluid after axillary dissection. Eur J Surg 165: 9-13.

9. Burak WE Jr. Goodman PS, Young DC,Farrar WB (1997) Seroma formation following axillary dissection for breast cancer: risk factors and lack of influence of bovine thrombin. J Surg Oncol 64: 27-31.

10. Browse DJ, Goble D, Jones PA (1996) Axillary node clearance: who wants to immobilize the shoulder? Eur J Surg Oncol 22: 569-70.

11. O'Hea BJ, Ho MN, Petrek JA (1999) External compression dressing versus standard dressing after axillary lymphadenectomy. Am J Surg 177: 450-3.

12. Lam CYW, Lim BH, Chiu PWY, Lee SW, et al. (2001) Effects of pressure garment on patients undergoing modified radical mastectomy. A prospective randomized trial. Ann Coll Surg HK 5: A17.

13. Siegel BM, Mayzel KA, Love SM (1990) Level I and II axillary dissection in the treatment of early-stage breast cancer. Arch Surg 25: 1144-7.

14. Singer N, Caplan A (2011) Mesenchymal stem cells: mechanisms of inflammation. Annu Rev Pathol 6: 457-8.

15. Jackson. (2012) Stem Cell Research & Therapy 3: 20.

16. Da Silva Meirelles L, Chagastelles PC, Nardi NB (2006) Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci 119: 2204-13.

17. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, et al. (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284: 143-7.

18. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, et al. (2006) Minimal criteria for defi ning multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8: 315-7.

19. Ponte AL, Marais E, Gallay N, Langonne A, Delorme B, et al. (2007) The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities. Stem Cells 25: 1737-45.

20. Sasaki M, Abe R, Fujita Y, Ando S, Inokuma D, et al. (2008) Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdiff erentiation into multiple skin cell type. J Immunol 180: 2581-2587.

21. Mishima Y, Lotz M (2008) Chemotaxis of human articular chondrocytes and mesenchymal stem cells. J Orthop Res 26: 1407-12.

22. Hemeda H, Jakob M, Ludwig AK, Giebel B, Lang S, et al. (2010) Interferon gamma and tumor necrosis factor-alpha diff erentially aff ect cytokine expression and migration properties of mesenchymal stem cells. Stem Cells Dev 19: 693-706.

23. Oh SJ, Jeltsch MM, Birkenhäger R, McCarthy JE, Weich HA, et al. (1997) VEGF and VEGF-C: specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane. Dev Biol. 188: 96-109.

24. Joukov V, Pajusola K, Kaipainen A, Chilov D, Lahtinen I, et al. (1996) A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR3) and KDR (VEGFR-2) receptor tyrosine kinases. EMBO J. 15: 1751.

25. Gruber R, Kandler B, Holzmann P, Vogele-Kadletz M, Losert U, et al. (2005) Bone marrow stromal cells can provide a local environment that favors migration and formation of tubular structures of endothelial cells. Tissue Eng 11: 896-903.

26. Kaigler D, Krebsbach PH, Polverini PJ, Mooney DJ (2003) Role of vascular endothe lial growth factor in bone marrow stromal cell modulation of endothelial cells. Tissue Eng 9: 95-103.

27. Lozito TP, Taboas JM, Kuo CK, Tuan RS (2009) Mesenchymal stem cell modification of endothelial matrix regulates their vascular diff erentiation. J Cell Biochem 107: 706-13.

28. Kato J, Tsuruda T, Kita T, Kitamura K, Eto T (2005) Adrenomedullin: a protective factor for blood vessels. Arterioscler Thromb Vasc Biol 25: 2480-7.

29. Renault MA, Roncalli J, Tongers J, Misener S, Thorne T, et al. (2009) The Hedgehog transcription factor Gli3 modulates angiogenesis. Circ Res 105: 818-26.

30. Bianco P, Robey P, Simmons P (2008) Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell 2: 313-9.

31. Sorrell JM, Baber MA, Caplan AI (2009) Infl uence of adult mesenchymal stem cells on in vitro vascular formation. Tissue Eng Part A 15: 1751-61.

32. Au P, Tam J, Fukumura D, Jain RK (2008) Bone marrow-derived mesenchymal stem cel ls facilitate engineering of long-lasting functional vasculature. Blood 111: 4551-8.

33. Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, et al. (2007) Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells 25: 2025-32.

34. Aggarwal S, Pittenger M (2005) Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 105: 1815-22.

35. Varin A, Gordon S (2009) Alternative activation of macrophages: immune function and cellular biology. Immunobiology 214: 630-41.

36. Peranteau WH, Zhang L, Muvarak N, Badillo AT, Radu A, et al. (2008) IL-10 overexpression decreases infl ammatory mediators and promotes regenerative healing in an adult model of scar formation. J Invest Dermatol 128: 1852-60.