

## Adult stem cells and repair through granulation tissue

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### 1. ABSTRACT

Macrophage recruitment and proliferation of both small vessels (endothelium and pericytes) and fibroblast-myofibroblasts are the fundamental and provisional cellular findings in repair through granulation tissue (RTGT). Endothelium and pericytes of preexisting microvasculature may act as progenitor cells of new endothelial cells and new pericyte-fibroblast-myofibroblasts, respectively. Likewise, fibroblasts may be progenitors of themselves, and of myofibroblasts and pericytes. Moreover, all these cells may originate from circulating progenitor cells or other progenitor cells. According to this extensive cellular plasticity, this work reviews the adult stem cells (ASC) and transit-

amplifying cells (TAC) related to the principal cellular components of RTGT. Moreover, we hypothesize that the perivascular region, with a heterogeneous pericyte-like cellular population, including pericytes, perivascular fibroblasts and homing cells from the bone marrow (fibrocytes and bone marrow mesenchymal cells), is the niche of progenitor cells in RTGT and the substrate of regulatory mechanisms (perivascular niche hypothesis). We also highlight RTGT as a "paracrine transitional organ" during involutive phenomena and cellular differentiation. Furthermore, we consider the combined role of both systems (ASC-TAC and RTGT) in tissue engineering and in pathological processes, such as fibrosis, organization, atherosclerosis, and tumor stroma.

### 2. INTRODUCTION

#### 2.1. ASC and TAC

Under normal physiologic conditions, the lost cells are replaced by means of a system comprising adult stem cells (ASC) and transit-amplifying cells (TAC), as well as the ASC niches, with their intrinsic and extrinsic regulatory mechanisms. ASC, able to self renew and to intervene in maintaining the structural and functional integrity of their original tissue, can express greater plasticity than traditionally attributed to them (1-5), adopting functional phenotypes and expression profiles of cells from other tissues (3, 4, 6-22). TAC are committed progenitors among the ASC and their terminally differentiated daughter cells. TAC, with more rapid though limited proliferation, low self-renewal and restricted differentiation, increase the number of differentiated cells produced by one ASC division. The ASC and TAC are located in one place, or structural unit (structural proliferative unit, for instance, the intestinal crypt). The ASC, in particular reside in a specialised physical location (for instance, between and immediately above Paneth cells in the small intestine crypt - 23), named niche (24-29), which constitutes a three-dimensional microenvironment where they are protected and controlled in their self-renewing capacity and differentiation. Cell contacts with neighbouring cells (adherens junctions – cadherins and catenins) and with extracellular matrix (basal membrane – integrins), and the balance of stimulatory and inhibitory signals that regulate cell quiescence (epidermal and basic fibroblast growth factors, mytogenic cytokines and WNTS signaling, BMP/TGF $\beta$ ) participate in this regulatory mechanism (30-36).

#### 2.2. Repair through granulation tissue

After injury, ASC intervene in the replacement of damaged or dead cells with new healthy cells using reparative mechanisms. Classically, from a broad perspective, repair includes two types of processes: regeneration and repair through granulation tissue (RTGT). Both types of repair processes use similar mechanisms and, to a greater or lesser extent, appear combined. Regeneration occurs when dead, degenerated or damaged cells are replaced by other cells of the same type. Related to this form of repair are metaplasia (replaced by another different adult cell type) and dysplasia (replaced by cells that undergo atypical cytologic changes in their organisation, shape and size). By means of this procedure, the parenchymal cells of the tissues may be replaced in normal or pathological conditions. RTGT occurs by definition through granulation tissue: a provisional tissue with macrophage recruitment and proliferation of small blood vessels and fibroblasts-myofibroblasts. During RTGT, the following findings may occur: a) perfect reconstruction of the original tissue stroma, parallel to the regeneration of parenchymal elements; b) stroma formation of proliferative elements different to the original parenchyma, such as tumor stroma; c) total or partial replacement of the specialized parenchymal elements by permanent nonspecialized fibrous tissue (scarring); d) creation of new masses of fibrous tissue in blood clots or inflammatory exudates with fibrin deposits, by a process

referred to as organization; and e) formation of other tissues, such as bone, cartilage and adipose.

#### 2.3. ASC and TAC in RTGT

The role of ASC and TAC in regeneration has been widely treated in several excellent original and review articles, while the role of these cells in RTGT has principally been considered separately in the various events of the latter. Since the formation of supporting stroma and/or of some tissues (bone, cartilage, adipose) from ASC can require similar mechanisms in tissue engineering to those in RTGT, an overall correlation of both systems, with a comprehensive review in this field (ASC in RTGT), is of interest. Furthermore, this would help to understand several RTGT-related pathological processes, such as thrombus organization, neoplasm growth and atherosclerosis. Given the above, the object of this article is to review the role, nature, location (niches) and regulatory systems of ASC and TAC that intervene in RTGT, and in its derived pathological processes.

### 3. REGIONS WITH RTGT CAPACITY

The regions with RTGT capacity are the most ubiquitous in all repair. However, they have a common characteristic: the presence, in or near, of an active preexisting pericytic microvasculature, where the repair phenomena initiate. The latter originate above all in the venous side of the circulation, specifically in the postcapillary venules (37, 38). Therefore, this microvasculature forms part of a substrate of a general inflammatory-reparative system in which the vessels not only intervene in recruitment of inflammatory cells and in new capillary formation (angiogenesis), but they may also contribute matrix-forming cells (fibroblasts-myofibroblasts, osteoblasts, chondroblasts), and contractile and adipose cells. Vessels of greater caliber in the circulation, such as the rat femoral vein, with a discontinuous internal elastic lamina and smooth muscle cells in their media layer, are also capable of contributing to RTGT (39-42).

The RTGT capacity of the regions has biological and clinical implications. In avascular tissues (e.g. cartilage and cornea), there is capacity of regeneration, but RTGT may only originate from neighbouring vascularized tissues. In this case, the intensity of RTGT component penetration into an avascular tissue depends on the properties of the latter (e.g. inhibitory action of antiangiogenic substances, as occurs in cartilage). In addition, the RTGT characteristics of a region may be conditioned by its regenerative capacity (interactions between regeneration and RTGT). For instance, in the central nervous system and cardiac muscle, where the regeneration is limited, the RTGT local precursor cells are generally involved in scar tissue replacement.

### 4. EVENTS IN RTGT

RTGT is a complex biological process that involves coagulation, inflammation, angiogenesis, proliferation of mesenchymal cells, vascular involution and remodelling. Despite the continuous and ordered nature of

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the process, these findings occur in several overlapping phases, according to predominant mechanisms.

### 5. INFLAMMATORY PHENOMENA ASSOCIATED WITH RTGT, WITH PARTICULAR REFERENCE TO RECRUITMENT OF CELLS AND RELEASE AND MOBILIZATION OF GROWTH FACTORS

An inflammatory response, with vascular dilatation, increased vascular permeability, and diapedesis of leukocytes may precede and accompany the RTGT. Indeed, the association of several inflammatory cells of hematopoietic origin (hematopoietic stem cells) with the RTGT is a well-known fact (43-48). The cells that accumulate within the lesion compartment include neutrophils, lymphocytes, mast cells and macrophages. Between 1 and 6 h, the PMNs predominate. Thereafter, the number of monocytes/macrophages increases, while the number of PMNs decreases dramatically. Several inflammatory mediators, such as vasoactive mediators and chemotactic factors, participate in these phenomena (49). Indeed, the signaling factors that begin the repair process, with intervention in inflammation and recruitment, migration, proliferation and differentiation of progenitor cells, include granulocyte colony-stimulating factor (G-CSF), granulocyte-monocyte colony-stimulating factor (GM-CSF), stem cell factor (SCF) (6), stromal cell-derived factor-1 (SDF-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-8 (IL-8), erythropoietin (EPO), interleukin-10 (IL-10) and vascular endothelial cell growth factor (VEGF). Therefore, numerous intercellular signaling pathways mediated by surface adhesion molecules and cytokines intervene in the initial phases of the RTGT. To this is added mobilization, by proteinases secreted by inflammatory cells, of factors stored in the heparin-like glycosaminoglycans of extracellular matrix, such as TGF- $\beta$ , FGF2 and VEGF (50, 51).

### 6. STEM CELLS AND RTGT

Overlapping with the inflammatory phenomena and cell recruitment, the formation of granulation tissue is initiated, and macrophages, vascular sprouts and fibroblasts progressively appear in the interstitium and move at the same time (52) between a provisional matrix, including fibrin, fibronectin and hyaluronic acid (53-55). Thereafter, concomitant proliferation of fibroblast/myofibroblasts and capillaries originates a highly vascularized granulation tissue, in which many different types of mesodermal stem cells, including endothelial precursor cells and multipotent adult precursor cells, may participate, which may even originate other cell lineages, such as chondroblasts, osteoblasts and preadipocytes. Bearing in mind the above, recruited inflammatory cells (macrophages, mastocytes, neutrophils and eosinophils), endothelial cells and mesenchymal cells, including, among others, matrix-forming cells (fibroblasts-myofibroblasts, chondroblasts and osteoblasts), preadipocytes and precursor of arterial myointimal cells intervene in tissue undergoing repair and in maintenance of injured tissues during postnatal life. The mesenchymal cells can be tissue-derived stem cells and/or

peripheral blood pluripotent stem cells (circulating progenitor cells), which form part of a system (for review, 29) comprising adult stem cells (ASC) and transit-amplifying cells (TAC), as well as the ASC niches, with their intrinsic and extrinsic regulatory mechanisms. Following, we will consider the progenitor cells related to the principal cellular components of this initial tissue: macrophages, vascular cells (endothelium and pericytes) and fibroblast-myofibroblasts.

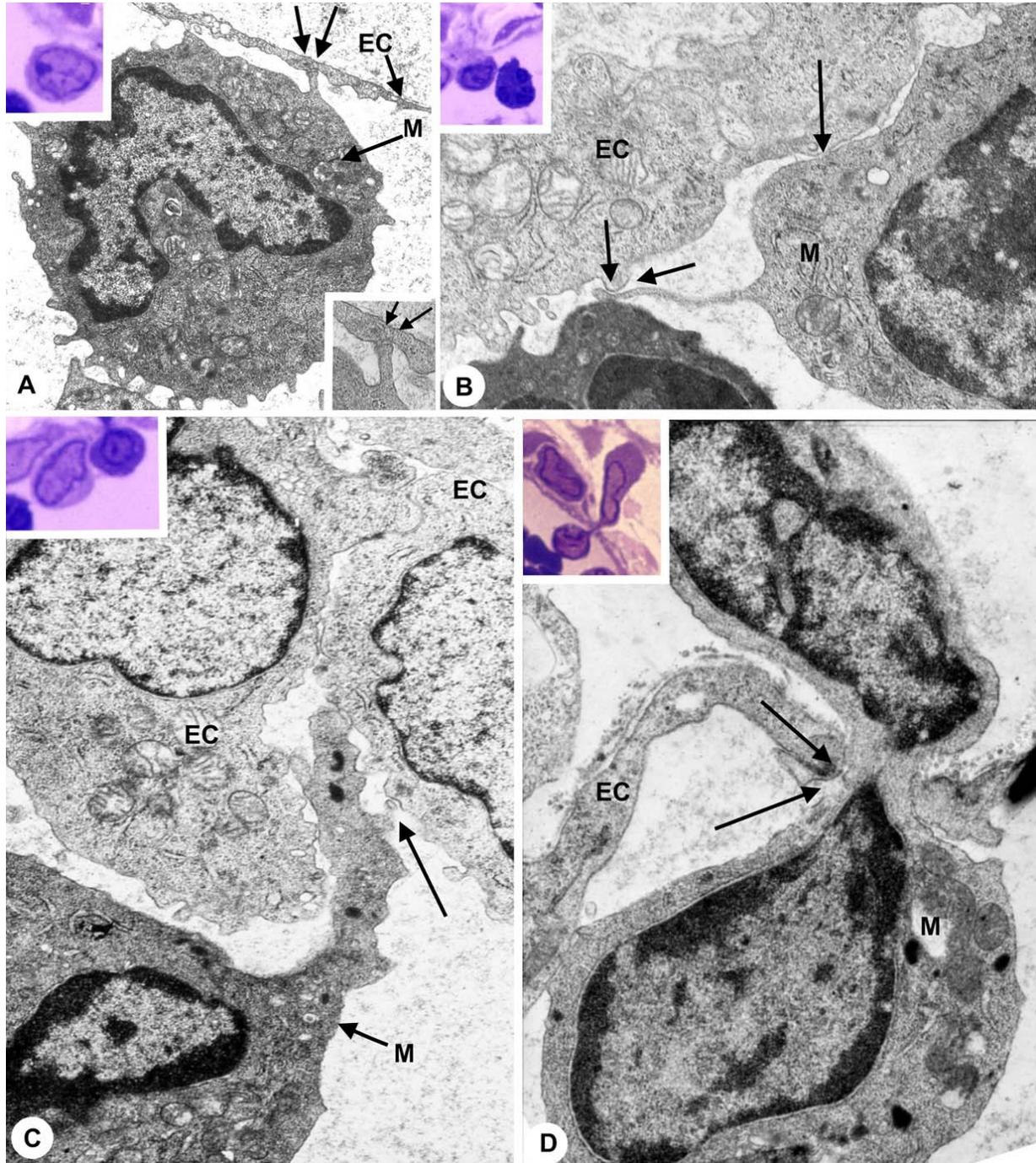
#### 6.1. Macrophages and progenitor cells

Macrophages that help remove damaged cellular and extracellular debris, with the capacity to release numerous cytokines (vascular endothelial growth factor, platelet derived growth factor,  $\alpha$  and  $\beta$  transforming growth factors, basic and acidic fibroblast growth factors, heparin-binding epidermal growth factor) play a pivotal role in inflammation and repair (56). The origin of macrophages from bone marrow-derived peripheral blood monocytes has been accepted traditionally (57, 58). Admittedly, along with the bone marrow progenitors and blood monocytes, they form part of the mononuclear phagocyte system (59, 60). Thus, predominantly in the initial phase of RTGT, monocytes are observed adhering to the endothelium of the parent vessels (Figure 1A and 1B), as well as passing through the endothelial junctions (Figure 1C and 1D) and the pericyte-endothelial space (Figure 2A, 2B and 2C). Frequently, the monocytes/macrophages, either individually or in small clusters of two or three, simultaneously appear trapped between the EC and the pericytes, within the basal lamina (Figure 2A, 2B and 2C). Although the hematopoietic cell lineage derived from progenitor cells in the bone marrow (committed myeloid progenitor cells) is evident, several issues are currently in question, such as: a) renewal and/or local proliferation, b) functional association and interactions with other cells, c) similarities between stem cells/progenitors and macrophages, and d) contribution of other cellular components to regeneration and RTGT via transdifferentiation and/or fusion.

The replacement and renewal of macrophages principally occur from monocyte recruitment. Recently, it has been found that a significant local proliferation (59, 60) and presence of tissue proliferating monocyte-like cells (61) are also involved in the replacement and renewal of macrophages.

Association between macrophages and other cells, such as endothelial cells, pericytes and fibroblast/myofibroblasts, is morphologically evident during RTGT (Figure 2D), suggesting interactive cooperation in migration, differentiation and functional activity.

Certain similarities between stem cells/progenitors and macrophages have been pointed out. Indeed, stem and progenitor cells share some characteristics of macrophages (62). For instance, adipocyte progenitors have certain phagocytic activity, and they can phagocytize microbes and apoptotic bodies (63, 64). Likewise, preadipocytes and macrophage phenotypes

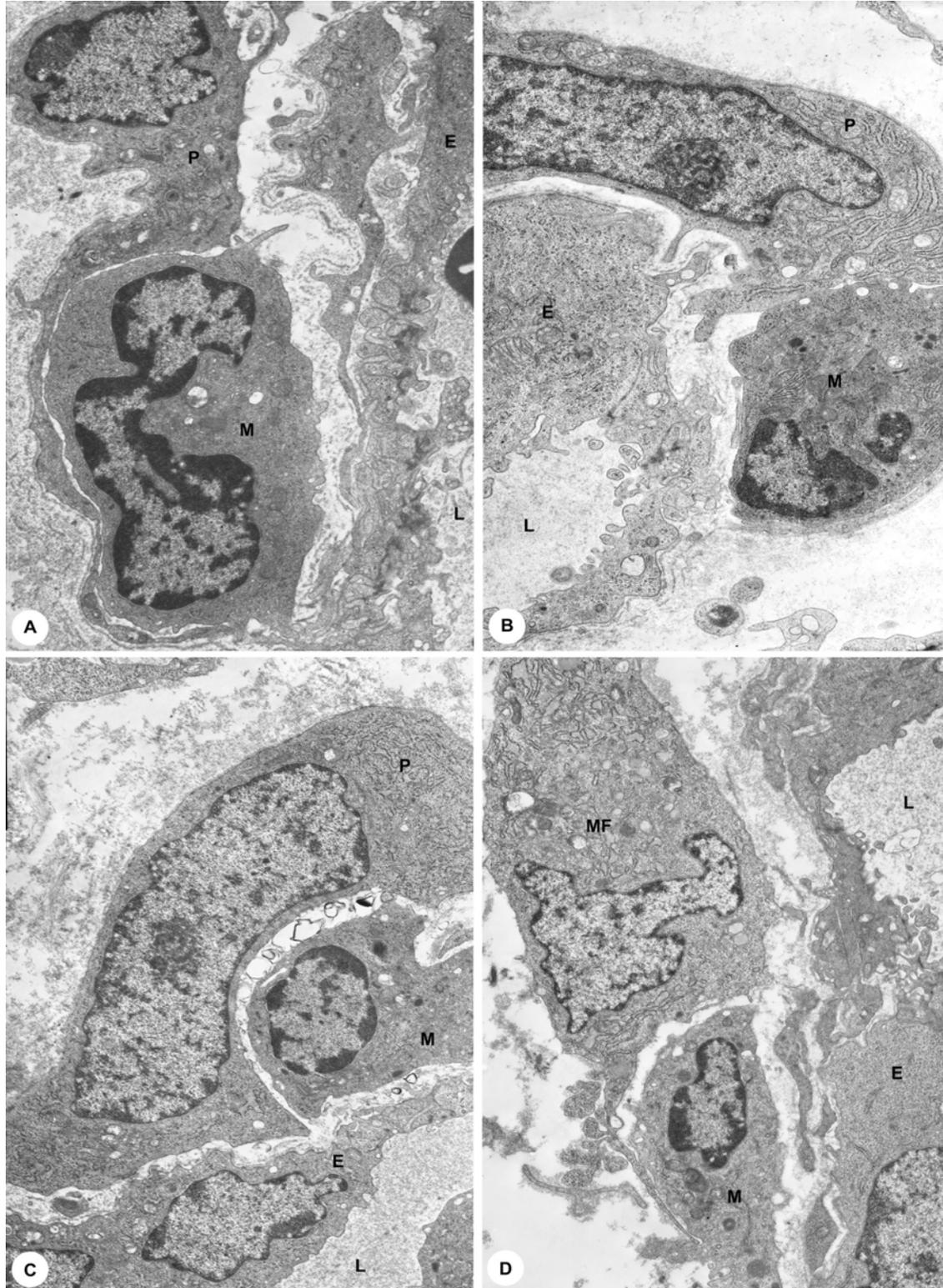


**Figure 1.** Recruitment of bone marrow-derived peripheral blood monocytes during RTGT. Monocytes (M) are observed adhering (arrows) to the endothelial cells (EC) of a capillary (Fig. 1A) and of a postcapillary venule (Fig. 1B), as well as passing through the endothelial junctions (Fig. 1C and 1D, arrows). (Uranyl acetate and lead citrate, x15000). In Fig. 1A a detail of the adherence is shown in the lower insert. The upper inserts correspond to semithin sections (Toluidine Blue, x1150)

are very similar, and conversion of preadipocytes to macrophages has been described (65).

Regarding their contribution of other cellular components to RTGT, certain subpopulations of monocytes/macrophages may acquire endothelial properties in

angiogenic conditions (66-74), and they have been observed organizing cell columns (tunneling) *in vitro* (75) and *in vivo* (75-78), suggesting that these cords could evolve into capillary-like structures (79, 80). In this way, monocytes / macrophages may also contribute to the control and regulation of neovascularization (75), enabling



**Figure 2.** Transmission electron photomicrographs showing association between macrophages (M) and pericytes (P) (Figs.2A, 2B and 2C) and with a fibroblast/myofibroblast (MF) (Fig.2D). L: microvascular lumen.E: endothelium.The macrophages appear contributing to the detachment of the activated pericytes in parent vessels previous to vascular sprouts, during the initial phases of RTGT (Figs.2A, 2B and 2C).Later the perivascular cells associated with macrophages acquire fibroblast/myofibroblast characteristics (Fig.2D). (Uranyl acetate and lead citrate, x15000).

the penetration of vascular progenitor cells via their tunneling activity (75, 81). Similarly, cells with both endothelial and monocyte markers have been demonstrated in tumors (82). In the inflamed cornea, CD11b+ macrophages contribute to lymphangiogenesis, originating tube-like structures that express markers of lymphatic endothelium (83). Therefore, monocyte/macrophages express greater plasticity than traditionally attributed and they may contribute to other differentiated adult lineages. Whether this plasticity of bone marrow cells occurs by transdifferentiation, fusion or functional adaptation is a controversial issue. Numerous works suggest cell fusion between bone marrow and tissue-specific cells resulting in one mechanism, which gives rise to bone marrow-derived nonhematopoietic cells (84-88), after forming polyploid cells—heterokaryons—and, subsequently, 2 euploid cells by means of cytoreductive division (87-89). On the contrary, other works propose a transdifferentiation of bone marrow cells into tissue-specific stem cells or intermediate progenitor cells (6, 90-95). Along these lines, some authors indicate the possibility that the bone marrow-derived cells improve the function of different organs (6, 90, 92, 96), expressing the specific function of the tissue of residence. Furthermore, peripheral blood mononuclear cells may contribute to granulation tissue acquiring myofibroblast-like characteristics (74, 97). The latter possibility will be addressed in other sections.

### **6.2. Endothelium and pericytes (preexisting microvasculature and new capillaries), ASC and TAC**

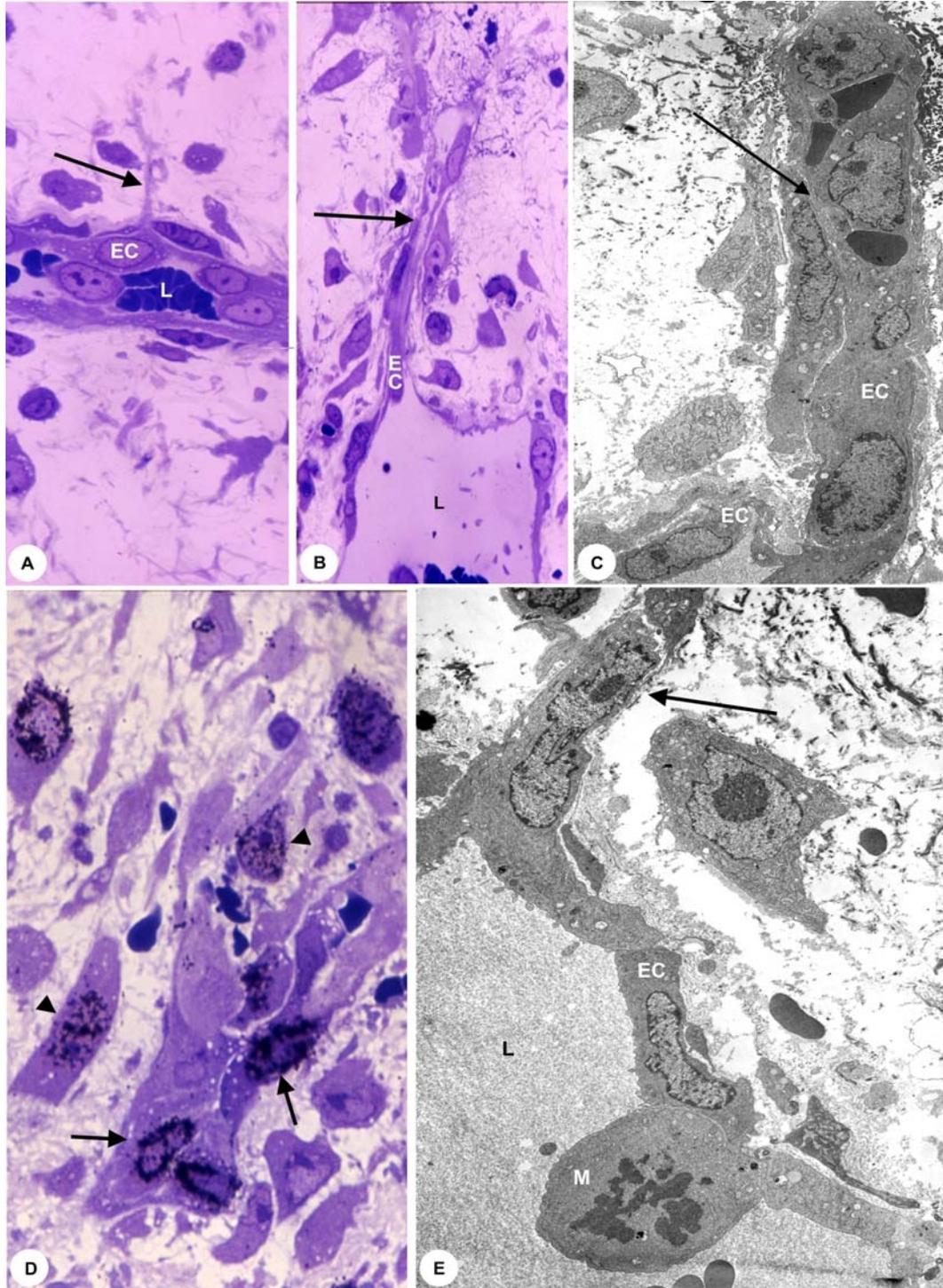
Endothelium and pericytes of preexisting microvasculature have been described as progenitor cells of the granulation tissue cellular components (endothelium, new pericytes and fibroblasts/myofibroblasts). For their part, other ASC and TAC may be involved in the origin of endothelium and pericytes of new capillaries. Consequently, the endothelium and pericytes may be considered both as progenitors and/or as descendants.

#### **6.2.1. Endothelium, ASC and TAC**

##### **6.2.1.1. Preexisting endothelium as progenitor cells**

Preexisting endothelium has been considered as the principal progenitor of new endothelium in angiogenesis. The latter is the neovascularization or formation of new blood vessels from the established microcirculation by a process of sprouting from preexisting vessels. The growth factors that activate endothelial cells (EC) include vascular endothelial growth factor and basic fibroblast growth factor, produced by macrophages and fibroblasts, among others. The events classically described during capillary growth *in vivo* include (38): a) EC and pericyte activation; b) degradation of the basal lamina of preexisting vessels by EC (proteolytic destruction of the extracellular matrix); c) EC migration from preexisting vessels towards the angiogenic stimulus; d) EC proliferation; e) migration and proliferation of pericytes from preexisting vessels; f) formation of a new capillary vessel lumen (vascular tube formation); g) appearance of pericytes around the new capillaries; h) changes in extracellular matrix with development of a new basal

lamina; i) capillary loop formation; j) early changes in the newly-formed vessels (persistence, involution and differentiation); and k) capillary network formation and eventually organization of larger microvessels. Traditionally, it has been considered that blood vessels grow by means of a movement of EC (98). This fact of EC migration is currently considered an important step during angiogenesis (99) and is directionally regulated by chemotactic, haptotactic and mechanotactic stimuli. In the initial phase of neo-vascularization, the EC degrade the vascular basement membrane of the parent vessel, protrude through its wall and begin to migrate into the interstitial space towards the angiogenic stimulus (Figure 3A). This mechanism involves macrophage angiogenic factors, which stimulate plasminogen activator and procollagenase release by the endothelial cells, with basement membrane degradation by proteases (plasmin and collagenase). Most researchers agree that these changes precede endothelial replication in such a way that migration and mitoses are independent phenomena (100-102). In other words, angiogenesis begins with pseudopodia of migrating EC (Figure 3A) and progresses to the proliferation of these cells (103-107). Therefore, angiogenic stimuli may operate through chemotaxis, and EC mitosis may be a secondary event (100, 101, 108). When the entire EC migrates into the interstitium, other EC follow and loose EC sprouts or cords are formed in the perivascular stroma (Figure 3B and 3C). Mature endothelial cells, normally in a resting state, show an extremely slow turnover rate (109-112) of 2 months or more. Thus, using <sup>3</sup>H-thymidine, the labeling index is lower than 1% in normal capillary and venular EC of the retina, liver (113), myocardium, stomach (113), striated muscle (113) and skin (113-116). For example, it is 0.01 % in capillary EC in the adult rat retina. Since the turnover rates of EC are extremely low, angiogenesis is generally a quiescent process in the healthy adult organism (117). Nevertheless, the EC can quickly convert to a proliferative state during angiogenesis and in several related processes, such as endothelium repopulation in organ transplants, repair of large vessel defects and thrombi recanalization (115, 118). However, EC proliferation is not essential, since angiogenesis has been shown to take place even in the absence of EC replication (119). During angiogenesis, endothelial DNA synthesis occurs in parent vessels before sprouting and according to some authors as early as 6 to 8 hours after an angiogenic stimulus is applied (115). The increase of the turnover rate of EC can be considerable (Figure 3D). For example, the <sup>3</sup>H-thymidine labeling index of EC increases to 9% in tumors (120). The time and the exact site of EC division are controversial. For some investigators, EC mitosis appear concomitant with sprouting (119), while most authors are of the opinion that EC begin in mitosis after they start to migrate. The EC mitosis appears in both the parent vessels (Figure 3E) and the newly formed vessels. In the latter, it has been pointed out that they occur at the tip (43, 121), but it is accepted that when capillary sprout budding begins, endothelial proliferation takes place in cells following the "leader EC" (Figure 3E), but not usually at their tips. In other words, the zone of replication is closer to the parent vessel (99, 108, 122-124). The ability of angiogenic stimuli to induce



**Figure 3.** Postcapillary venule and capillary preexisting endothelium as progenitor cells. Initial phase of neovascularization during RTGT. Activated endothelial cells (EC) degrade the vascular basement membrane of parent vessels (L: lumen of vessel) and begin to migrate into interstitial space (Fig.3A, arrow) and when the entire EC migrates into the interstitium other EC follow, originating loose sprouts or cords in the perivascular stroma (Fig.3B and 3C - arrows). A considerable increase of <sup>3</sup>H-thymidine labeling is observed in EC (Fig.3D - arrows) and in perivascular cells (Fig.3D - arrowheads). Fig.3E shows a mitosis (M) in an EC of a parent vessel following the "leader" migrating ECs, which originate a cord in the perivascular stroma (arrow). Fig. A, B and D: Semithin sections (Toluidine Blue, x1150). Fig. C and E: Transmission electron photomicrographs (Uranyl acetate and lead citrate, x15000).

replication in confluent EC is associated with disruption of cell-cell contacts (125). The replicative state and its ability to respond to endogenous mitogens may depend on cytoskeletal organization, such as microtubule destabilization or changes in the cell shape (126). Finally, the collagen in the interstitium seems to have an influence on EC proliferation (127, 128).

On the other hand, transdifferentiation of endothelial cells into smooth muscle-like cells has been suggested (129, 130). Similarly, transformation of microvascular endothelial cells into myofibroblasts has been described in different circumstances (129, 131-136).

#### **6.2.1.2. Other endothelial cell precursors (Endothelium as descendent cells)**

Postnatal neovascularization may also originate by a similar mechanism to vasculogenesis. The latter is the process by which some vessels develop in the embryo. Histogenically, vasculogenesis is defined as “*in situ*” capillary development from differentiating endothelial progenitor cells known as angioblasts. Until recently, blood vessel formation in postnatal life was only considered to be angiogenesis, which, though quiescent in the adult organism, may develop rapidly in several circumstances. Recently, numerous studies have contributed findings suggesting that endothelial stem cells may persist in postnatal life and may participate in neovascularization by means of a mechanism similar to vasculogenesis. In other words, the recruitment of cells during endothelialization or formation of new blood vessels in postnatal life may occur by migration of preexisting endothelial cells or by the incorporation of angioblast-like endothelial precursor cells from the circulation (Circulating angioblasts-CD-34+) (137).

Precursors of endothelial cells or endothelial progenitor cells (EPCs) have been described in bone marrow and peripheral blood (138, 139), with the possibility of homing to sites, differentiating into ECs *in situ* and contributing to new blood vessel formation (137, 140-145). Growth factors, such as VEGF and macrophage-colony stimulating factor, intervene in the recruitment of these cells (146, 147). In fact, multipotent adult progenitor cells cultured with VEGF differentiate into angioblasts CD34+, VE-cadherin+ and Flk1+ cells and subsequently into cells that express endothelial markers and that have *in vitro* functional characteristics indistinguishable from those of mature endothelial cells, able to form tubes and express markers of endothelial cells (148). Likewise, these cells can contribute to neoangiogenesis *in vivo* during RTGT and tumorigenesis (146, 148, 149). Thus, a higher population of endothelial precursor cells is associated with inflammatory breast tumors (150). Therefore, endothelial progenitor cells may contribute to support the integrity of the vascular endothelium by means of neoangiogenesis and rejuvenation of the endothelial monolayer (137, 151, 152). For instance, undifferentiated progenitor cells may participate in vascular remodeling from the recipient to the graft in heart transplants (153-155), although this concept is currently a matter of intense debate, since there are discrepancies in the rates of chimerism in damaged vessels and hearts (153,

154, 156-159). Indeed, some authors indicate that the majority of the cells in the vessel wall are recipient-derived after aortic allografts (154, 160-162), cardiac transplantation (155, 160) or vein grafting (163). On the contrary, other authors have described minimal contribution from recipient cells. Thus, endothelial repopulation by bone marrow-derived recipient cells is found to be an early event in transplanted allograft hearts, which decreases in frequency over time (164).

Two types of endothelial progenitor cells in the peripheral blood have recently been described: the early EPCs (137, 165-167) or monocyte-derived circulating angiogenic cells (71, 168), and the late EPCs (166, 167, 169) or outgrowth endothelial cells (OECs) (165, 170). The early EPCs are a heterogeneous population, show early growth, express CD34, CD31, Flk-1, Tie-2, VE-cadherin, KDR, CD14, CD105, vWF, CD45, CD11c, CD163, VEGFR-2 (71, 137, 165, 171, 172) and are incapable of tube formation (137, 165). They produce VEGF, IL-8, HGF, G-CSF (137, 173) and low level nitric oxide, and have a good angiogenic potential (137), although proliferative capacity is limited (173). The late EPCs or OECs are a homogenous population (137), show late outgrowth (137, 165, 170), express Flk-1, vWF, CD36, VE-Cadherin, CD31, VEGFR-2, Tie-2 (165, 170), and are capable of tube formation (137, 165). They have low level cytokine secretion (137) and high level nitric oxide production (137, 165), and also have a good angiogenic potential (137) with highly proliferative capacity (143). The early EPCs predominantly originate from CD14+ precursors, while the OECs come from a CD14- population of cells (165). Recently, it has been pointed out that the level of circulating CD34+KDR+ endothelial progenitor cells predicts the occurrence of cardiovascular events and death from cardiovascular causes (174). Likewise, there may be a higher presence of restenosis when the circulating endothelial progenitor cells decrease (175). Furthermore, the numbers of circulating CD34+ and CD133+KDR+ endothelial progenitor cells increase after acute myocardial infarction (176), and there is impaired function of progenitor cells in patients with congestive heart failure (177). Mobilized peripheral blood mononuclear cells (easily non invasively obtained from the peripheral blood, with CD-34+ cells increased, and rich in angiogenic factors and cytokines), obtained from peripheral blood mononuclear cells after granulocyte colony stimulating factor intervention, have been effective in clinical application for severe arteriosclerosis obliterans of lower extremities and for severe diabetic foot ischemia (178-180).

#### **6.2.2. Pericytes, ASC and TAC**

##### **6.2.2.1. Preexisting pericytes as precursor cells**

In addition to participating in the maintenance of blood vessel wall integrity, perivascular cells (pericytes, adventitial or Rouget cells, pericyte-like cells) (181, 182) retain considerable mesenchymal potentiality and may have the capacity to differentiate into other cell types (183-190), such as fibroblasts (47, 191), chondroblasts (192), osteoblasts (193-196), preadipocytes (191, 197), vascular smooth muscle cells and myointimal cells (198, 199). In the initial phases of RTGT, the pericytic microvasculature

undergoes a sudden, brief and intense pericyte proliferation (37). In this way, autoradiographic studies show an increased amount of label in pericytes of postcapillary venules and capillaries (Figure 3D) (37, 101, 114, 115, 200, 201). Besides, sequential morphologic findings in the pericytes during the initial phase of granulation tissue formation agree with the hypothesis that pericytes may be an important source of new fibroblasts (129, 183). These sequential morphologic findings include: a) the pericytes, bulging from preexisting vessels, shorten their processes and increase their somatic volume (Figure 2B and 2C and 4B); b) the nuclei contain prominent nucleoli and their cytoplasm shows numerous ribosomes, either singly or in aggregates (Figure 2B and 2C); c) multiple profiles of rough endoplasmic reticulum are observed (Figure 2B and 2C); d) the pericyte basal lamina is frequently disrupted and fragmented; and e) numerous pericytes project into the extravascular space, appear detached from the vessel walls and adopt transitional cell forms between themselves and fibroblast-like cells (Figure 2D) (37). As mentioned above, the migrating monocytes contribute to the detachment and mobilization of the activated pericytes in the pre-existing pericytic microvasculature (Figure 2A, 2B and 2C).

Using Monastral Blue as a tracer for labeling cells in the walls of pericytic microvasculature, the marker was first observed in pericytes (Figure 4A) and subsequently in pericytes bulging from preexisting vessels (Figure 4B, 4C and 4D), and in fibroblast-myofibroblasts (Figure 4E and F) during granulation tissue formation (37), as well as in chondroblasts (202) (Figure 4G), osteoblasts (Figure 4H) (195) and myointimal cells after specific induction (203, 204).

Moreover, cells specifically expressing known markers of pericytes also express markers characteristic of stem cell population (205). Endosialin, which may be a marker of mesenchymal stem cells, has been identified in activated myofibroblasts and pericytes (206, 207). Mesenchymal stem cell populations have been described residing in the microvasculature of the tissue origin (perivascular niche) (29, 37, 183, 189, 192, 199, 208-211). Thus, the majority of dental pulp stem cells express pericyte associated antigen (208) and co-express Notch 3 (regulating stem cell fate specification) and RgsT (marker for pericytes) (209), suggesting a perivascular niche of postnatal mesenchymal stem cells. Likewise, a population of multipotent CD34-positive, adipose stromal cells shares pericyte (chondroitin sulfate proteoglycan, CD140a and CD140b) and mesenchymal (CD10; CD13 and CD90) surface markers (212). Although the mechanisms controlling pericyte differentiation are poorly defined, Wnt/beta-catenin signaling stimulates chondrogenic and inhibits adipogenic differentiation of the pericytes (213).

In soft tissue lesions, some authors consider pericytes as the progenitor cells of several pseudosarcomatous processes (214, 215), malignant fibrous histiocytoma (216) and mixed liposarcoma (217). Pericytes and endothelial precursor cells are also important

participants among the many cells that give rise to progressing malignant disease (218).

### 6.2.2.2. Other pericyte precursors (pericytes as descendant cells)

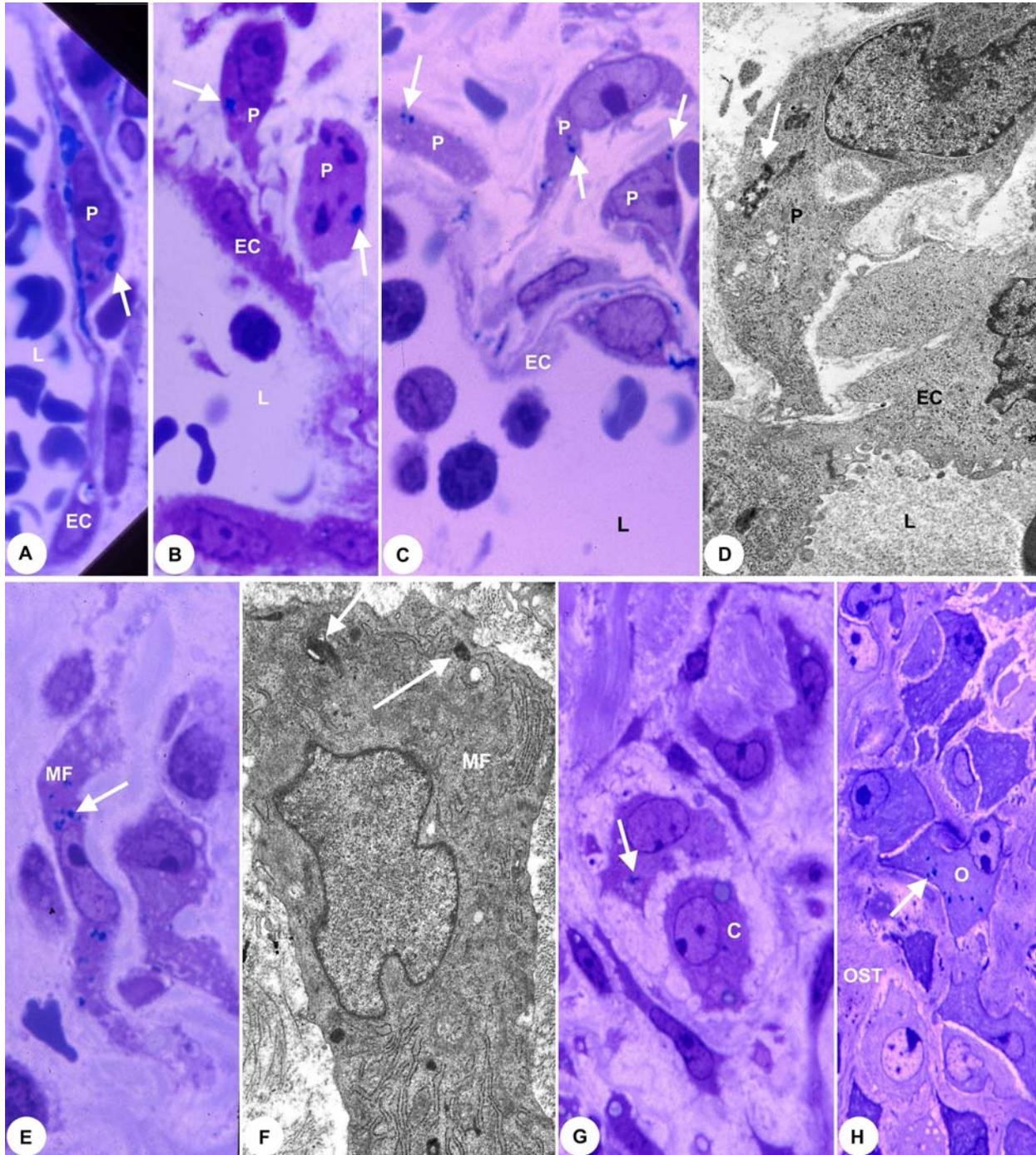
Recruitment of pericytes to newly formed vessels from fibroblast and bone marrow progenitor cells has been described (these progenitors will be considered in sections 6.3.1. and 6.3.2). Here we present the controversy about the participation of the bone marrow in pericyte and endothelial cell origin).

Although bone marrow progenitor cells can be recruited during the formation of new vessels and vasculature, remodelling (219-221), there is controversy about their participation in pericyte and endothelial cell origin. As mentioned above, using neovascularization models, several authors point out those BM-derived precursors give rise to endothelial cells (146, 150, 222-224); while others have proposed that bone marrow precursor cells only develop pericytes but not endothelial cells (219-221). Recently, it has been indicated (221) that new corneal vessels have a dual source: bone marrow-derived precursor cells (53% of all neovascular pericytes) and pre-existing limbal capillaries (47% of all neovascular pericytes). Of the bone marrow-derived pericytes, 96% expressed CD45 and 92% CD11b, which suggested their hematopoietic origin. Using mouse chimera in brain repair after ischemia (225), two populations of bone marrow-derived cells were observed: one in the brain parenchyma (predominantly microglia) and another associated with remodeling blood vessels in perivascular location. The latter were negative for endothelial cell markers, but expressed desmin and were immunoreactive for angiogenic factors, endothelial growth factor and transforming growth factor beta, suggesting pericytes. Mobilization and recruitment of bone marrow-derived pericyte progenitor cells have also been described in tumors (219, 226, 227). Evidence that mature vessels develop from pericyte/macrophages networks and that almost all macrophages and more than half of the pericytes derived from the bone marrow have been shown using subcutaneous matrigel plugs (81). By contrast, only 10% of endothelial cells exhibit a bone marrow origin (81).

Pericyte progenitor cells have been described from non-endothelial mesenchymal cells isolated from the rat aorta. The latter, cultured in a serum-free medium with fibroblast growth factor, proliferated slowly and formed spheroidal colonies, expressing CD34, Tie-2, NG2, nestin and PDGF  $\alpha$  and  $\beta$  receptors. When cocultured in collagen with isolated endothelial cells, they transformed into pericytes (228).

## 6.3. Fibroblast/myofibroblasts, ASC and TAC

The origin of the heterogeneous population of fibroblast/myofibroblasts, which respond to mediators of inflammation and intervene in the integrity of the tissues, and in the production (matrix-synthesizing cells), deposition and degradation (matrix-degrading cells) of extracellular matrix proteins, in contraction (myofibroblasts) to reduce the size of the wound, in growth



**Figure 4.** Pericytes as progenitor cells. Monastral Blue (arrows) labeled pericytes (P) in preexisting postcapillary venules (L: Lumen; EC: endothelial cells) are observed (Figs.4A, 4B, 4C and 4D). Bulging pericytes shorten their processes, increase their somatic volume and appear detached from the vessel wall (Fig.4B, 4C and 4D). Subsequently, the marker is observed in fibroblast-myofibroblasts during granulation tissue formation (Figs.4E and 4F), and in chondroblasts (C) (Fig.4G) and osteoblasts (O) (Fig.4H - OST: osteoid) after specific induction. Fig.4A, 4B, 4C, 4E, 4G and 4H correspond to semithin sections (Toluidine Blue, x1150) and Figs.4D and 4F to ultrathin sections (Uranyl acetate and lead citrate, x12000).

factor secretion and in the proliferation and differentiation of other cells (229-232), may be from tissue-derived stem cells and/or peripheral blood pluripotent stem cells

(circulating progenitor cells). Among the principal putative progenitor tissue cells are the fibroblasts themselves and the pericytes. According to the outline of this work, below

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we will consider the fibroblasts as precursor or descendent cells.

### 6.3.1. Preexisting fibroblasts as precursor cells

A conventional hypothesis is that local relatively quiescent fibroblasts around the injured tissue migrate, proliferate and originate the new activated fibroblasts and myofibroblasts, with extracellular matrix protein production and wound contraction (233-235). Therefore, fibroblasts, normally involved in their quiescent state in slow turnover of the extracellular matrix (primary producers of type I, III and V collagen and fibronectin, contributors of the basement membrane by secretion of laminine and type IV collagen, and with remodelling capacity by means of fibroblast-derived matrix metalloproteinases) undergo a change in phenotype to a proliferative, synthetic (Figure 5A) and contractile state (myofibroblasts) (Figure 5B) (236). Indeed, in the margin of lesions, the resting fibroblasts proliferate, express integrin receptors (that bind fibronectin and fibrin on fibroblasts - 55, 237), migrate (by means of an active fibroblast-derived proteolytic system, including collagenases, gelatinase A, plasminogen activator and stromelysin - 238, 239) and differentiate into myofibroblasts, with extracellular matrix protein production (240, 241), secretion of growth factors and chemotactic factors, migration, contraction (production of alpha smooth muscle actin) (235) and parenchyma interactions (dynamic cross-talk between fibroblasts and parenchyma cells). The myofibroblasts temporarily acquire their expression of  $\alpha$ -smooth muscle actin, which disappears progressively (between 15 and 30 days). It is generally accepted that collagen deposition continues long after myofibroblasts decline. Therefore, myofibroblasts are temporarily activated before collagen producing fibroblasts (232). Growth factors, such as transforming growth factor  $\beta$ 1 (242) and platelet derived growth factor (243), contribute to activate the local fibroblasts. In this way, other cells may influence their proliferation, differentiation, extracellular matrix synthesis and survival. For instance, adipose-derived stem cells have the capacity to promote human dermal fibroblast migration, proliferation, and secretion by cell-to-cell direct contact and by paracrine activation through secretory factors, such as PDGF, insulin-like growth factor, bFGF, TGF- $\beta$ , HGF and VEGF (244). As mentioned above, endosialin, a marker of mesenchymal stem cells, is expressed by myofibroblasts and pericytes (206).

Induced pluripotent stem cells (IP cells) can be generated from adult human fibroblasts (245). Indeed, cells similar to human embryonic stem cells in morphology, proliferation, surface markers, gene expression, promoter activities, *in vitro* differentiation, telomerase activity and teratoma formation were generated from adult human fibroblasts by retrovirus-mediated transfection of four transcription factors: Oct3/4, Sox2, c-Myc and Klf4 (245). Therefore, IPS cells can be derived from somatic cells and may thus lead to important drug discoveries and advances in regenerative medicine (246).

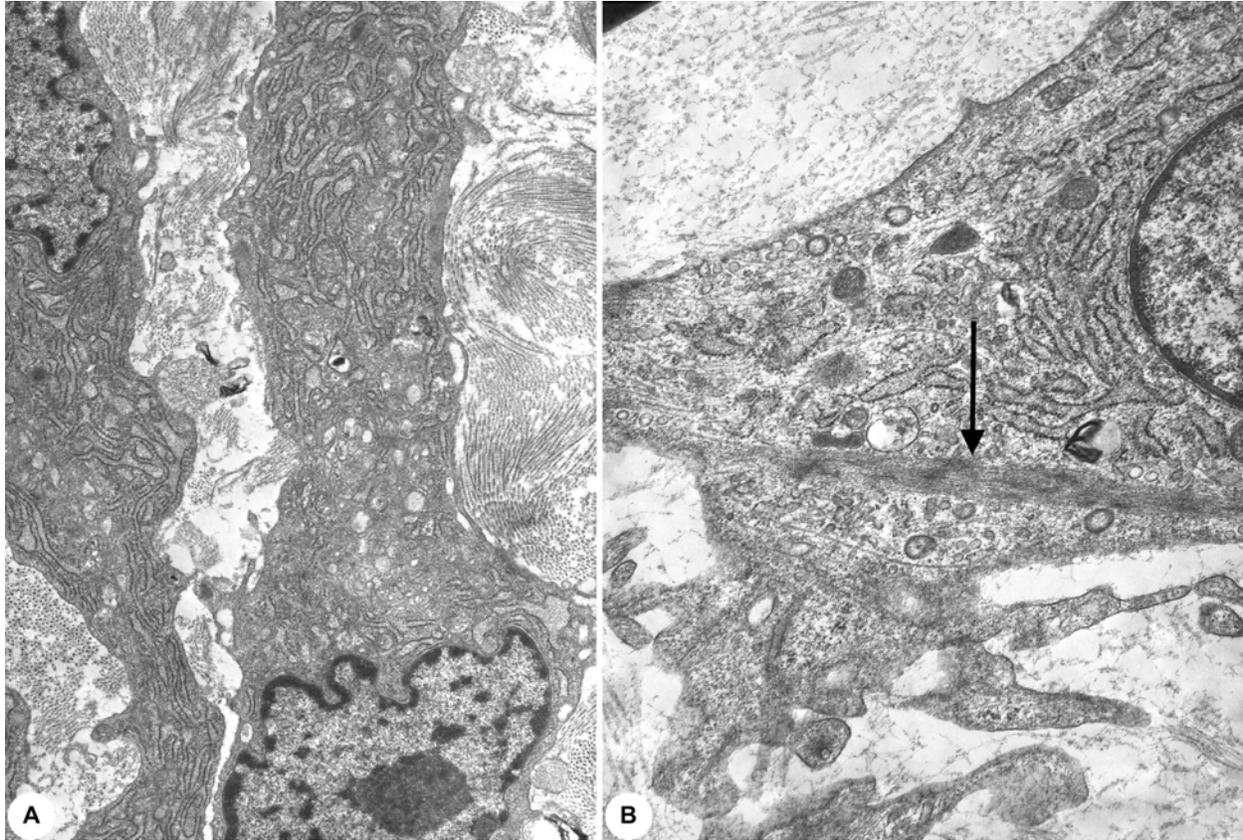
### 6.3.2. Other fibroblasts/myofibroblasts precursors (fibroblasts/myofibroblasts as descendent cells)

Although RTGT fibroblast/myofibroblasts originally derive from resident tissue fibroblasts in the

proximity of the RTGT (55, 237), this possibility does not preclude that pericyte, bone marrow derived cells or other transdifferentiated cells contribute to their heterogenous fibroblast/myofibroblast population (247). The origin from pericytes has been previously considered (section 6.2.2.1.). The bone marrow precursors, bone marrow mesenchymal cells and fibrocytes, will be discussed below.

Since 1970, fibroblast colony formation from monolayer cultures of bone marrow and blood cells (fibroblast colony-forming units) has been demonstrated (248-251), evidencing a bone marrow origin for fibroblasts. A rare cell within human bone marrow mesenchymal stem cell culture (multipotent adult progenitor cells or MAPCs) has been identified (148, 251-253) and immature mesenchymal cells derived from the bone marrow appear to be constantly repopulating normal and injured connective tissues (254-255). In general, bone marrow mesenchymal AS cells are located in the complex system of the bone marrow stroma (bone marrow stromal cells), and they can be isolated by means of Stro-1+ antibody recognition (256, 257). These cells have the capacity to differentiate into mesenchymal lineage cells and, with appropriate environmental conditions into cells of different embryonic origin, such as cells with visceral mesoderm, neuroectoderm and endoderm characteristics. In other words, these cells have high capacity of transdifferentiation and plasticity (20, 258-260). Indeed, the bone marrow mesenchymal cells may differentiate phenotypically into adipose, cartilage, bone, vascular smooth muscle, skeletal and cardiac muscle, hepatocytes, neural elements and hematopoietic-supportive stromal cells (6, 9, 15, 17, 147, 260-268). Epidermal growth factor is considered as a candidate for *ex vivo* expansion of bone marrow-derived mesenchymal ASC (269). Transcription factors, which regulate the expression of the differentiation genes of the aforementioned cells, participate in this differentiation process. For example, C/EBP and PPAR $\gamma$  families and other transcription factors intervene in adipocyte (270, 271) and Cbfa1/Runx2 in osteocyte (272, 273) differentiation. Besides, there are regulation control mechanisms such as hormones and growth factors. Using bone marrow mesenchymal ASC, alveolar bone cells and periosteal cells for tissue-engineered bone formation, it has been demonstrated that the periosteal cells originate approximately double the amount of newly formed bone than bone marrow mesenchymal cells (274). Other sections of this work describe the role of transplanted bone marrow cells in organ and solid tissue regeneration.

A bone marrow-derived circulating population of mesenchymal progenitors, termed "fibrocytes" (275-279) or "fibrocyte precursors", which rapidly enter sites of tissue injury, was identified a decade ago (275). Subsequent studies have demonstrated that these cells express markers of leukocytes (CD45, LSP1), monocyte lineage (CD11a, CD11b, CD13, CD32, CD64), as well as hematopoietic stem cell/progenitor antigens (CD34, CD105) and fibroblast products (collagen I and III, fibronectin, vimentin MMP9) (275-288). Adherent cultured fibrocytes develop a spindle-shaped morphology (275) and express MHC, class II and co-stimulatory molecules (CD80 and CD



**Figure 5.** Activated fibroblasts (Fig 5A) and myofibroblasts (Fig 5B) during granulation tissue formation. The rough endoplasmic reticulum is well developed in both. A bundle of cytoplasmic microfilaments (arrow) with dense bodies is observed in a myofibroblast. Transmission electron photomicrographs (Uranyl acetate and lead citrate, x15000).

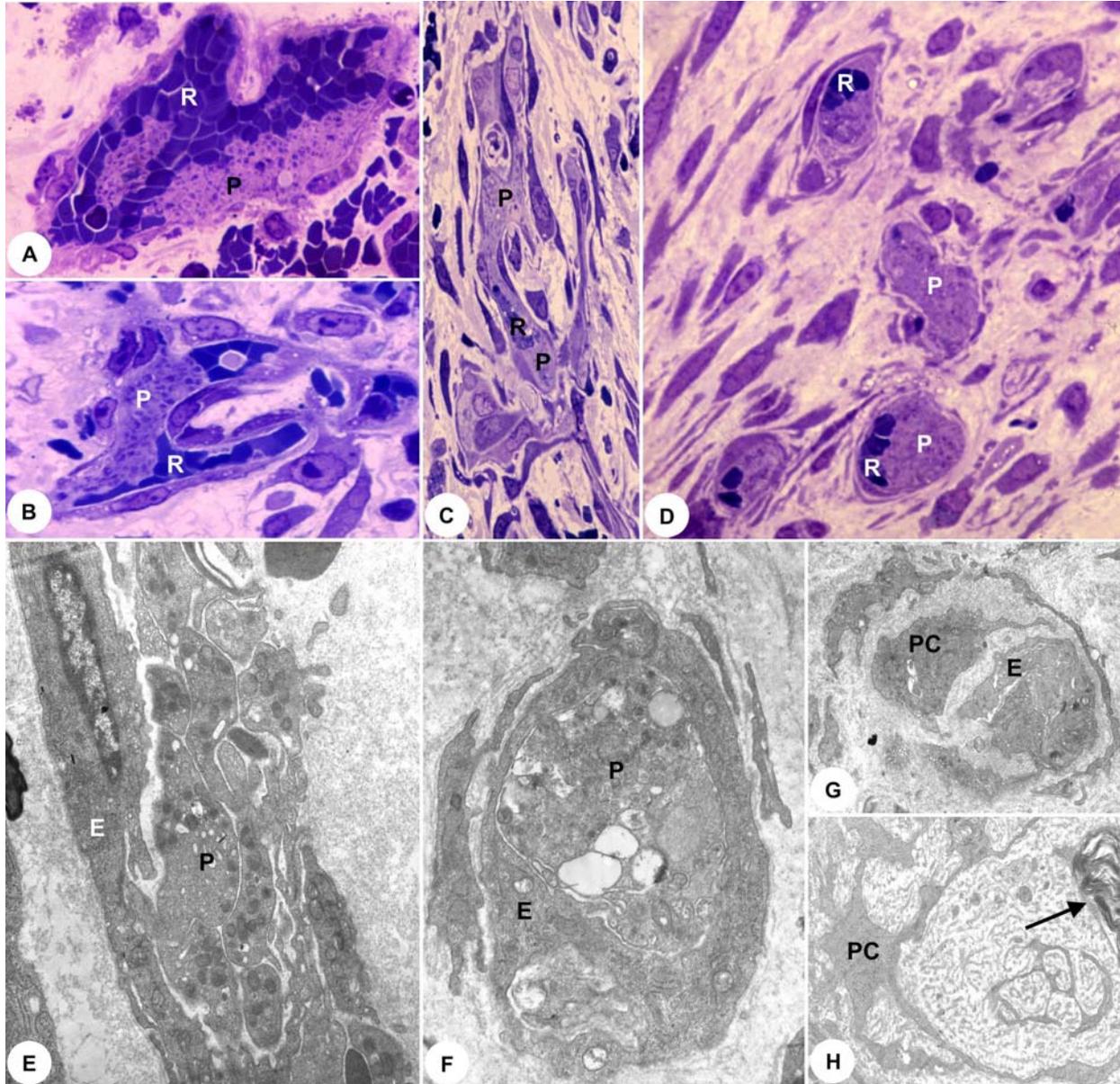
86). Recently, it has been pointed out that CD34+ fibrocytes, which are present in the connective tissue of virtually all human organs, derive from circulating CD14+ monocytes (289). These cells secrete numerous cytokines and have the property of expressing smooth muscle actin, while retaining CD34 expression, when they acquire myofibroblast-like differentiation (277). These cells have the ability to present antigen *in vitro* and *in vivo* (276, 280, 290), and cultured fibrocytes *in vitro* and *in vivo* facilitate angiogenesis by means of proteolysis of the basal lamina (secretion of active matrix metalloproteinase 9-MMP-9) and by secretion of growth factors, such as VEGF,  $\beta$  FGF and PDGF (291). As we shall see below, fibrocytes intervene in development of fibrotic lesions, connective tissue disease, atherosclerosis and in tumor stroma formation. On the other hand, the use of marrow-derived stem cells as a therapeutic procedure has been considered, for instance, to accelerate healing in chronic ulcers (292).

An immunosuppressive effect on adult dendritic cells differentiated from CD 34+ hemopoietic progenitor cells has been contributed, suggesting that mesenchymal stem cells license adult CD34+ hemopoietic progenitor cells to differentiate into regulatory dendritic cells through activation of the Notch pathway (293).

Another postulated origin is that epithelial cells undergo epithelial to mesenchymal transdifferentiation (see below).

## 7. INVOLUTIVE PHENOMENA. RTGT AS A “PARACRINE TRANSITIONAL ORGAN”

Several components of the granulation tissue undergo involution, which is highly evident in the newly formed vessels. Indeed, angiogenesis ceases and most of the endothelial cells disintegrate drastically because of apoptosis, only persisting the preferential vasculature. In this mechanism intervene antiangiogenesis factors (angioprotein, angiostatin and endostatin) (294) and thrombospondins 1 and 2, among other matrix molecules (295). At first, the numerous disintegrating vessels show marked intravascular accumulation of factor-releasing platelets (platelet thrombus) (Figure 6A, 6B, 6C, 6D and 6E), and the granulation tissue becomes a “paracrine transitional organ”. Subsequently, homogenized platelets, endothelial cell debris and basal membrane residues are observed (Figure 6F, 6G and 6H). The fibroblasts acquire myofibroblast phenotype, with cytoplasmic actin-containing filaments and cell-matrix and cell-cell linkages (296), intervening in tissue contraction, collagen synthesis and catabolism of collagen in combination with matrix



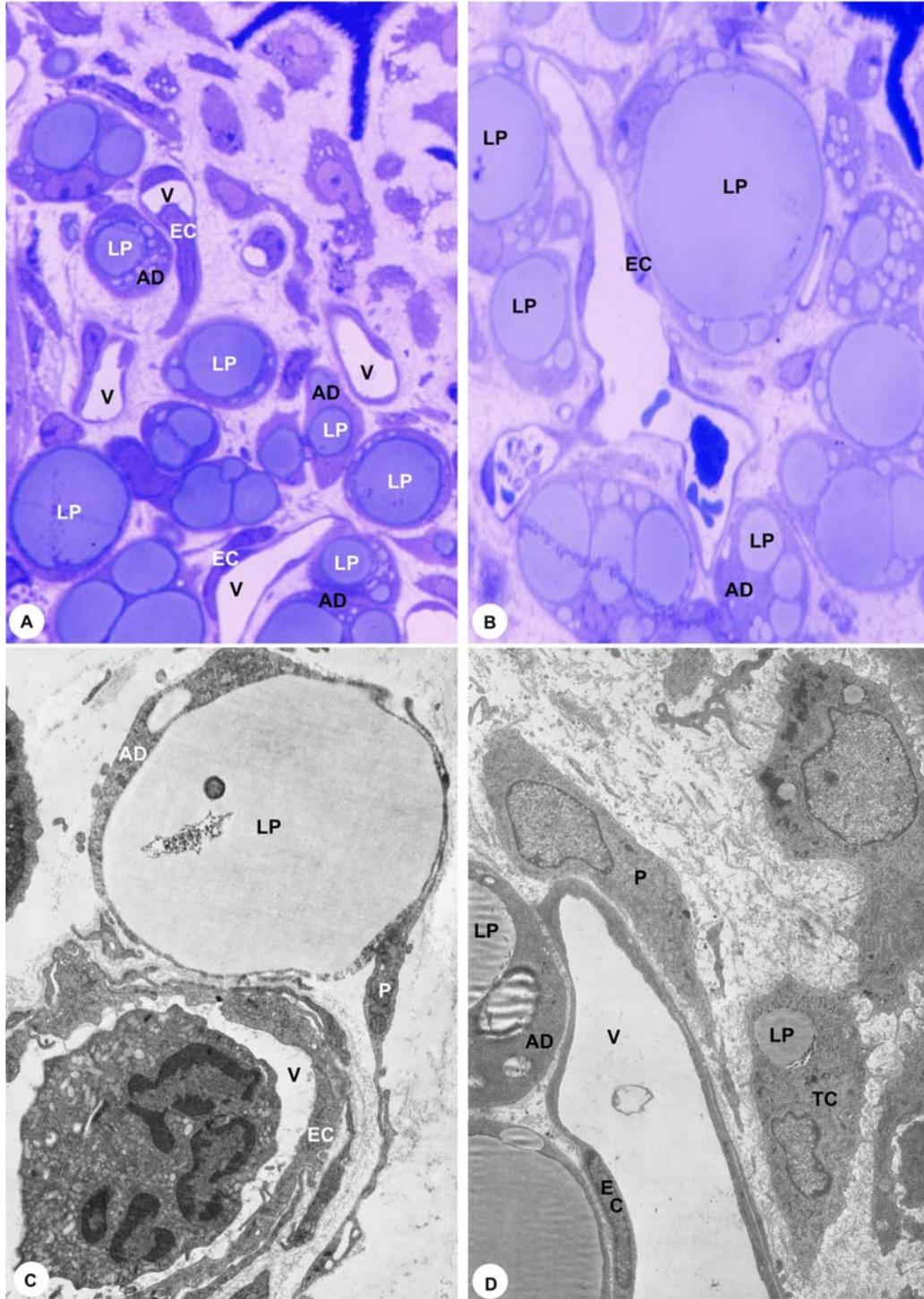
**Figure 6.** Involution phenomena in most of the newly-formed vessels during RTGT, with intravascular accumulation of factor-releasing platelets. RTGT as a “paracrine transitional organ”. In semithin sections, platelet thrombus (P) and accumulates of red cells (R) are present in numerous disintegrating vessels during the involution of several components of the granulation tissue (Figs. 6A, 6B, 6C and 6D, x1500). Figs. 6E, 6F, 6G and 6H show ultrastructural images of different stages of the involutive vessels (E: Endothelial cells, P: Platelets). Fig. E: Recently aggregated platelets. Fig. F: Homogenized platelets in the vascular lumen, Figs 6G and 6H: disintegrating endothelial cells with cellular debris (membrane body - arrow), basal membrane aggregate and persistent pericytic cells (PC) are observed. Transmission electron photomicrographs (Uranyl acetate and lead citrate, x15000).

metalloproteinases and inhibitors of metalloproteinases (297).

### 8. RTGT AND CELLULAR DIFFERENTIATION, DEDIFFERENTIATION, TRANSDIFFERENTIATION AND FUSION

As mentioned above, the putative cells with the capacity to originate myofibroblasts during RTGT, such as

fibroblasts, pericytes and marrow stromal cells, can give rise to other cell lineages and differentiate “*in vitro*” and “*in vivo*” into osteoblasts (Figure 4H), chondroblasts (Figure 4G), preadipocytes (Figure 7), or smooth muscle cells by means of growth factors and specialized induction (183, 195, 202, 204, 298-307). This generalized system may complete the repair from locally resident mesenchymal cells that provide tissue-specific progeny, such as adipose, muscle, periosteum, trabecular bone, synovium and dermis-



**Figure 7.** In semithin and ultrathin sections, adipoblasts (AD), with lipidic vacuoles (LP), are observed around newly-formed vessels (V) near endothelial cells. In Fig. 7C, the adipoblast appears enveloped by a long thin process of a pericyte (P). In Fig. 7D, different stages of adipoblast developments, suggesting a pericytic origin, are observed with transitional cells (TC) between both. Figs. A and B: Semithin sections, (Toluidine Blue, x1500). Figs C and D: Transmission electron photomicrographs (Uranyl acetate and lead citrate, x15000).

derived mesenchymal cells (195, 303). Furthermore, these mesenchymal cells are highly plastic and they may also

produce progeny of endodermal and ectodermal lines (20, 258, 271, 308, 309). Cell contacts with neighbouring cells

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and cell environment interactions intervene in the cellular differentiation (see above). On the other hand, differentiation may not entirely be a unidirectional process during RTGT and dedifferentiation leads to the reversion towards a more immature phenotype. For instance, by means of reversine, myotubes may undergo dedifferentiation back into progenitor cells, which may originate osteoblasts or adipocytes (310). Likewise, without reverting to a more primitive phenotype, mesenchymal stem cells may be capable of transdifferentiating into various phenotypes including astrocytes and neurons (12, 16, 311-315). Finally, cell fusion may occur, although it seems to be biologically irrelevant for its extreme rarity (316), except for macrophages, which are able to fuse among themselves and with other cell types (317).

## 9. ASC, RTGT AND TISSUE ENGINEERING

Future directions of research in tissue engineering include the development of multi-tissue organs, imitating what occurs during embryonic development and in adult-life repair processes. Indeed, in embryonic development, a bidirectional molecular dialog between parenchymal cells and stromal cells is necessary for normal organ development and function (318-321). In adult life, the repair process reproduces these interactions between regenerative elements (parenchyma) and RTGT components (stroma). In this way, RTGT lend the regenerative parenchyma morphofunctional support and facilitate a multistep mechanism, involving angiogenesis and organization by recruitment of fibroblast-myofibroblasts and by producing and remodeling extracellular matrix components. For instance, in skin wounds, fibrin clot forms a provisional scaffold for cell migration, proliferation and differentiation. In tissue engineering, parenchyma-stroma interactions similar to RTGT appear to be essential and they may play an active and instructive role in programming the final tissue structure and function. In other words, it is necessary to develop prototype tissue engineered matrices to support the simultaneous growth of different cell types (322) and a rapid induction of angiogenesis (322-327). The strategies in tissue engineering may utilize: a) cell suspensions or cell-sheets, b) biomolecules, c) matrices in combination with cells and/or biomolecules, and d) 3-D environments or scaffolds with seeding and culturing specific cell types (328). The scaffolds for tissue engineering should have several properties, such as degradability, biocompatibility, non-immunogenicity, easy reproduction and the possibility to incorporate and deliver bioactive molecules (growth factors, peptides, lyophilized cell fractions, etc.). Among these conditions are the mechanical properties, since stiff or soft scaffolds may be used. For instance, the latter are more suitable for adipose tissue engineering (329, 330). In addition, in these strategies, it is fundamental to promote regeneration and repair. Indeed, optimum procedures, combining scaffolds, cells and/or biomolecules, should be capable of inducing adhesion, migration, proliferation, differentiation, angiogenesis and production of new extracellular matrix, in a manner similar to that which occurs during regeneration and RTGT, in which the process results in the formation of new structures that reproduce the original morphology and function.

## 10. ASC AND RTGT IN PATHOLOGY

### 10.1. ASC, Organization, abnormal RTGT and Fibrosis

Examples of organization are the creation of new masses of fibrous tissue in blood clots or inflammatory exudates with fibrin deposits through granulation tissue (331). Thus, organization of thrombus initiates with leukocyte and macrophage infiltration (inflammatory stage), followed by neovascularization, and fibroblast/myofibroblast proliferation (proliferative stage) and progressive collagen deposition and contraction, while myofibroblasts decline (contraction stage) (332). To this can be added microvascular involution, persistence of preferential vessels and recanalization. Monocytes/macrophages play a central role in thrombus organization (333). For example, the gene for a chemokine link to macrophage activation CXCL14 is upregulated (332).

Abnormal RTGT may occur by defect or excess. An example of deficient RTGT are diabetic ulcers, in which ASC descendants are modified in their proliferation, differentiation and functional activity, with impaired neovascularization, increasing levels of proteinases and decreasing synthesis of collagen. Several factors are involved in these modifications, such as vascular disease with subsequent ischemia (anoxia and reducing nutrients), impaired granulocytic chemotaxis and function with infections and prolonged inflammation, associated neuropathy and defective macrophage function (334, 335).

Examples of excessive RTGT are hypertrophic scars and keloids with higher collagen production in which several factors intervene, such as increased and exaggerated responses to fibrogenic cytokines (enhanced expression of TGF- $\beta$ , mRNA (336), mutations in regulatory genes and abnormal epidermal mesenchymal interactions - 337, 338-). Fibrocytes also contribute to the fibroblast population in these lesions (281, 339).

Examples of fibrotic lesions are idiopathic pulmonary fibrosis and systemic fibroses in which an important contribution of bone marrow-derived cells in the early stages has been pointed out (276, 287, 288, 340-343). Evasion of myofibroblasts from immune surveillance has been proposed as a mechanism for tissue fibrosis. Indeed, this mechanism may occur since myofibroblasts possess Fas/FasL-pathway-dependent characteristics that allow them to escape from immune surveillance and resulting organ fibrosis (345). Recently, transformation of microvascular endothelial cells into myofibroblasts has been considered as having a potential role in the etiology and pathology of fibrotic disease (136, 346).

### 10.2. ASC, RTGT and atherosclerosis

In atherosclerosis, as in RTGT, inflammatory phenomena precede and accompany the process, quiescent cells are induced to proliferate rapidly, new blood vessels are formed, stromal cells migrate, the extracellular matrix is invaded, the new tissue is remodeled and the same factors initiate and regulate the process. In this way, the cellular

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events in the formation of atherosclerotic lesions after injury include regeneration of endothelial monolayer, infiltration of monocyte cells and myointimal cell proliferation (347). The regeneration of the endothelial monolayer may have the same sources as those previously described for neovascularization, namely, by migrating and proliferating preexisting neighbouring endothelial cells or by circulating progenitor endothelial cells (bone marrow-derived cells expressing CD133 or CD34 - 137, 139, 142-)(see above).

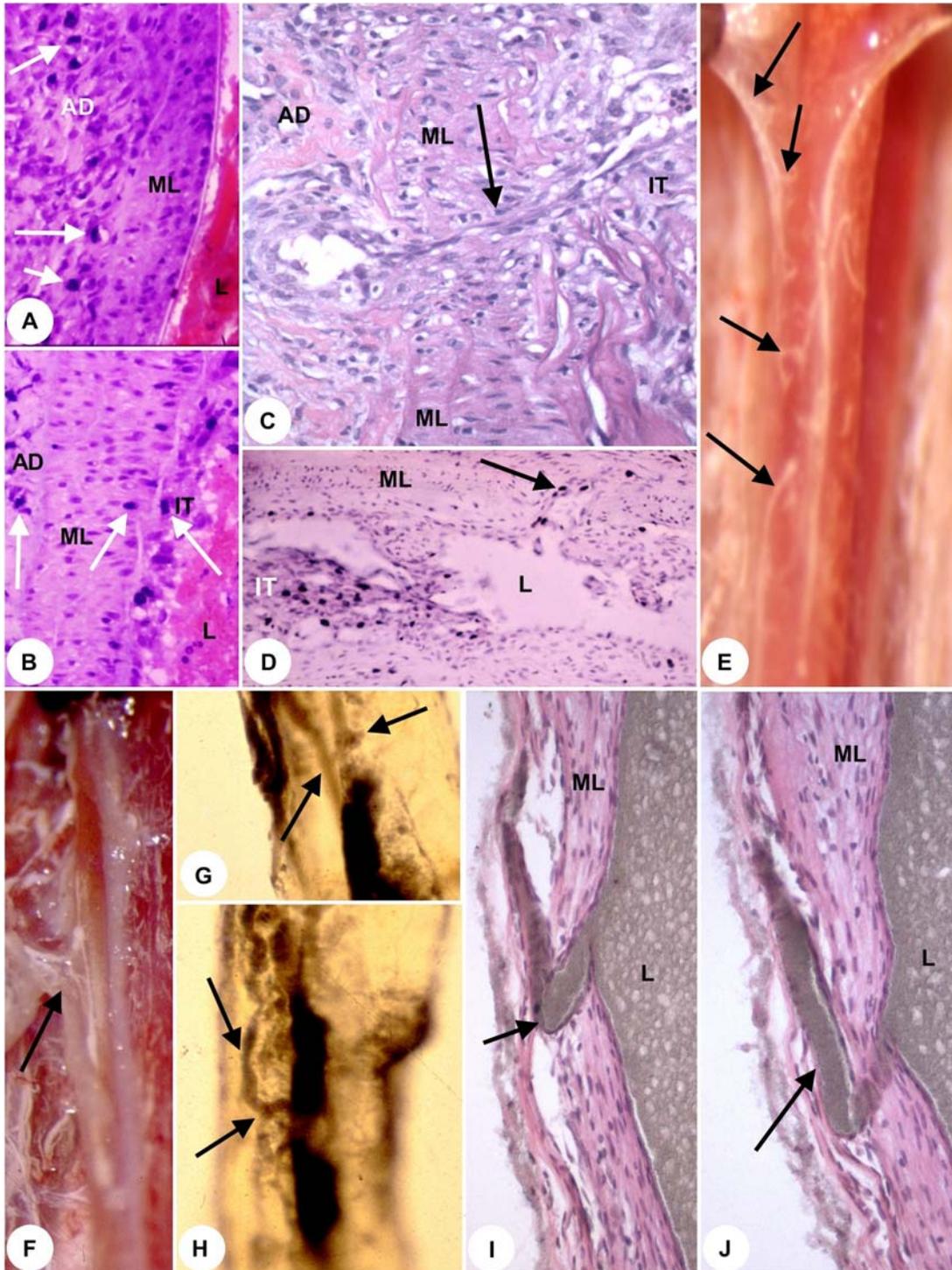
The traditional hypothesis is that myointimal cells in atherosclerotic lesions are derived from the medial smooth muscle cells (348-351), which migrate from the media into the intima, acquiring a synthetic phenotype with matrix synthesis. This hypothesis is now shrouded in doubt and the myointimal cell origin remains the subject of ongoing debate, since myointimal cells may be considered from a variety of sources (352). Indeed, the following possibilities may be considered: arterial media layer origin (SMCs and SMC related cells), adventitial progenitor cells and bone-marrow-derived circulating cells.

The hypothesis of arterial media layer SMC origin (348, 349, 351, 353-365) is based on the following: a) the cells present in the intimal thickening (myointimal cells - neointimal SMC cells) correspond in appearance to smooth muscle cells (348, 354, 355, 357-360, 362-364, 366), b) these myointimal cells show the same early enzymatic reaction as cells of the innermost third part of the media layer (356, 361), c) muscle cells from the media layer have been observed crossing the "gaps" of the internal elastic lamina, suggesting a capacity to move through this membrane (354, 357, 363, 366), and d) tritiated thymidine incorporates in the internal zone of the media layer, prior to appearing in the intimal layer (353, 367). Nevertheless, differences between media and neointimal SMC cytoskeletal features, growth pattern, responses to growth factors /cytokines and matrix synthesis/degradation have been described (368). An origin of myointimal cell from a preexisting and distinct subpopulation of the media layer SMC has also been pointed out (369).

The hypothesis of adventitial progenitor cells (199, 203, 204, 370-376) is based on the following: a) In autoradiographic studies on the incorporation of <sup>3</sup>H-thymidine, during intimal thickening developing in occluded arterial segments, DNA synthesis was first seen in the adventitia, fundamentally in the vasa-vasorum pericytes, later in the adjacent media and subsequently in the intimal thickening (Figure 8A, 8B and 8D) (199), with contribution of myofibroblasts to neointimal formation (377). Coronary adventitial fibroblasts display proliferation, collagen synthesis and phenotypic heterogeneity in response to stimulation, whereas medial SMCs maintain a highly differentiated phenotype (371). Abundant progenitor cells expressing stem cell markers (Sca-1; C-kit; CD-34 and FIK-1) are present in the adventitia (372, 374) and can differentiate into myofibroblasts, migrate to arterial media or intima layers and differentiate into SMCs (372, 374, 376). Sca-1+ cells obtained from explanted cultures of

adventitial tissues and transferred to the adventitial side of vein grafts were found in atherosclerotic lesions of the intima (372). The adventitia may contribute progenitor cells from the interstitium (fibroblasts) or from the vasa-vasorum. When human vascular adventitial fibroblasts were cultured in appropriate media, they showed myogenic differentiation, with increased expression of smooth muscle actin and calponin (378). Regarding vasa-vasorum, microvessel penetration into the arterial wall from the adventitial layer has been observed in atherosclerosis, not only in its later stages, but also in the earliest stages of its precursor lesions, such as intimal thickening (Figure 8C, 8E, 8F, 8G, 8H, 8I and 8J) (41, 199). This initial response may be considered as a particular form of granulation tissue formation and is followed by a rapid microvascular involution. In this way, it has been postulated that arterial intimal thickening results from a similar mechanism to that of the organization of thrombus, with subsequent events depending on whether or not the arterial circulation has been interrupted. On interruption, there is both a penetration of the vasa-vasorum and a myointimal differentiation from the adventitial recruited cells (pericytes, fibroblasts or circulating progenitor cells), whereas when the arterial circulation has remained unchanged there is no vasa-vasorum penetration and the intimal thickening originates from recruited cells migrating from the arterial vasa-vasorum and adventitia (199, 204). Using a technique that specifically labels venules, predominantly postcapillary venules, in addition to recruited macrophages, newly formed endothelial cells and a supplementary population of fibroblast- myofibroblasts and myointimal cells were contributed from the periarterial microvascularization during arterial intimal thickening formation (204). The fibroblasts and the vasa-vasorum pericytes are the principal candidates in adventitial participation in the arterial myointimal cells (199, 372, 374, 376). The aberrant differentiation of pericytes may contribute to the development and progression of atherosclerosis and calcific vasculopathies (213).

The hypothesis of bone-marrow-derived circulating cells is based on the presence of marrow stromal cells as stem cells for non-hematopoietic tissues (379) and on the discovery of circulating fibrocytes as collagen-producing cells of the peripheral blood (287, 380), which appear in the fibrous cap and in lipid-rich areas of human and experimentally-induced atherosclerotic plaques (381-384). Indeed, bone marrow provides inflammatory cells (lymphocytes and monocytes that become foam cells) and myofibroblast/myointimal cells, whose balance affects plaque stability (385, 386). These precursor cells have been considered in other sections of this paper. In this order, bone-marrow-derived mesenchymal cells can serve as a new cell source of smooth muscle cells in vessel engineering (387). Likewise, repopulation of endothelium and medial smooth muscle cells from both circulating and adjacent ends of non-affected artery cells has been demonstrated in rat patent arterial segments devoid of mural cells (adventitial, smooth muscle and endothelial cells) by local application of glycerol (Figure 9A) (42). The morphologic events in the early stages of cellular recruitment is reminiscent of those occurring in granulation



**Figure 8.** Adventitia contribution to intimal thickening (IT) formation. In autoradiographic studies with  $^3\text{H}$ -thymidine, expression of DNA synthesis (arrows) is first seen in the adventitia (AD) (Fig.8A, HE, x120) and subsequently in the media layer (ML) and in the intimal thickening (IT). (Fig.8B, HE, x120) L: Arterial lumen. Microscopic image of microvessel penetration from adventitial microcirculation crossing the arterial medial layer (arrows) and reaching the intimal thickening (Fig.8C, HE, x160). In Fig.8D (HE, x160)  $^3\text{H}$ -labelled cells are observed in a microvessel penetrating the media layer and in cells of the intimal thickening. Using a contrast technique, microvessels penetrating arterial media layer are clearly observed (arrows) in stereoscopic images (Figs.8E-8F, x60) in transillumination images (Figs.8G and 8H, x120) and in series of microscopic images (Figs.8I and 8J, HE x160).

tissue, with the following steps: a) reendothelialization (Figure 9A), apparently from adjacent ends of non-affected artery; b) presence of monocytes between endothelium and internal elastic lamina (Figure 9B); c) migration towards the media layer of monocytes and endothelial cells, crossing the elastic internal lamina fenestrations (Figure 9C); d) formation of vascular channels with endothelial and mural cells in the innermost area of the media layer with continuity between arterial lumen endothelial cells and those in tunnelized structures (Figure 9D); e) involution of the newly-formed vascular channels, presenting platelets and red cells in their lumens (Figure 9E) and, simultaneously, proliferation of spindle cells, which finally repopulate the arterial media layer acquiring smooth muscle cell phenotype (Figure 9F).

### 10.3. ASC, RTGT and tumor stroma

The tumor stroma is a major factor influencing the growth and progression of cancer (388), including survival, migration, proliferation, invasion and metastasis. This tissue microenvironment is a complex and dynamic structure with similar characteristics, biological markers and components to RTGT, as well as with the same origin. These similarities also include induction of angiogenesis and stromal acquisition of the myofibroblast phenotype. Indeed, as occurs with RTGT, the tumor stroma population of cells consists of vascular elements (endothelium and pericytes), fibroblast-myofibroblasts and macrophages, with variable association of other inflammatory cells, arranged in a modified extracellular matrix (388-395).

As with RTGT, in tumor stroma growth intervene interactions between parenchymal (tumoral) cells and activated stromal cells, as well as several cellular and extracellular matrix molecules. Unlike normal connective tissue, which behaves as an antiprogessive environment of the neoplasia, the tumor stroma after tumor-like genetic lesions (396-398) acquires an active role in cancer progression with paracrine-acting factors. Thus, the tumor stroma provides physical architecture and blood supply (oxygen and nutrients), removes metabolic and biological waste and contributes growth factors, cytokines and extracellular matrix proteins, including adhesion proteins and proteases (394, 399-403). For instance, macrophages, fibroblasts and endothelial cells express and secrete metalloproteinases (404), which hydrolyze collagen, laminin, fibronectin and vitronectin (402, 405). Actively recruited tumor-associated macrophages release V-G factor stimulators of angiogenesis (VEGF, HGF, MMP2, IL-8) as well as hypoxia-induced transcription factors. An enhancing role of tumor-associated myofibroblasts, facilitating the invasiveness of colon tumors, has been demonstrated by means of co-injection of activated fibroblasts and tumor cells (406). The difference between tumor fibroblast-myofibroblasts and activated fibroblasts in RTGT is that tumor fibroblast-myofibroblasts change their phenotype and do not undergo apoptosis and elimination, remaining perpetually activated. The origin of tumor fibroblasts may be tissue-resident pericytes and fibroblasts (407), bone marrow-derived mesenchymal cells (394, 408-411), fibrocytes (289, 410) or parenchymal and local cancer cell

transdifferentiation (412). Endosialin, a marker of mesenchymal stem cells, is expressed by tumor-associated myofibroblasts and pericytes (206, 207) (See above). CD34<sup>+</sup> fibrocytes, which act as antigen presenting cells during carcinoma invasion, lose CD34 positivity expression for a gain of alpha-SMA expression (myofibroblast characteristic), contributing to the stroma tumor and to tumor escape from host immune control (289). Mesenchymal stem cells from post-natal bone marrow are considered as an emerging tool for cell-mediated gene therapy in several pathologic processes, including cancer therapy. Indeed, the homing of mesenchymal cells is favored in sites of active tumorigenesis, and these cells may be used as cell carriers for delivering anticancer factors (cytokines, interferons, replicable adenovirus, pro-drugs, among others) (413).

## 12. OVERVIEW AND CLINICAL PROMISE

The extensive cellular plasticity of the principal cellular components in RTGT (local and circulating bone marrow derived progenitor cells), supported by so many different lines of evidence (Table 1), is reasonably based, but relatively recent and some of the different capabilities of being precursor or descendent cells are not very defined. Therefore, further research is needed to confirm which of these proposed precursor cells are genuine pluripotential stem cells or which are only capable of expressing different properties and functional roles.

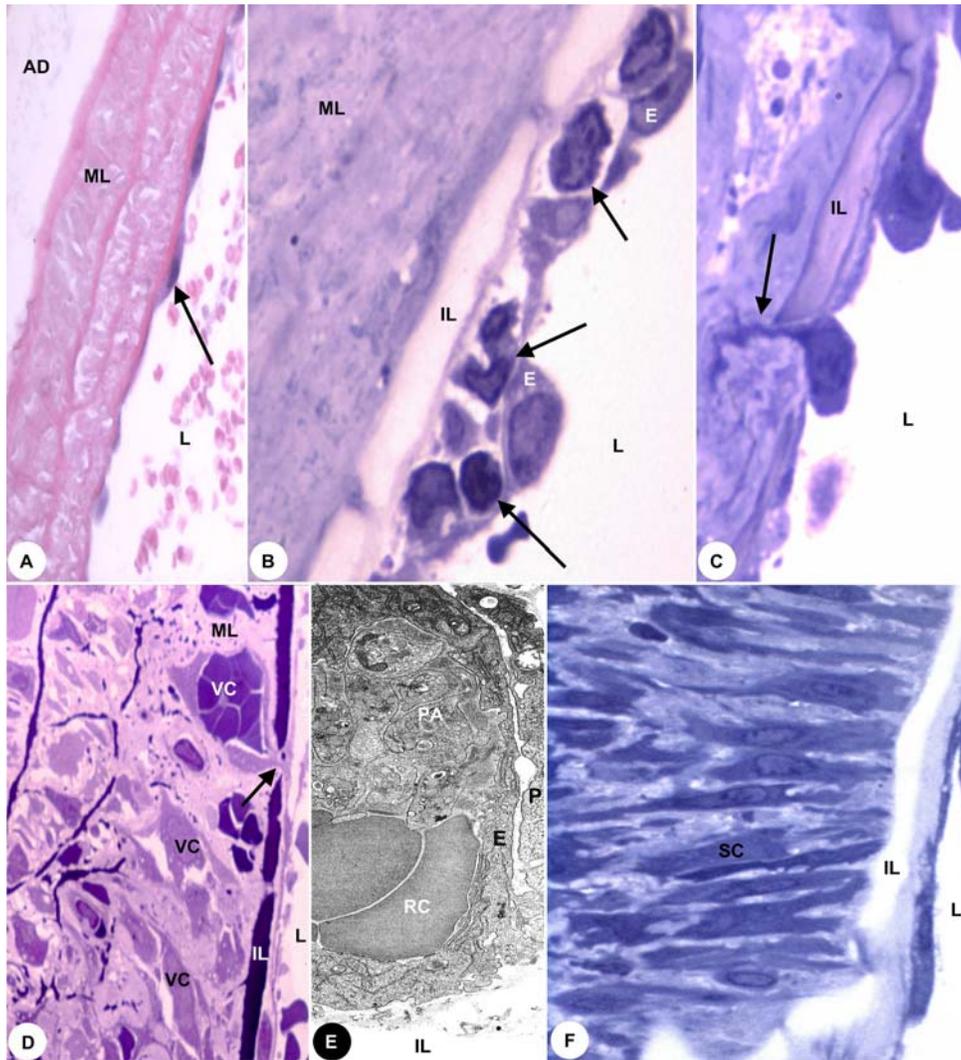
In all likelihood, these precursor cells reside in virtually all postnatal tissues and organs (414) and, in our opinion, the perivascular niche, with pericyte-like cells, including pericytes, homing cells from the bone marrow (fibrocytes and MSC) and perivascular fibroblasts, is the most solid hypothesis, now emerging (29, 37, 183-205, 208-215, 370, 415-421). In this hypothesis (Figure 10), the perivascular region (with pericyte-like cells) is the niche of progenitor cells and the substrate of regulatory mechanisms. Indeed, pericyte-like cells, originate new-pericytes, fibroblast-myofibroblasts (and related cells) and some subsets of macrophages. The regulatory mechanisms include: a) regulation of quiescent and angiogenic stages of blood vessels (cell-cell contacts and soluble factors produced by pericytes and EC), b) mesenchymal cell proliferation and differentiation control, and c) interactions between transmigrating cells (e.g. monocytes) and perivascular niche resident cells.

This hypothesis is difficult to confirm owing to the following: a) the heterogenous cellular population in a perivascular location with like-morphology (416); b) the need to identify the descendent cells in a location far from the niche (415, 422); c) the cells in the putative niche express several molecular markers, none of which is general or specific; and d) the markers are not continually expressed in the pericytic niche and descendent cells. This variable expression depends on species, location, diverse characteristics, functional state (422), distinct overlapping populations, and the quiescent or angiogenic stage of blood vessels (423). There is even controversy among laboratories. Other procedures may be required in addition

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**Table 1.** The local and bone marrow derived circulating progenitor cells in RTGT

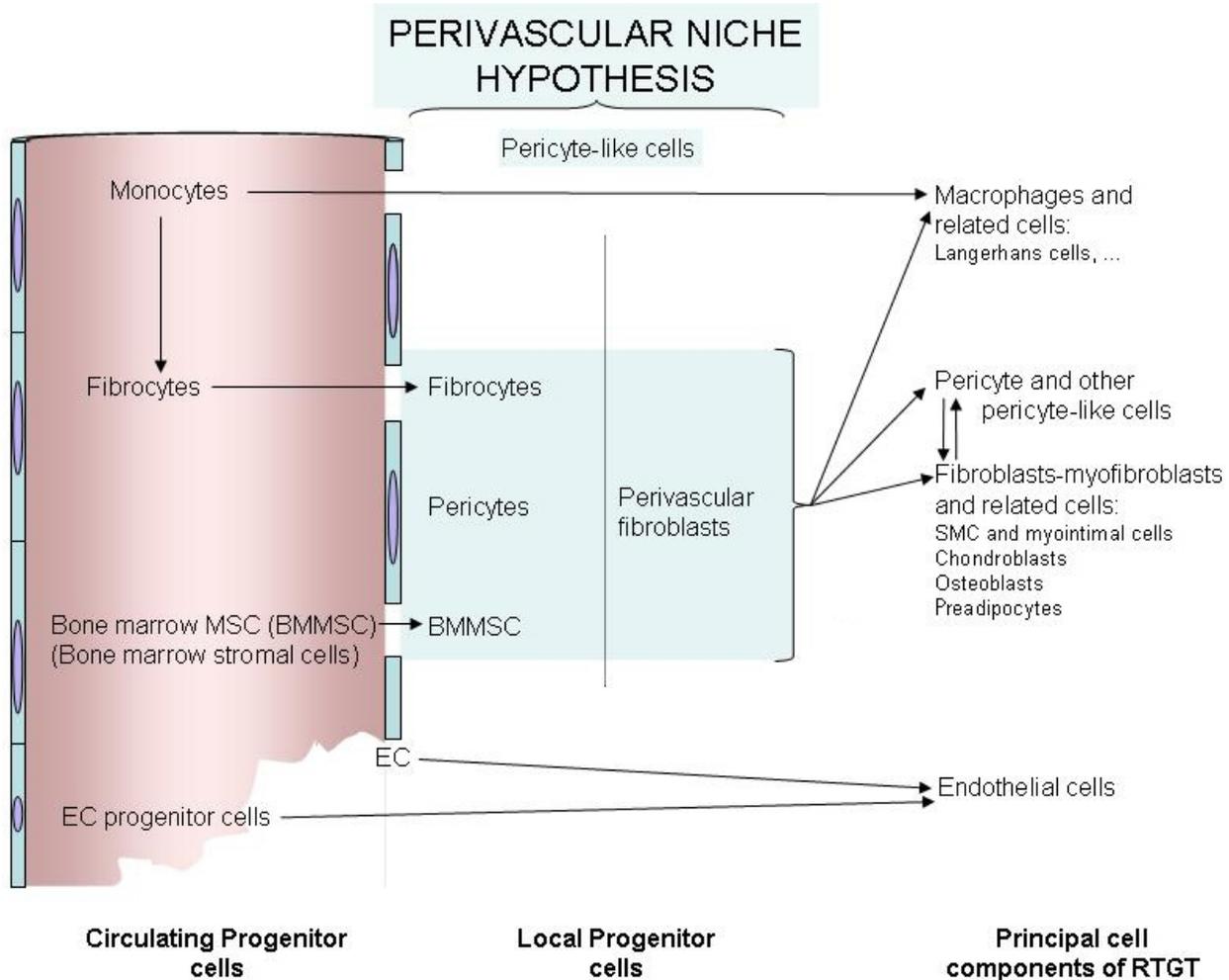
| Circulating progenitors   | Local progenitors, Ref   | Principal cell components in rtgt (descendent cells)  |
|---|--|---|
| Monocytes 57-61   | Some pericyte-like cells 416   | Macrophages   |
| Fibrocytes 275-289<br>Bone marrow mesenchymal (stromal) cells 212, 219-221, 247-251 | Pericytes 29, 37, 129, 183-215, 370<br>Fibroblasts 52, 233-241, 245, 370-376 | Pericytes<br>Fibroblast-myofibroblasts and related cells<br>Smooth muscle cells<br>Myointimal cells<br>Chondroblasts<br>Osteoblasts<br>Adipocytes |
| EC progenitor cells 137-155, 165-180  | Endothelial cells 98-128   | Endothelial cells   |



**Figure 9.** Cellular repopulation of arterial wall previously devoid of cells after periarterial glycerol application. Fig. 9A, Endothelial cells (arrows) migrating on the intima surface of affected segment. The adventitia (AD) and media layer (ML) are devoid of cells. Fig. 9B, Activated new endothelial cells (E) and monocytes (arrows) adhered to the elastic internal lamina (IL). Fig. 9C, a cell crossing a fenestration of the IL (arrow). Fig. 9D, Vascular channels (VC), some with red cells in their lumens, in continuation with luminal neoendothelium (arrow), observed in the innermost part of the media layer. Fig. 9E, Ultrastructural image of one of the newly-formed channels, with platelet aggregates (PA) and red cells (RC), and with a pericytic cell (P) on its surface. E: Endothelial cell. Fig. 9F, the arterial wall repopulated by cells with smooth muscle phenotype (SC). Figs. 9A, 9B, 9C, 9D and Fig. 9F correspond to semithin sections (Toluidine Blue, x1150) and Fig. 9E to ultrathin section (Uranyl acetate and lead citrate, x15000).

to the morphology, gene expression and phenotypic criteria for specific location of MSC niches. In this way, we have

selectively labeled cells in the wall of the pericytic microvasculature of adipose tissue (a putative vascular



**Figure 10.** Diagram of the perivascular niche hypothesis. The perivascular region (with pericyte-like cells) is the niche of progenitor cells and the substrate of regulatory mechanisms: 1) the pericyte-like cells, a heterogeneous population of mural cells, such as pericytes, homing cells from the bone marrow (fibrocytes and BMMSCs) and perivascular fibroblasts, originate new pericytes, fibroblast-myofibroblasts (and related cells) and some subsets of macrophages, 2) the regulatory mechanisms include: a) regulation of quiescent and angiogenic stages of blood vessels (cell-cell contacts and soluble factors produced by pericytes and EC), b) mesenchymal cell proliferation and differentiation control, and c) interactions between transmigrating cells (e.g. monocytes) and perivascular niche resident cells.

niche of MSC), using an exogenous marker, which has been subsequently observed in culture cells of adherent MSC obtained from this tissue (nonpublished observations).

The mesenchymal stem cells isolated from various tissues and involved in RTGT (with innate ability to home to sites of tissue repair) are a therapeutic promise, which will increase when their lineage, full functional differentiation capacity and requirements for favoring cell renewal over differentiation during expansion in cultures is better understood (paradox between “*in vitro*” promise and “*in vivo*” efficacy -424). Clinical applications could involve the following (394, 395, 424): 1) to engineer different tissues both “*ex vivo*” and “*in vivo*”, such as cartilage (e.g. joint, nose, ear and trachea), bone (e.g. craniofacial and long bone defects) and myocardium (acute myocardial

infarction), 2) to produce growth factors (e.g. member of the BMP family), proteins (e.g. protein deficiency disorders-hemophilias), collagen and trophic factors, 3) to induce angiogenesis and inhibit apoptosis, 4) to form “guiding strands” to promote direct growth of new axons during central nervous system or spinal cord injury, 5) to provide stromal support for transplanted cells (e.g. bone marrow transplants), and 6) to modify the tumor associated stroma and/or use as delivery vehicles for anti-cancer therapies. In this way, the future strategies include (394, 395): a) modification of the genetically altered tumor stroma mesenchymal stem and descendent cells (unlike homeostatic RTGT cells, they might initiate and/or enhance tumor growth); b) use of mesenchymal stem cells as cellular delivery vehicles of antitumor agents (specific tropism of mesenchymal stem cells that survive and proliferate inside the tumor and that may act as a “mini

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pump”, e.g., active and passive immunotherapy, therapeutic gene products, interferon  $\beta$  (394) (See above); c) actions to alter the expression of some cell surface receptors and to inhibit tumor promoting interactions, targeting one or multiple molecules (growth factors, growth factor receptors, adhesion molecules and enzymes - e.g., recombinant humanized anti-VEGF mab Bevacizumab and anti-CD105 antibody-); d) modulation of the tumor microenvironment by eliminating the stromal cells; and e) interference with the remodelling of the extracellular matrix (e.g.inhibitors of proteases - MMPS-).

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