

Review

Adult stem and transit-amplifying cell location

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Summary. Adult stem cells (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, adopting functional phenotypes and expression profiles of cells from other tissues. Therefore, they could be useful to regenerative medicine and tissue engineering. Transit-amplifying cells (TAC) are committed progenitors among the ASC and their terminally differentiated daughter cells. The ASC reside in a specialized physical location named niche, which constitutes a three-dimensional microenvironment where ASC and TAC are protected and controlled in their self-renewing capacity and differentiation. The niche can be located near or far from the recruitment point, requiring a short or long-distance cellular migration, respectively. This paper briefly reviews the current status of research about ASC plasticity, transdifferentiation, fusion and functional adaptation mechanisms. Subsequently, ASC and TAC occurrence, characteristics and location have been considered in the skin, cornea, respiratory tract, teeth, gastrointestinal tract, liver, pancreas, salivary glands, kidney, breast, prostate, endometrium, mesenchyma, bone marrow, skeletal and cardiac muscle, nervous system and pituitary gland. Moreover, the role of cancer ASC has also been revised.

Key words: Stem cells, Transit-amplifying cells, Skin, Cornea, Respiratory, Gastrointestinal, Prostate, Bone marrow, Nervous system, Pituitary

Stem cells

Stem cells, capable of unlimited, prolonged or long-term self-renewal and of differentiating into multiple cellular progenies or lineages, are made up of embryonic stem cells (ESC) and the paradoxically named adult stem cells (ASC).

Traditionally, ESC comprise the zygote, the descendants of the first two divisions and those from the inner cell mass of blastocyst. The zygote (fertilized oocyte) and the descendants of the first two divisions are considered to be totipotent, able to give rise to the embryo and to the placenta and supporting tissues. Those from the inner cell mass of blastocyst have been attributed with a pluripotent potential and therefore with the capacity to generate all or most cell lineages derived from the three embryonic germ layers: ectoderm (skin and neural lineages), mesoderm (blood, fat, cartilage, bone and muscle) and endoderm (digestive and respiratory systems) (Gardner and Beddington, 1988; Smith, 2001). During development, ESC divide and originate distinct subpopulations, including non-self-regenerating progenitors that undergo terminal differentiation.

ASC cells, somatic stem cells, or organ-specific adult stem cells are small subpopulations of quiescent-slow-cycling-undifferentiated resident cells, with high proliferative and pluripotent potentiality and the ability to self-renew and to originate daughter cells, which finally differentiate into functionally mature cells, regenerating all the cell types of the tissue where they are located. Their proliferative reserve exceeds an individual lifetime. These ASC present few organelles and a large nuclear cytoplasmic ratio and may express specific antigens, including Sca-1 (Stem cell antigen1) (Spangrude et al., 1988; Welm et al., 2002; Asakura, 2003; Montanaro et al., 2003; Falcatori et al., 2004; Matsuura et al., 2004; Burger et al., 2005), integrins (Collins et al., 2001; Richardson et al., 2005) (Suzuki et al., 2000; Tani et al., 2000), c-Kit (CD117), CD34, Oct-4 (Oct-3, NFA-3, or Pou5f1), Nanog, nestin, Bmi-1, bcl2—an antiapoptotic protein— (Potten et al., 1997; Domen et al., 2000; Tiberio et al., 2002; Salm et al., 2005) and CD 133, also known as AC133 or prominin-1 (Lendahl et al., 1990; Yin et al., 1997; Gussoni et al., 1999; Corbeil et al., 2000; Niwa et al., 2000; Peichev et al., 2000; Tropepe et al., 2000; Uchida et al., 2000; Toma et al., 2001; Jiang et al., 2002; Welm et al., 2002; Beltrami et al., 2003; Mitsui et al., 2003; Molofsky et al., 2003; Park et al., 2003; Falcatori et al., 2004; Fernandes

et al., 2004; Richardson et al., 2004). The signaling pathways of Notch, Wnt, and sonic hedgehog (Shh) are related to ASC renewal (Gaiano and Fishell, 2002; Hitoshi et al., 2002; Ho and Scott 2002; de Santa Barbara et al., 2003; Pinto et al., 2003; Reya et al., 2003; Alvarez-Buylla and Lim 2004; Beachy et al., 2004; Dontu et al., 2004; Liu et al., 2004, 2005; Reya and Clevers 2005). ASC have been considered as located in a characteristic niche and traditionally as restricted in their differentiation potential to formation of differentiated lineages within their tissue of origin (multi-lineage potential), able to substitute damaged cells and to intervene in maintaining the structural and functional integrity of the tissues (Labat, 2001; Alison et al., 2002). These latter concepts have been modified and will be considered below, along with examples of the characteristics and location of the ASC in the wide variety of tissues where they are present.

ASC and transit-amplifying cells (TAC)

ASC may originate differentiated progeny through asymmetric or symmetric divisions. The asymmetric cell division gives rise to one ASC and one daughter cell already committed to differentiation into specific phenotypes. The symmetric division originates two identical ASC or two daughter cells committed to differentiation. Most mammalian self-renewing tissues use the latter mechanism. Hence, not all progenitor cells are ASC. Indeed, there are ASC and “transit-amplifying cells” (TAC) or committed precursor cells—committed progenitor or multipotent progenitor cells. The latter, with more rapid though limited proliferation, low self-renewal and restricted differentiation, increase the number of differentiated cells produced by one ASC division. Therefore, the transit-amplifying cells are committed progenitors between the ASC and all their terminally differentiated daughter cells. The ASC and TAC are located in one place or structural unit, such as the intestinal crypt or the gastric glands (Slack, 2000). These histological units are considered as “structural-proliferative units” (Potten, 1978), where one or few ASC feed a differentiated compartment.

ASC niches and regulatory systems

The ASC reside in a specialized physical location known as a niche (Schofield, 1978; Watt and Hogan 2000; Spradling et al., 2001; Fuchs et al., 2004; Ohlstein et al., 2004), which constitutes a three-dimensional microenvironment containing, in addition to the ASC, neighbouring differentiated cell types, extracellular matrix and mesenchymal cells. Ohlstein et al. (2004) define the niche as a specific location in a tissue where stem cells can reside for an indefinite period of time and produce progeny cells while self-renewing. The niche may be located near the recruitment point with a short-distance migration, or at a far-off site requiring a remarkably long-distant cellular migration, a property that these cells share with metastatic cancer cells. The

complexity of the niche oscillates between isolated ASC, such as the muscle satellite cells, and organized ASC compartments or reservoirs in tissues that undergo continued turnover. The niche contributes a regulatory system, which maintains and governs the location, adhesiveness, retention, homing (recruiting) and mobilization, quiescence or activation, symmetric or asymmetric division and differentiation of the ASC. For example, symmetrical divisions may originate two ASC or two TAC, controlling the number of ASC and TAC. In short, the niche supplies a restricted microenvironment where the ASC and TAC are protected and controlled in their self-renewing capacity and differentiation. The regulatory system can be intrinsic or extrinsic to the ASC and TAC cells. An intrinsic property is the greater or lesser capacity of ASC cells for self renewal (Harrison and Zhong, 1992). Likewise, the tumor suppressor gene PTEN and the polycomb gene *Bmi1*, among others, have been described as a negative regulator of neural stem/progenitor cell proliferation (Groszer et al., 2001) and as playing an important role in the maintenance of adult self-renewing hematopoietic stem cells (Park et al., 2003), respectively. The extrinsic regulatory system comprises cell contacts with neighbouring cells and extracellular matrix, and soluble factors, such as epidermal and basic fibroblast growth factors, cytokines and hormones. The adherens junctions, with the participation of cadherins and catenins, intervene in the cell contacts between ASC and neighbouring differentiated cells. The integrins mediate the adhesion between the ASC and the basal membrane and, along with the adherens junctions, contribute to ASC retention and recruiting. The balance of stimulatory and inhibitory signals that regulate cell quiescence and proliferation, such as mitogenic cytokines and WNTS signaling or inhibitory effects of morphogenetic protein/transforming growth factor β superfamily (BMP/TGF β) (Cashman et al., 1992; Podolsky, 1993; Johe et al., 1996; Fortunel et al., 2000; Crowe et al., 2004; Salm et al., 2005; Niemann, 2006) contribute to the extrinsic regulatory system. Thus, Notch and beta 1-integrins are co-expressed and cooperate with the epidermal growth factor receptors in neural progenitors (Campos et al., 2006). An example of the specialised microenvironment of the niche is the relationship between the osteoblastic lineage and the development of normal haematopoiesis in the bone marrow (Zhou et al., 1995; Deguchi et al., 1999; Jacenko et al., 2002; Calvi et al., 2003; Adams et al., 2006). Indeed, the hematopoietic stem cells reside very close to the endostal surface of bone (Lord et al., 1975; Gong, 1978), and it has been pointed out that these cells, by means of transmembrane-spanning calcium-sensing receptor, respond to high concentrations of calcium ions. Therefore, the ionic mineral content of the niche may dictate the localization of hematopoietic stem cells in bone (Adams et al., 2006).

Plasticity of ASC

Recent studies (Orkin, 2000; Blau et al., 2001;

Krause et al., 2001; Minguell et al., 2001; Morrison, 2001) have highlighted numerous findings showing that AS normally residing in a tissue have marked plasticity, the term used to describe the multipotency of the ASC, and that they are capable of reacquiring totipotency, owing to the fact that their restrictions may not be irreversible. In other words, they may express greater plasticity than traditionally attributed, since they may cross over lineage barriers and be reprogrammed, adopting the functional phenotypes and expression profiles of cells from other tissues. Consequently, these cells may be useful in regenerative medicine and tissue engineering.

Therefore, they may contribute to the differentiated adult lineages native to other tissues and organs (Ferrari et al., 1998; Bjornson et al., 1999; Jackson and Goodell, 1999; Kopen et al., 1999; Petersen et al., 1999; Brazelton et al., 2000; Clarke et al., 2000; Galli et al., 2000; Lagasse et al., 2000; Mezey et al., 2000; Krause et al., 2001; Minguell et al., 2001; Orlic et al., 2001; Korblyng et al., 2002; Badiavas et al., 2003; Pearton et al., 2004) by AS relocation to a new niche with exposure to appropriate local environmental stimuli (Jiang et al., 2002; Wagers and Weissman, 2004; Richardson et al., 2005) or by the importation of soluble factors, such as the intervention of growth factors capable of inducing stem cell differentiation. In recent years, this issue has provoked considerable controversy, which will be discussed below.

Fusion, transdifferentiation and functional adaptation mechanisms

Adult differentiated cells may convert into cells of a different phenotype by transdifferentiation (Eisenberg and Eisenberg, 2003; Meivar-Levy and Ferber, 2003; Shen et al., 2003). For example, pancreatic duct and acinar cells can transdifferentiate into endocrine cells *in vivo* (Bockman and Merlino, 1992; Gu and Sarvetnick, 1993; Gu et al., 1994; Wang et al., 1995; Song et al., 1999; Gmyr et al., 2000).

Numerous works suggest cell fusion between bone marrow and tissue-specific cells resulting in one mechanism, which gives rise to BM-derived nonhematopoietic cells (Terada et al., 2002; Ying et al., 2002; Alvarez-Dolado et al., 2003; Vassilopoulos et al., 2003; Wang et al., 2003), after forming polyploid cells—heterokaryons—and subsequently 2 euploid cells by means of cytoreductive division (Vassilopoulos et al., 2003; Weimann et al., 2003; Wang et al., 2003). On the contrary, other works propose a transdifferentiation of BM cells into tissue-specific stem cells or intermediate progenitor cells (Ferrari et al., 1998; LaBarge and Blau, 2002; Deb et al., 2003; Janus et al., 2003; Tran et al., 2003; Harris et al., 2004; Jang et al., 2004). Likewise, some authors indicate the possibility that the BM-derived cells improve the function of different organs (Ferrari et al., 1998; LaBarge and Blau, 2002; Janus et al., 2003; Yamada et al., 2004), expressing the specific function of the tissue of residence.

Skin ASC

Skin constitutes a larger, easily accessible and immune privileged reservoir of ASC for cell-based therapy (Shi et al., 2006). Following, we consider the epidermal and dermal ASC, as well as the nail and melanocyte ASC.

Epidermal and hair ASC

Epidermal and hair ASC (Figs. 1-3) are located in interfollicular epidermis, bulge region of the hair follicle (upper region of the root sheath) and germinal matrix of growing hair follicles (Watt, 2001; Potten and Booth, 2002; Alonso and Fuchs, 2003a,b). Integrins are an important marker of epidermal ASC (Jones and Watt, 1993; Jones, 1996; Crowe et al., 2004) and their decreased expression is related to terminal differentiation. P63 is also a possible marker (Pelligrini et al., 2001, Crowe et al., 2004), while telomerase expression is decreased (Bickenbach et al., 1998; Crowe et al., 2004).

ASC in interfollicular epidermis

To compensate for the constant loss of surface squames, the epidermis contains the so-called epidermal proliferative units, made up of columns each containing a stem cell located within basal cells, since not all basal layer cells are stem cells. The ASC in the basal layer are unipotent, with the capacity of regenerating the epidermis (So and Epstein, 2004; Morasso and Tomic-Canic, 2005; Shi et al., 2006). As mentioned above, there are stem cells and “transit-amplifying cells”. In the epidermis, the “transit-amplifying cells” have the ability to divide three to five times before all of their daughters terminally differentiate (Watt, 2001). Several authors point to a single stem cell in the middle of the cluster of 10 basal cells in the epidermal proliferative unit (Potten, 1974, 1981). The proliferative organization depends on the anatomical region, basically on epidermal thickness and on the existence of flat or undulating basal layer (Fig. 1A-C).

Hair follicle ASC

Hair follicle epithelial stem cells are located in the germinal matrix and in the bulge region or upper outer root sheath. Hair follicle dermal stem cells are found in the papilla and dermal sheath. Hair follicle ASC expressing nestin may differentiate into keratinocytes, neurons, glial cells, smooth muscle cells and Schwann cells (Hoffman, 2006). The knowledge of hair follicle ASC and stem cell technology procedures, such as isolation, cultivation and propagation, is important for hair follicle bioengineering (Stenn and Cotsarelis, 2005).

Germinal matrix bulb of growing hair follicles

When the follicle is growing (anagen), the germinal

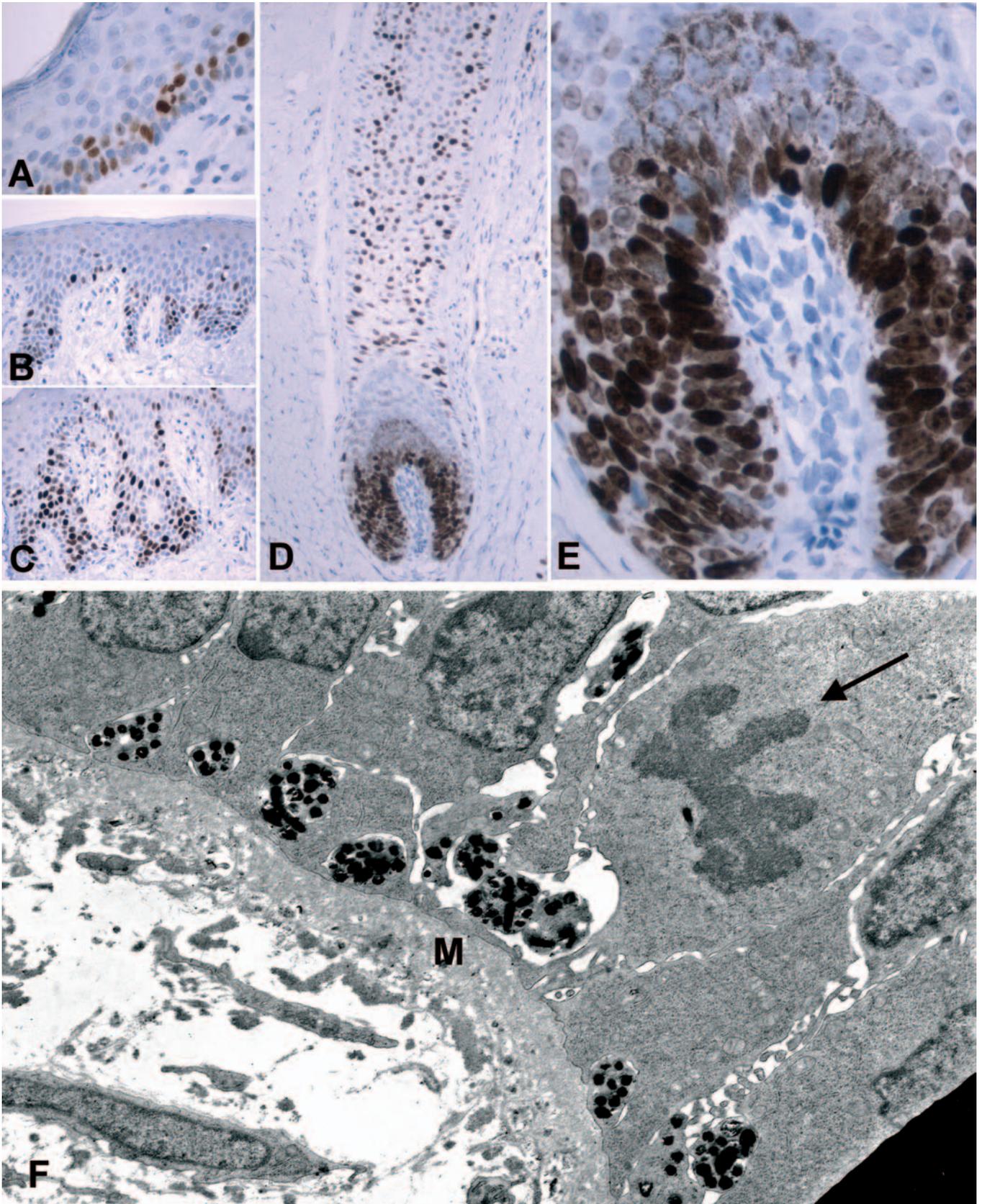


Fig. 1. Epidermal progenitor cells, Ki positive, are shown in skin with flat (A x 120) and undulating basal layer (B, C x 40 and x 80, respectively). Numerous epithelial progenitor cells are observed in the germinal matrix bulb of a growing hair follicle (D, E Ki67, x 40 and x 240, respectively). Transmission electron photomicrograph of the germinal matrix bulb showing an epithelial progenitor cell in mitosis (arrow) and a specialized rich extracellular matrix (M) situated between the epithelial and dermal components (F, Uranyl acetate and lead citrate, x 12.000).

or matrix region undergoes proliferative activity (Fig. 1D-F). Although some findings suggest that ASC are located in the lowest areas of the follicle matrix or germinal region of the hair bulb, their proliferating progenitor cells are regenerated by ASC located in the bulge region (see below).

Bulge region or upper outer root sheath ASC

In haired epidermis, ASC capable of regenerating epidermis, hair follicles, and probably sebaceous glands are mainly located in or around the bulge region of the hair follicle, specifically near the basal layer of the outer root sheath (Cotsarelis et al., 1990; Lavker and Sun, 2000; Taylor et al., 2000; Alonso and Fuchs, 2003a,b; Blanpain et al., 2004; Christiano, 2004; Morris et al., 2004; Tumber et al., 2004). This region, which expresses cytokeratin 15 (Lyle et al., 1998), is localized at and above the site of arrector pili muscle attachment up to the level of the sebaceous gland (Ohyama et al., 2006). Indeed, follicle-derived cells can lead to regeneration of the complete skin (Prouty et al., 1996, 1997). Epithelial populations can generate follicles, sebaceous glands (Fig. 2A) and epidermis (Taylor et al., 2000; Oshima et al., 2001). Likewise, it is likely that the bulge region repopulates the germinal matrix with stem cells at each cycle (Oshima et al., 2001). Indeed, at the base of the resting follicle, the bulge ASC proliferate and regenerate the highly proliferative progenitor germinal matrix (bulb) cells that originate a new hair. Subsequently, the ASC return to a quiescent state. Wnt/beta-catenin exerts a direct effect on the cell compartment by inducing quiescent ASC to enter the cell cycle, and beta-catenin is required for maintenance of the stem cell pool in the tissue (Niemann, 2006). Tcf3 and left 1 regulate lineage differentiation of multipotent ASC (Merrill et al., 2001). In this way, high levels of Wnt signaling induce bulge ASC to acquire the hair shaft lineage (Gat et al., 1998), while its inhibition can determine epidermal and sebaceous gland differentiation of these bulge cells (Huelsen et al., 2001; Merrill et al., 2001). Ohyama et al. (2006) have suggested that CD200 intervenes as a regulator of the immune-privileged state of the hair follicle.

Hair follicle dermal ASC

The adult hair follicle dermis not only intervenes by inducing the formation of hair follicles and controlling cyclic regeneration, but also contains mesenchymal cell populations (Figs. 1F, 2B-E), with stem cell properties. The follicle dermal ASC with bcl2 expression (Fig. 2C) not only incorporate into the hair-supporting papilla, but also intervene in the dermis of adjoining skin (Paus and Cotzarelis, 1999; Jahoda and Reynolds, 2001; Gharzi et al., 2003). Therefore, these cells participate in wound healing (Jahoda and Reynolds, 2001; Gharzi et al., 2003). Likewise, adipogenic and osteogenic differentiation has been demonstrated in rodent models and in human hair follicle-derived dermal papilla and

dermal sheath cultures (Jahoda et al., 2003; Richardson et al., 2005a,b). Recently, Lako et al. (2002) have demonstrated that the hair follicle dermal compartment contains cells that have hematopoietic stem cell activity. Moreover, Toma et al. (2001) and Richardson et al. (2005) have pointed to the possibility of neural phenotype induction. In a comparative study of hair follicle dermal ASC and bone marrow mesenchymal ASC, Hoogduijn et al. (2006) observed that both cell populations showed: 1) a fibroblastic morphology in serum-containing culture medium, with a doubling time of 27 hours, 2) expression of CD44, CD73 and CD96, 3) the capacity to differentiate into osteoblasts, adipocytes, chondrocytes and myocytes, 4) expression of neuroprogenitor cell markers and 5) clonal expansion capacity. Telomerase activity was also identified.

Nail ASC

The epithelium in the intermediate nail matrix (easily identified by the presence of acanthosis with mamelons, protuberances or undulations) possesses very active dividing cells (keratinoblasts), which constitute the nail plate (Fig. 3A-C). Integrins, such as $\alpha 2$, $\alpha 3$ and $\beta 1$ subunits are expressed in the basal and suprabasal layers of the nail matrix, but only in the basal layer of skin epidermis (Cameli et al., 1994). Cultured human nail matrix cells are larger than epidermal keratinocytes, with a higher euchromatin/heterochromatin ratio and a lower nucleus/cytoplasm ratio. Likewise, they have a higher growth rate (Picardo et al., 1994).

Melanocyte ASC

In most hair follicles, the niche of melanocyte ASC, with a dominant role in the fate of melanocyte stem cell progeny, has been located in their lower permanent portion through the hair cycle (Fig. 3D,E) (Nishimura et al., 2002). The melanocyte AS cells are also located in the bulge region (Steingrimsson et al., 2005).

Corneal epithelium ASC

The limbal zone has been shown to be the site of corneal epithelial ASC (Schermer et al., 1986; Lavker et al., 2004), and reconstruction of the damaged corneas by transplantation of autologous limbal epithelial cells is possible (Tsai et al., 2000). Corneal epithelium has been demonstrated to originate hair when it is influenced by embryonic skin dermis (Pearson et al., 2004). As with limbal epithelial cell transplantation, bone marrow-derived mesenchymal AS cells may also reconstruct damaged rat corneal surface in all likelihood by inhibiting inflammation and angiogenesis rather than epithelial differentiation (Ma et al., 2006).

Respiratory tract ASC

ASC and TAC of the proximal conducting airway epithelium of the nose, paranasal sinuses, nasopharynx,

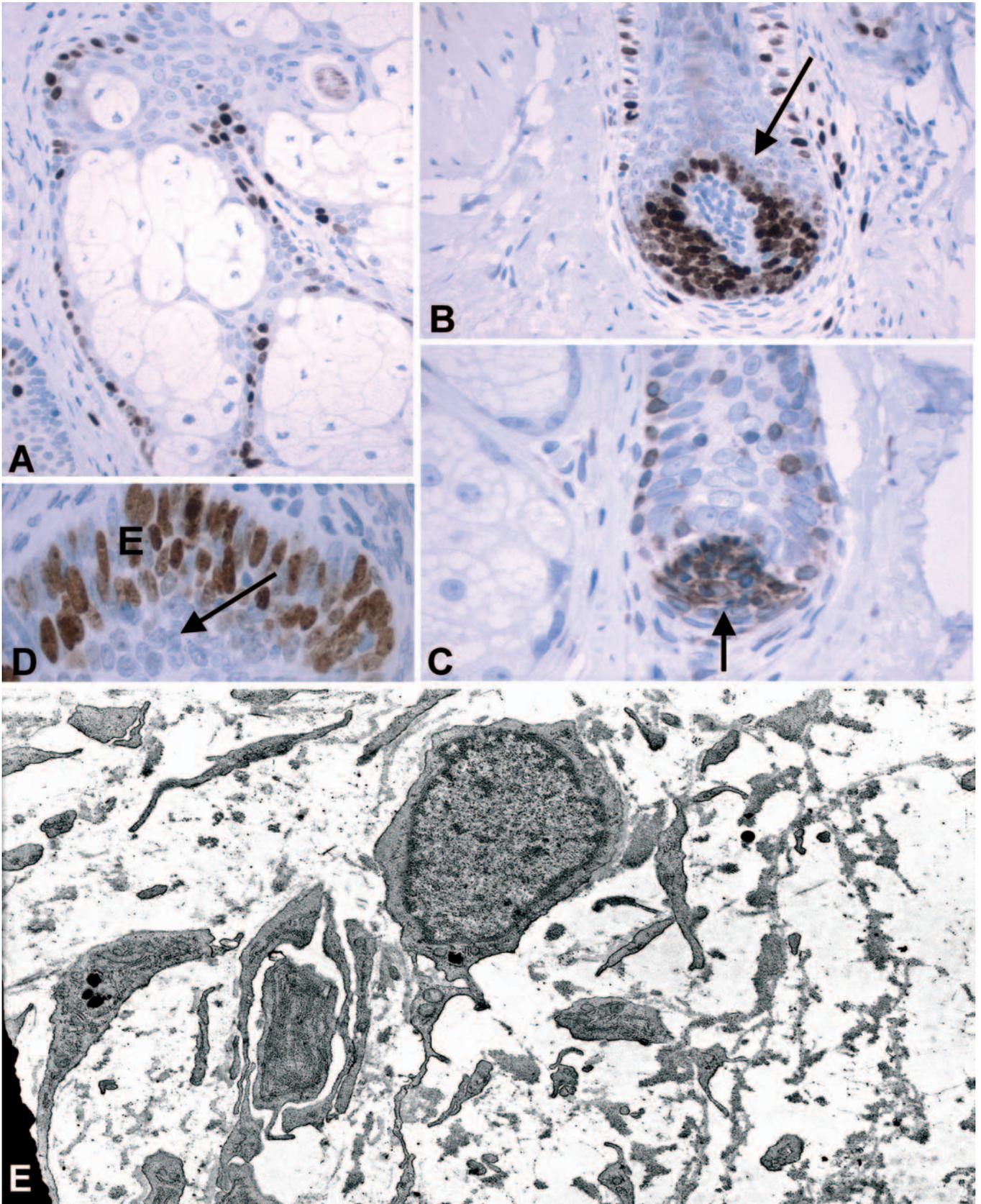


Fig. 2. Progenitor cells in a sebaceous gland (A, Ki 67, x 90). While Ki 67 is expressed in the epithelial component of the germinal matrix bulb of a growing hair follicle (B, arrow, x 120), the expression of bcl2 is present in the dermal papillar cells (C, arrow, x 120). Detail of epithelial (E) and dermal cells (arrows) of the matrix bulb (D, Ki 67, x 240). Ultrastructural characteristics of the progenitor cells in dermal papilla (E, Uranyl acetate and lead citrate, x 10,000).

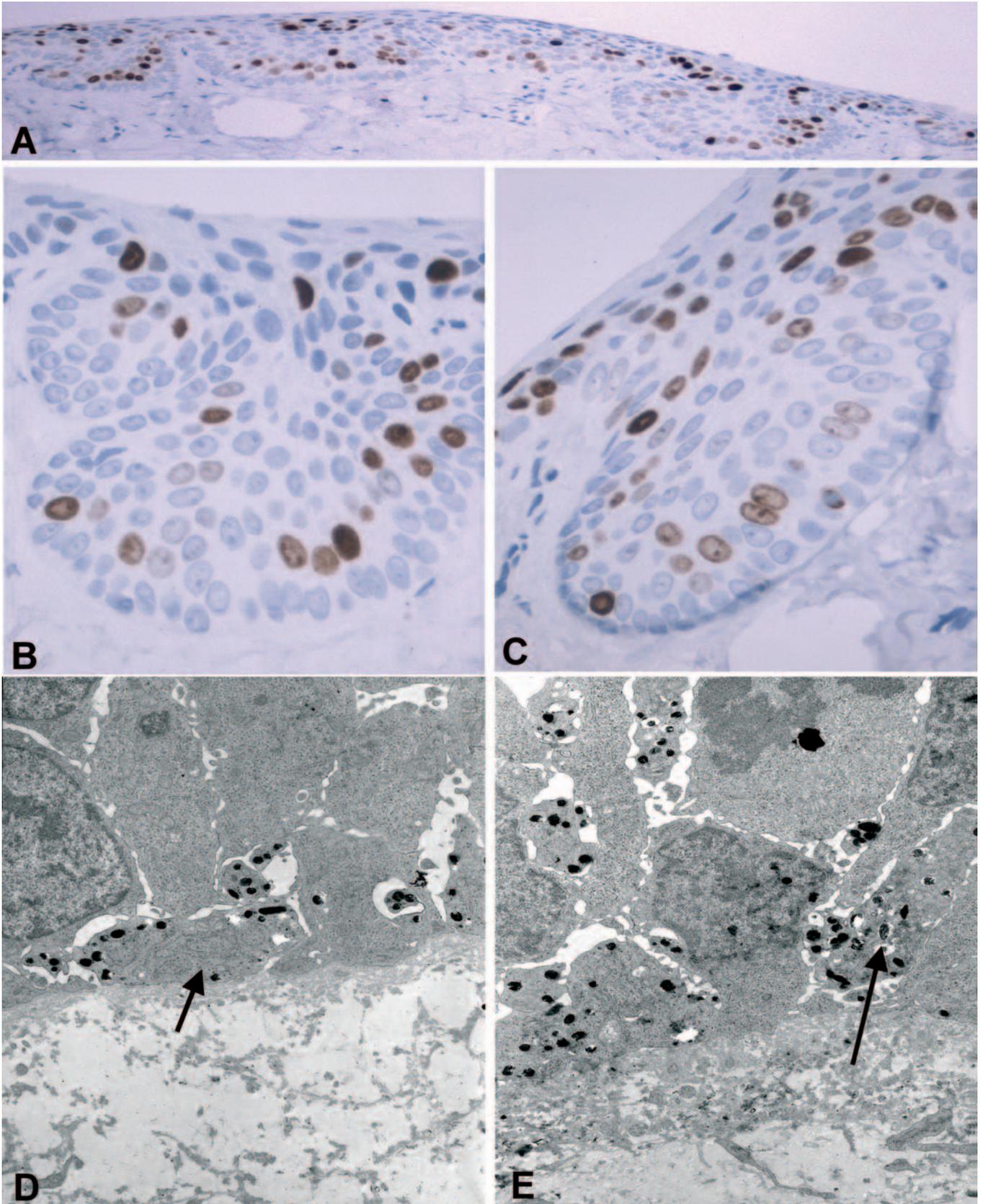


Fig. 3. Intermediate nail matrix, with mamelons and presence of progenitor cells (A-C, Ki 67, x 30, x 180 and x 180, respectively). Melanocyte in the bulb region (arrows) (D, E, Uranyl acetate and lead citrate, x10.000).

larynx, trachea and bronchi, with basal, secretory, ciliated and neuroendocrine cells, are located at or near the basement membrane (Delplanque et al., 2000; Kotton et al., 2001; Poulson et al., 2001) and in the gland duct (Duan et al., 1998). Bronchioalveolar ASC have been identified at the bronchioalveolar duct junction (junction between the conducting and respiratory epithelium in terminal bronchioles) (Fig. 4A), which proliferate during epithelial cell renewal *in vivo*, with self-renewal and multi-potentiality (Kim et al., 2005). In the bronchiole and alveolus, the Clara cells and the type II pneumocytes (Fig. 4B,C) have been referred to respectively as TAC (Otto, 2002).

Dental ASC

Some cells of dental pulp (Fig. 4D,E) have mesenchymal characteristics. Cultured human mesenchymal ASC derived from dental pulp and periodontal ligament have the capacity to generate clonogenic cell clusters and express a heterogeneous assortment of markers associated with dentine, bone, smooth muscle, neural tissue and endothelium (Shi et al., 2005). Likewise, progenitor cells derived from dental follicle showing putative ASC markers (Notch-1 and nestin) have been isolated (Morszeck et al., 2005).

Gastrointestinal tract ASC

In the gastric glands or gastric units (Brittan and Wright, 2002), the ASC and TAC are located in the neck/isthmus region (Modlin et al., 2003) and the daughter cells migrate bi-directionally (Karam, 1999) to originate the mucous epithelium of the foveolus, and the mucus-secreting cells of the cardiac and pyloric glands and the chief, parietal and mucous neck cells of the straight fundic glands of composite cell distribution. Apparently, preneck committed precursor cells differentiate into chief cells, while parietal cells differentiate from preparietal cell precursors within the isthmus (Karam, 1999). The ASC and TAC make up around 3% of the gastric epithelium (Modlin et al., 2003). Probably, the endocrine cells also derive from a common ASC (Brittan and Wright, 2002). The niche of the ASC in the gastric gland includes extracellular substrates and myofibroblasts. The latter are the subepithelial myofibroblasts and the interstitial cells of Cajal. The subepithelial myofibroblasts secrete growth factors (hepatocyte growth factor, transforming growth factor B and keratinocyte growth factor), whose receptors are in the epithelial cells (Powell et al., 1999). The interstitial cells of Cajal may regulate neuroendocrine enterochromaffin cell proliferation (Laufer et al., 2001). Recently, interactions between gastric epithelial stem cells and *Helicobacter pylori* indicate that proliferating and non-proliferating gastric ASC provide a habitat for *Helicobacter pylori* able to support their persistence in a gastric ecosystem that has lost its acid barrier, increasing risk of tumorigenesis (Oh et al., 2006).

In the intestine, AS are located in the crypts. Specifically, in the small intestine and the descending colon, AS are presumed to be situated in the base of the crypt, while they reside in the mid-crypt of the ascending colon. Probably, all four lineages (unitarian hypothesis) of the small intestine, absorptive or columnar, goblet or mucous, endocrine and Paneth cells, originate from ASC and TAC located between the Lieberkühn crypt-base columnar cells, above the Paneth cells (Cheng and Leblond, 1974a-c; Gordon et al., 1992; Bjerknes and Cheng 1999; Dekaney et al., 2005), occupying two thirds of the height of the crypt (Potten and Loeffler, 1990; Slack, 2000). This stem-cell zone expresses RNA-binding protein Musashi-1 (Msi-1) (Kayahara et al., 2003; Potten et al., 2003), which is significant in asymmetric cell division by neural stem cells (Sakakibara et al., 1996). According to the authors, the number of stem cells per crypt varies from one to six (Gordon et al., 1992; Cosentino et al., 1996; Potten, 1998; Bjerknes and Cheng 1999; Winton, 2001), around 1.1% of the whole small epithelium (Dekaney, 2005). Although intestinal epithelial cells arise from the crypt intestinal stem cells, bone marrow-derived cells can also contribute to the regeneration of the gastrointestinal epithelium (Krause et al., 2001; Okamoto et al., 2002; Okamoto and Watanabe, 2003). In this way, fusion of bone marrow-derived cells with normal and transformed intestinal ASC has been described (Rizvi et al., 2006).

Hepatic ASC

In the adult liver, cells with hepatic potential are the hepatocytes themselves and a potential stem cell compartment located within the intrahepatic biliary tree (Grisham and Thorgeirsson, 1997; Alison, 1998; Forbes et al., 2002). The latter are considered bi-potential offspring of the stem cells and therefore analogous to the committed progenitors or transit-amplifying cells (Grompe, 2005). The hepatocytes are capable of regeneration after moderate cell loss and after their transplantation in animals can undergo significant clonal expansion. The potential ASC within the smallest branches of the intrahepatic biliary tree and the terminal hepatic ductules (Hering's canals) react to more severe liver injury, and they originate cords of so-called "oval cells" that can differentiate into biliary epithelial cells and hepatocytes (Grisham and Porta, 1964; Sell, 1990; Shiojiri et al., 1991; Fausto et al., 1993; Grisham and Thorgeirsson, 1997; Petersen et al., 1998; Paku, 2001). Therefore, the terminal biliar ductules constitute the primary hepatic ASC niche (Paku et al., 2001). Periductal proliferating cells have been observed (Sell and Salman, 1984), and blast-like cells located near the bile ducts have been regarded as one of the possible origins of oval cells (Novikoff et al., 1996). Hepatic differentiation may also occur in extrahepatic bile ducts (Park et al., 1991) and in the pancreas (Rao et al., 1991; Krakowski et al., 1999). Other locations for hepatic ASC have been suggested in bile ducts (Sirica et al., 1990; Nomoto et al., 1992; Golding et al., 1995; Novikoff et

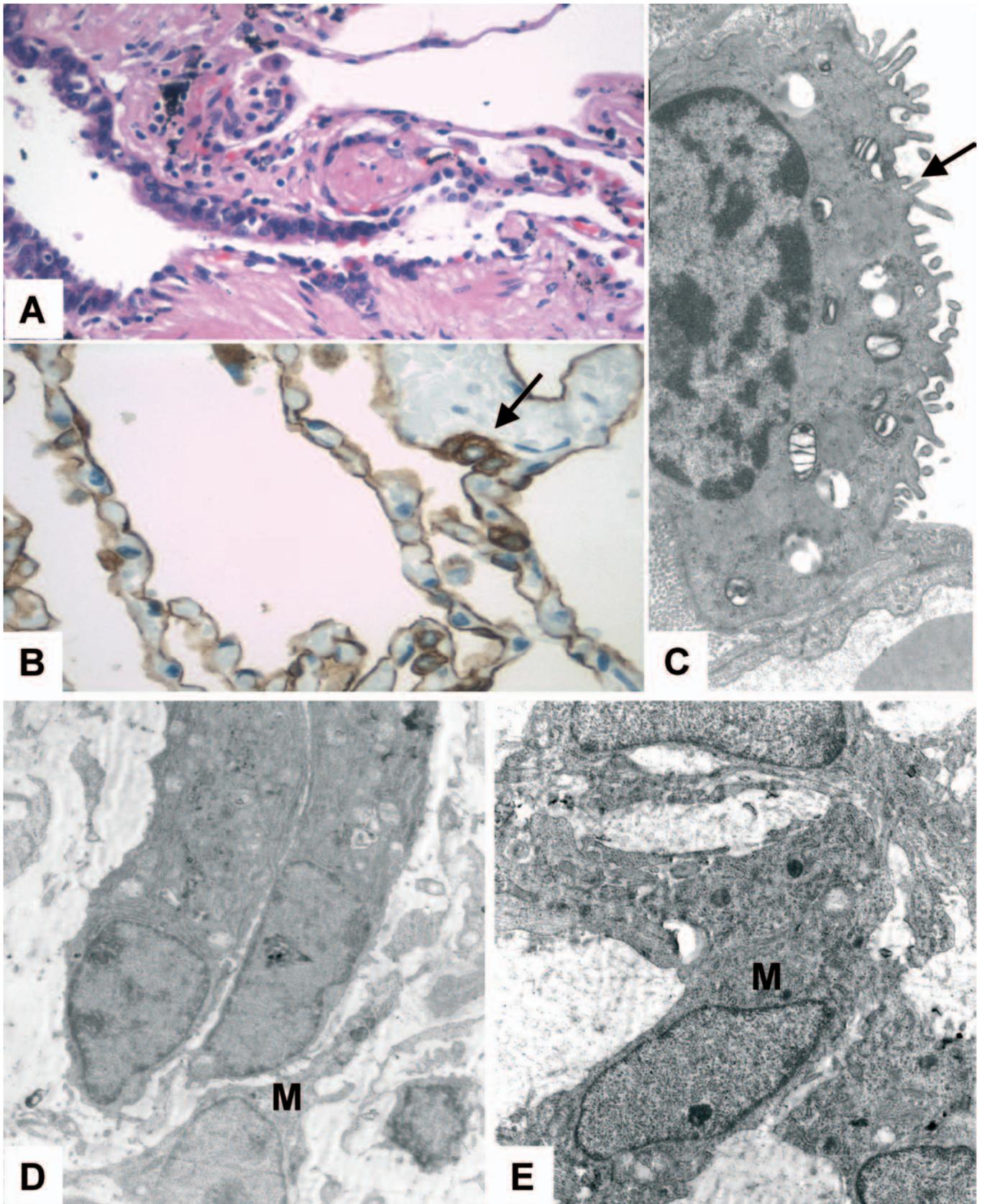


Fig. 4. Junction between the conducting and respiratory epithelium in terminal bronchioles (bronchioalveolar duct "junction") is shown in **A** (H-E, x 120). Type II pneumocytes are present in **B** (arrow) (CK, x 120) and **C** (arrow) (transmission electron photomicrograph, Uranyl acetate and lead citrate, x 12,000). **D and E**, Ultrastructure of the mesenchymal cells (M) in dental pulp (Uranyl acetate and lead citrate, x 10,000).

al., 1996; Alison et al., 1996; Novikoff and Yam, 1998). Bone marrow ASC can also give rise to oval cells and hepatocytes (Petersen et al., 1999; Theise et al., 2000), being considered by some authors as the ultimate source of hepatic progenitor cells (Wessells, 1967; Pictet et al., 1972; Bach et al., 1997; Shapiro et al., 2000; Oliver et al., 2004; Zhang et al., 2005). However, the numbers of hepatocytes derived from bone marrow are exceedingly low and could also originate by fusion of macrophages with pre-existing hepatocytes (Gepts and Lecompte, 1981; Kloppel et al., 1985; Grompe, 2005). Neuro D-betacellulin gene therapy induces islet neogenesis with small numbers of insulin-producing cells in the liver of diabetic mice (Kojima et al., 2003), and pituitary transcription factor 1 induces transient differentiation of hepatic ASC into prolactin-producing cells *in vivo* (Lee et al., 2005).

Pancreatic ASC

The stem cells in the pancreas can be the duct cells or the pre-existing differentiated cells themselves (Fig. 5), acinar or endocrine (Wang et al., 1995; Bonner-Weir et al., 2000; Zulewski et al., 2001; Petropavlovskaja and Rosenberg, 2002; Rooman et al., 2002; Gao et al., 2003; Zhang et al., 2005). Pancreatic duct cells, with a low rate of neogenesis in the normal adult, have the capacity to expand and to differentiate during growth and regeneration (Gu and Sarvetnick, 1994; Kritzik et al., 2000; Bonner-Weir and Sharma, 2002). In this way, they are able to regress and dedifferentiate (Sharma et al., 1999). In normal conditions, the expansion is probably suppressed by effects of matrix components and soluble factors such as TGF- β (Bonner-Weir et al., 1997). During regeneration and in nesidioblastosis (Fig. 5), expansion of the duct and acini cells is produced. In these conditions, the cells serve as multipotent progenitors or functional stem cells, with subsequent differentiation into duct, acini and islet cells, depending on matrix components or soluble factors. Regeneration of pancreatic beta cells from intra-islet precursor cells has also been described in an experimental model of diabetes (Guz et al., 2001). In this way, multipotential nestin-positive stem cells isolated from pancreatic islets differentiate *ex vivo* into endocrine and exocrine pancreatic cells (Zulewski et al., 2001). Likewise, some ductal and acinar cells, expressing the receptor for hepatocyte growth factor, may be pancreatic ASC, with a capacity to differentiate into multiple pancreatic lineage cells (Suzuki et al., 2004). A population of small cells in pancreas islets may also be progenitor cells (Petropavlovskaja and Rosenberg, 2002). Transdifferentiation of acinar cells into duct-like structures is possible in pancreatic lesions, and subsequently islet neogenesis (Bockman and Merlino, 1992; Gu and Sarvetnick, 1993; Gu et al., 1994; Wang et al., 1995; Song et al., 1999; Gmyr et al., 2000). Recent studies have shown that pancreatic acinar cells possess sufficient plasticity to transdifferentiate into pancreatic endocrine cells *in vitro*. Indeed, insulin-secreting cells

can be derived from adult mouse pancreatic exocrine cells by suspension culture in the presence of EGF and nicotinamide (Minami et al., 2005). This possibility was primarily suggested by the histological observations of amylase/insulin double-positive cells, as well as by islet neogenesis after formation of a large quantity of ductal structures in partial pancreatectomy models and duct ligations (Bonner-Weir et al., 1993; Bouwens, 1998). The overexpression of members of the EGF family may be important in the proliferation of precursor cells (Bockman and Merlino, 1992; Song et al., 1999). Thus, overexpressing TGF alpha, ductal hyperplasia and islet neogenesis occur in most pancreas (Bockman and Merlino, 1992; Song et al., 1999). Expression of mesenchymal AS cells from human pancreatic ductal epithelium has been described (Seeberger et al., 2006). These cells, expressing CD13, CD29, CD44, CD49b, CD54, CD90 and CD105, had the *in vitro* capacity to differentiate into bone, cartilage, adipocytes, hepatocytes and pancreatic endocrine cells (Seeberger et al., 2006).

Salivary gland ASC

The presence of AS/progenitor cells has been described in salivary glands (Kishi et al., 2006) located in intercalated duct. Previously, the intercalated ductal cells had been highlighted as probably contributing to the differentiated acinar cells (Man et al., 2001).

Renal ASC

Renal papilla has been described as a niche for kidney ASC (Oliver et al., 2004), which are probably involved in renal repair. Indeed, during kidney repair of transient renal ischemia, papillary AS slow-cycling cells proliferate, disappear from the papilla and may migrate towards the site of maximum injury. When these cells were injected into renal cortex, they incorporated into the kidney parenchyma. Likewise, papillary ASC were multi-potent *in vitro* (Oliver et al., 2004). Another possibility is that kidney repair after injury occurs by division of terminally differentiated cells. Thus, Lin et al. (2005) have provided evidence that the cells composing regenerating tubules are derived from renal tubular epithelial cells. Bearing in mind the above, tubular renal regeneration may originate from resident progenitor cells, dedifferentiated cells, or from cells originating from outside the kidney, by means of transdifferentiation.

In this way, some authors have contributed the possibility that bone marrow cells may become renal epithelial cells. Indeed, male patients who received a renal transplant from a female recipient showed Y chromosome-positive renal tubular cells (ranging from 0.6-6.8%), suggesting that circulating cells may populate the renal tubule. Experimentally, Y chromosome-positive tubule cells have been also demonstrated in female mice with male bone marrow transplantation. Nevertheless, as previously mentioned, endogenous renal cells have been described as the most important

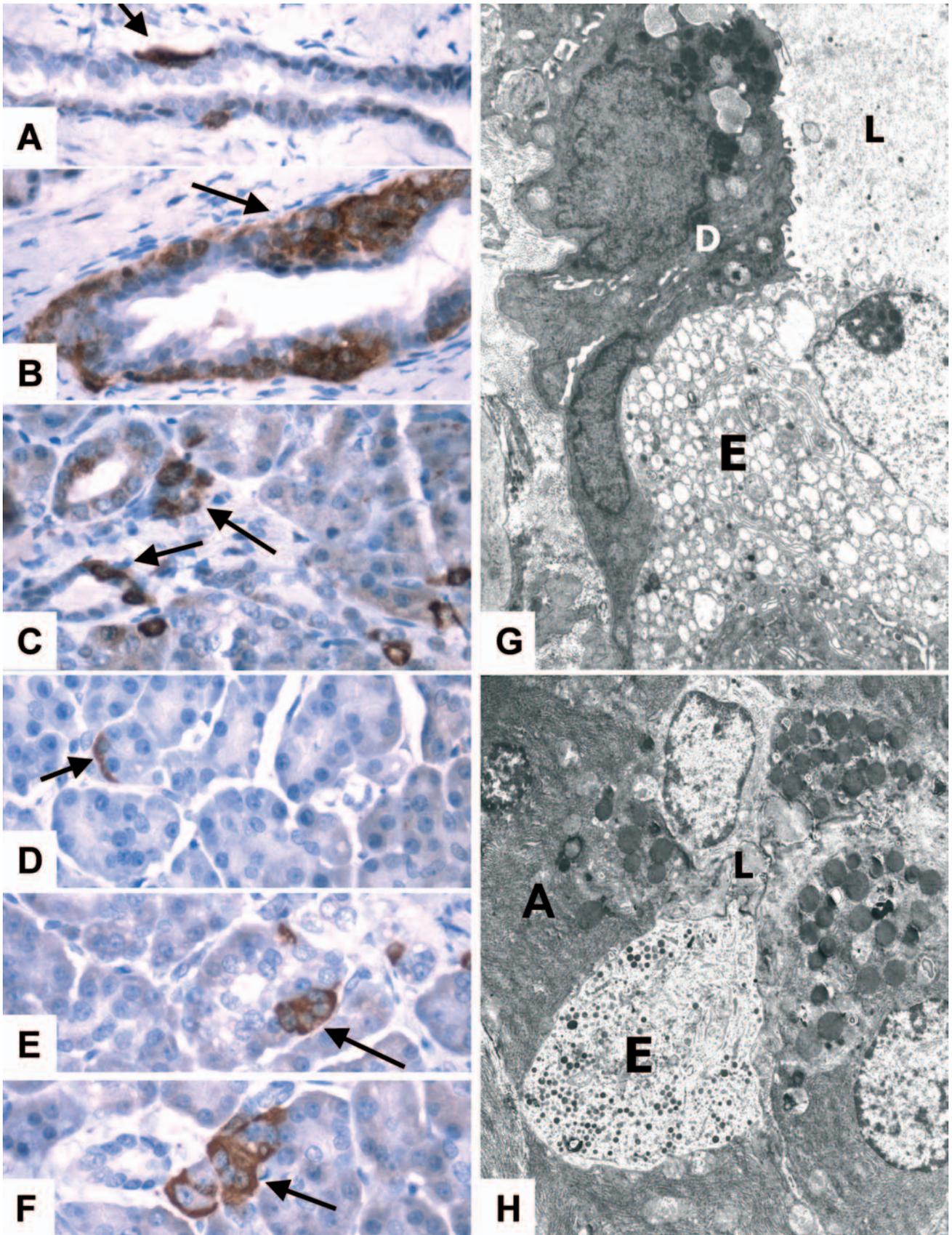


Fig. 5. Pancreatic endocrine cells, showing chromogranin and synaptophysin positivity, are shown in basal portions of ducts (A-C, arrows, x 240) and in acini (D-F arrows, x 240) from a patient with nesidioblastosis (process with active formation of endocrine cells by multipotent cells). Transmission electron photomicrographs of endocrine cells originated in a duct (G) and in an acini (H) of a pancreatectomized rat. E: endocrine cells; D: ductal cell; A: acinar cell; L: lumen of duct and acini. (Uranyl acetate and lead citrate x10,000).

source of cells in tubular repair. In this way, restoration of tubular epithelial cells during repair of the postischemic kidney has been reported occurring independently of bone marrow-derived stem cells (Duffield and Bonventre, 2005; Duffield et al., 2005), or with only some bone marrow-derived cells incorporated into the injured tubule as epithelial cells (Lin et al., 2005).

Mammary gland ASC

Adult stem cells are located in mammary gland ducts and lobules and they are a rapidly cycling population with molecular features indicative of a basal position in the mammary epithelium (Stingl et al., 2006). They are numerous in end buds during emerging ductal networks (Daniel and Silberstein, 1987). In mouse and rat, three division-competent, structurally distinct cell populations have been described in mammary epithelium (Chepko and Smith, 1997). Indeed, based on cell size and nuclear and cytoplasmic staining characteristics, large light cells and small light cells have been established. The small light cells, distributed within mammary duct, are the least differentiated and may be stem cells, and the large light cells are direct precursors to terminally differentiated cells: secretory and myoepithelial cells (Chepko and Smith, 1997). Mammary gland in mice can be regenerated by transplantation of epithelial fragments (DeOme et al., 1959; Daniel et al., 1968; Kordon and Smith, 1998). Likewise, it has been demonstrated that a single cell can reconstitute a complete mammary gland *in vivo* (Shackleton et al., 2006). Subsequently, the single cell contributes to both luminal and myoepithelial cells and is capable of generating functional lobuloalveolar units during pregnancy (Shackleton et al., 2006). Therefore, both ductal and lobular cells as well as luminal and myoepithelial cells originate from single stem cells.

Prostatic ASC

In the mouse, the prostatic ASC niche is located in the proximal region of ducts (Tsujimura et al., 2002). This region overexpresses *bcl2*, which protects AS cells from apoptosis (Salm et al., 2005), while the distal duct region has low *bcl2* expression—an apoptosis unprotected region. TGF- β and androgens are regulators of prostatic tissue homeostasis (Salm et al., 2005). Thus, Salm et al. (2005) have demonstrated that, in quiescent conditions, the proximal region of duct, where the prostatic niche is located, shows high levels of TGF- β signaling, with a proximal distal decreasing TGF- β gradient.

Endometrial ASC

A small population of epithelial (0.22%) and stromal (1.25%) cells with the property of clonogenicity has been demonstrated in the endometrium, suggesting that these are AS cells (Gargett, 2004). This hypothesis

agrees with the presence of this cell type in a highly proliferative cyclically regenerating tissue. Inactive endometrium also contains clonogenic epithelial and stromal cells. Moreover, clonogenicity of epithelial and stromal cells does not vary significantly between proliferative, secretory and inactive endometrium (Schwab et al., 2005). The precise characterization of these cells is particularly interesting in order to contribute new findings concerning endometriosis, adenomyosis, endometrial hyperplasia and other endometrial disorders.

Mesenchymal ASC

Mesenchymal stem cells have the capacity to generate bone, cartilage, muscle and fat tissue (Pittenger et al., 1999, 2004; Zuk et al., 2001; Javazon et al., 2004). Likewise, they may cross the mesodermal lineage and differentiate into hepatocytes (Lee et al., 2004; Seo et al., 2005), pancreatic endocrine cells (Sordi et al., 2005; Seeberger et al., 2006) or other injured cells (Barbash et al., 2003; Pittenger et al., 2004; Sordi et al., 2005). These cells have no hematopoietic and endothelial markers (CD45, CD11c and CD31), expressing CD90, SH2 (endoglobin or CD105), SH3 or SH4 (CD73 and STRO-1) (Simmons and Torok-Storb, 1991; Pittenger et al., 1999) and have been isolated, by means of their rapid expansion in serum-containing medium and their adherence, from several tissues, such as bone marrow, amniotic fluid, peripheral blood, adipose tissue, dermis, articular synovium, compact bone, muscle and brain (Friedenstein et al., 1974; Pittenger et al., 1999; Zvaifler et al., 2000; Campagnoli et al., 2001; De Bari et al., 2001; Jiang et al., 2002a b; Zuk et al., 2002; De Ugarte et al., 2003; in 't Anker et al., 2003a,b; Javazon et al., 2004). The resident mesenchymal stem cells in adult tissues intervene in the repair and maintenance of injured tissues.

Bone marrow mesenchymal ASC

A rare cell within human bone marrow mesenchymal stem cell culture (multipotent adult progenitor cells or MAPCs) has been identified (Friedenstein, 1973; Owen and Friedenstein, 1988; Reyes et al., 2001, 2002). In general, bone marrow mesenchymal ASC 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 (Stewart et al., 1999; Walsh et al., 2000). These cells have the capacity to differentiate into mesenchymal lineage cells and, with appropriate environmental conditions, also into cells of different embryonic origin, such as cells with visceral mesoderm, neuroectoderm and endoderm characteristics - in other words, with high capacity of transdifferentiation and plasticity (Bianco and Gehron Robey, 2000; Jiang et al., 2002a,b, Tao and Ma, 2003; Abderrahim-Ferkoune et al., 2004; Ahdjoudj et al., 2004). Indeed, MAPCs may differentiate phenotypically into adipose, cartilage, bone,

vascular smooth muscle, skeletal and cardiac muscle, hepatocytes, neural elements and hematopoietic-supportive stromal cells (Friedenstein, 1973; Owen and Friedenstein, 1988; Bennett et al., 1991; Pereira et al., 1995, 1998; Ferrari et al., 1998; Takahashi et al., 1999; Dennis et al., 1999; Kopen et al., 1999; Lagasse et al., 2000; Orlic et al., 2001; Jiang et al., 2002a,b; Toma et al., 2002; Ahdjoudj et al., 2004; Pittenger and Martin, 2004; Mankani et al., 2006). Epidermal growth factor is considered as a candidate for *ex vivo* expansion of bone marrow-derived mesenchymal ASC (Tamana et al., 2006). Transcription factors, which regulate the expression of the differentiation genes of the aforementioned cells, intervene in this differentiation process. For example, C/EBP and PPAR γ families and other transcription factors intervene in adipocyte (Hicok et al., 1998; Ahdjoudj et al., 2001) and Cbfa1/Runx2 in osteocyte (Qi et al., 2003; Shui et al., 2003) differentiation. Likewise, 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 (Zhu et al., 2006). Other sections of this work describe the role of transplanted bone marrow cells in organ and solid tissue regeneration.

Peripheral blood monocytes as pluripotent stem cells

A human peripheral blood monocyte-derived subset with the appearance of fibroblasts has been highlighted as acting as pluripotent stem cells (Zhao et al., 2003; Romagnani et al., 2005). In this subset, monocyte and hematopoietic stem cell markers, such as CD45, CD34 and CD14, have been described. Indeed, a capacity of this peripheral monocyte subset has been shown to differentiate into macrophages by lipopolysaccharide, T-lymphocytes by IL-2, endothelial cells by vascular endothelial cell growth factor, epithelial cells by epidermal growth factor, neuronal cells by nerve growth factor and liver cells by hepatocyte growth factor. Monocytes/macrophages may acquire endothelial properties in angiogenic conditions (Schmeisser et al., 2001; Havemann et al., 2003; Rehman et al., 2003; Urbich et al., 2003; Nowak et al., 2004), and they have been observed organizing cell columns (tunneling) *in vitro* (Anghelina et al., 2006) and *in vivo* (Moldovan et al., 2000; Anghelina et al., 2002, 2004, 2006), suggesting that these cords could evolve into capillary-like structures (Moldovan, 2002; Moldovan and Asahara, 2003). Likewise, cells with both endothelial and monocyte markers have been demonstrated in tumors (Conejo-Garcia et al., 2005). Monocytes/macrophages may also contribute to the control and regulation of neovascularization (Bendeck, 2000; Anghelina et al., 2006), enabling the penetration of vascular progenitor cells via their tunneling activity (Anghelina et al., 2006).

Adipose AC

Adipose tissue contains mesenchymal ASC and committed adipogenic and vascular cells (Dixon-Shanies et al., 1975; Hausman and Martin, 1989; Ailhaud et al., 1992; Zuk et al., 2001, 2002; De Ugarte et al., 2003; Wickham et al., 2003; Rodriguez et al., 2004, 2005a,b; Fraser et al., 2006; Cho et al., 2006), with the capacity of adipogenic, chondrogenic, myogenic and osteogenic differentiation *in vitro* (Smas and Sul, 1993; Abderrahim-Ferkoune et al., 2004). The biology, multilineage differentiation ability, growth kinetics, gene transduction efficiency and cell senescence of multipotent adipose-derived stem cells are similar, although not identical to bone marrow mesenchymal stem cells, sharing the expression of Stro-1, CD90, CD44, SH3, and CD105. However, adipose ASC present CD49d and not CD45, CD31 or CD106, while bone marrow ASC show positivity for CD45, CD31 and CD106 and not for CD49d (De Ugarte et al., 2003; Fraser et al., 2006). An unresolved issue arises if there is a single ASC type or a heterogenous cell population with several committed progenitors in the adipose tissue. At present, multipotent and oligopotent cells have been demonstrated with the generation of clones of adipose ASC which express adipose, cartilage, bone and neuronal lineages (Zuk et al., 2002; Rodriguez et al., 2005a; Fraser et al., 2006; Guilak et al., 2006). In this way, adipose ASC or progenitor cells have been indicated with the capacity to differentiate into adipose (Deslex et al., 1987; Zuk et al., 2001, 2002; Rodriguez et al., 2004), cartilage (Erickson et al., 2002; Dragoo et al., 2003; Winter et al., 2003; Awad et al., 2004), bone (Zuk et al., 2001, 2002; Huang et al., 2002; Cowan et al., 2004; Hicok et al., 2004), endothelial (Miranville et al., 2004), hematopoietic (Cousin et al., 2003), skeletal (Mizuno et al., 2002; Rodriguez et al., 2005b; Bacou et al., 2004) and cardiac (Rangappa et al., 2003; Gaustad et al., 2004; Planat-Benard et al., 2004) muscle, hepatic (Seo et al., 2005), pancreatic endocrine (Timper et al., 2006) and neuronal (Safford et al., 2002; Ashjian et al., 2003; Kang et al., 2003) cells. The ASC in adipose tissue have an important potential for use in tissue-engineering, since adipose tissue is an abundant and easily procured source, enabling extraction of a voluminous quantity where, in addition, the frequency of these ASC, after removing adipocytes, is far greater than in bone marrow. Likewise, as with bone marrow mesenchymal cells, the adipose ASC are immunoprivileged (Rodriguez et al., 2005b), which is interesting for transplantation (Tse et al., 2003).

Vascular as cells

Blood vessel endothelial progenitors

Angiogenesis is the neovascularization or formation of new blood vessels from the established microcirculation by a process of sprouting from pre-existing vessels. Vasculogenesis 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 pre-existing endothelial cells or by the incorporation of angioblast-like endothelial precursor cells from the circulation.

Besides the inflammatory phenomena which occur prior to and during angiogenesis, the events classically described during capillary growth *in vivo* include (Díaz-Flores et al., 1994): a) EC and pericyte activation; b) degradation of the basal lamina of pre-existing vessels by EC (proteolytic destruction of the extracellular matrix); c) EC migration from pre-existing vessels towards the angiogenic stimulus; d) EC proliferation; e) migration and proliferation of pericytes from pre-existing vessels; f) formation of a new capillary vessel lumen (vascular tube formation); g) appearance of pericytes around the new capillaries (pericytes in angiogenesis); 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.

Precursors of endothelial cells have been described in bone marrow and peripheral blood (Watt et al., 1995; Peichev et al., 2000) with the possibility of contributing to new blood vessel formation (Rafii et al., 1994; Asahara et al., 1997; Nishikawa et al., 1998; Gehling et al., 2000; Lin et al., 2000; Quirici et al., 2001; Bagley et al., 2003). In this way, 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 (Reyes et al., 2002). Likewise, these cells can contribute to neoangiogenesis *in vivo* during wound healing and tumorigenesis (De Bont et al., 2001; Reyes et al., 2002). Thus, a higher population of endothelial precursor cells is associated with inflammatory breast tumors (Shirakawa et al., 2002).

Therefore, endothelial progenitor cells may contribute to support the integrity of the vascular endothelium by means of neoangiogenesis and rejuvenation of the endothelial monolayer (Asahara et al., 1997; Werner et al., 2003; Kong et al., 2004). Thus, undifferentiated progenitor cells may participate in vascular remodeling from the recipient to the graft in

heart transplants (Saiura et al., 2001; Shimizu et al., 2001; Sata et al., 2002), although this concept is currently a matter of intense debate, since there are discrepancies in the rates of chimerism in damaged vessels and hearts (Goodell et al., 1996; Jackson et al., 2001; Shimizu et al., 2001; Saiura et al., 2001; Laflamme et al., 2002; Quaini et al., 2002; Corbel et al., 2003). Indeed, some authors indicate that the majority of the cells in the vessel wall are recipient-derived after aortic allografts (Hillebrands et al., 2001; Shimizu et al., 2001; Hu et al., 2002a, 2003), cardiac transplantation (Hillebrands et al., 2001; Sata et al., 2002) or vein grafting (Hu et al., 2002b). On the contrary, minimal contribution from recipient cells has been described by other authors. Rezaei et al. (2005) report that endothelial repopulation by bone marrow-derived recipient cells is found to be an early event in transplanted allograft hearts, which decreased in frequency over time.

Two types of endothelial progenitor cells (EPC) in the peripheral blood have been recently described: the early EPCs (Asahara et al., 1997; Gulati et al., 2003; Hur et al., 2004; Yoon et al., 2005) or monocyte-derived circulating angiogenic cells (Rehman et al., 2003, 2004), and the late EPCs (Shi et al., 1998; Hur et al., 2004; Yoon et al., 2005) or outgrowth endothelial cells (OECs) (Gulati et al., 2003; Ingram et al., 2005). The early EPCs have a heterogeneous population, show early growth, express CD34, CD31, Flk-1, Tie-2, VE-cadherin, KDR, CD14, CD105, vWF, CD45, CD11c, CD163, VEGFR-2 (Asahara et al., 1997; Kalka et al., 2000; Assmus et al., 2002; Rehman et al., 2003; Gulati et al., 2003), are incapable of tube formation (Asahara et al., 1997; Gulati et al., 2003), produce VEGF, IL-8, HGF, G-CSF (Asahara et al., 1997; Murasawa et al., 2002) and low level nitric oxide, and have a good angiogenic potential (Asahara et al., 1997), although proliferative capacity is limited (Murasawa et al., 2002). The late EPCs or OECs have a homogenous population (Asahara et al., 1997), show late outgrowth (Asahara et al., 1997; Gulati et al., 2003; Ingram et al., 2005), express Flk-1, vWF, CD36, VE-Cadherin, CD31, VEGFR-2, Tie-2 (Gulati et al., 2003; Ingram et al., 2005), are capable of tube formation (Asahara et al., 1997; Gulati et al., 2003), have low level cytokine secretion (Asahara et al., 1997) and high level nitric oxide production (Asahara et al., 1997; Gulati et al., 2003), and also have a good angiogenic potential (Asahara et al., 1997) with highly proliferative capacity (Lin et al., 2000). The early EPCs predominantly originate from CD14+ precursors, while the OECs come from a CD14- population of cells (Gulati et al., 2003).

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 (Werner et al., 2005). Likewise, there may be a higher presence of restenosis when the circulating endothelial progenitor cells decrease (George et al., 2003). Furthermore, the numbers of circulating CD34+ and CD133+KDR+ endothelial progenitor cells increase after acute myocardial infarction (Shintani et al., 2001), and there is impaired

function of progenitor cells in patients with congestive heart failure (Heeschen et al., 2004).

Lymphatic endothelial ASC

According to the authors, newly-formed lymphatic vessels originate from pre-existing lymphatic endothelial cells (He et al., 2004) and/or from bone marrow-derived circulating endothelial precursor cells (Religa et al., 2005). Indeed, it has been demonstrated that the lymphatic sprouts are produced by the local lymphatic network during tumor lymphangiogenesis, with little if any incorporation of bone marrow-derived endothelial progenitor cells (He et al., 2004). On the contrary, in a corneal lymphangiogenesis model of irradiated mice and in tumoral lymphangiogenesis, Religa et al., (2005) have shown that bone marrow-derived circulating endothelial precursor cells, expressing CD133/CD34, VEGFR-2 and VEGFR-3, may play a role in lymphangiogenesis and might also be involved in tumor lymphangiogenesis and participate in lymphatic metastasis.

Pericytes as ASC and pericyte precursor cells

It has been suggested that perivascular cells (pericytes, adventitial or Rouget cells) (Rouget, 1873; Zimmermann, 1923) retaining considerable mesenchymal potentiality may have the capacity to differentiate into other cell types (Fig. 6), such as fibroblasts (Ross et al., 1970; Farrington-Rock et al., 2004), chondroblasts (Díaz-Flores et al., 1988), osteoblasts (Takahashi and Urist, 1986; Schor et al., 1990; Díaz-Flores et al., 1992; Collet and Canfield, 2005), preadipocytes (Richardson et al., 1982; Farrington-Rock et al., 2004) vascular smooth muscle cells and myointimal cells (Movat and Fernando, 1964; Díaz-Flores and Domínguez, 1985). Likewise, some authors consider pericytes as the progenitor cells of several pseudosarcomatous soft tissue lesions (Díaz-Flores et al., 1989), malignant fibrous histiocytoma (Iwasaki et al., 1987) and mixoid liposarcoma (Bolen and Thorning, 1980). Pericytes and endothelial precursor cells are also important participants among the many cells that give rise to progressing malignant disease (Bagley et al., 2005). Recently, pericytes have been considered as having the capacity for differentiation into mesenchymal cell lineages (Brachvogel et al., 2005). Indeed, cells specifically expressing known markers of pericytes also express markers characteristic for stem cell population (Brachvogel et al., 2005). Pericytes and vascular smooth muscle cells of testicular blood vessels have been considered as the progenitors of testosterone-producing Leydig cells (Davidoff 2004). Indeed, during Leydig cell regeneration, after their experimental elimination, pericytes and vascular smooth muscle cells, expressing nestin, undergo pronounced cell division activity.

There is controversy about pericyte and endothelial origin from bone marrow cells. Using neovascularization models, several authors point out that bone marrow-

derived precursors give rise to endothelial cells (Asahara et al., 1999; Asahara and Isner, 2002; Shirakawa et al., 2002; Asahara, 2003; Asahara and Kawamoto, 2004), while others have proposed that bone marrow precursor cells only develop pericytes but not endothelial cells (Rajantie et al., 2004; Ziegelhoeffer et al., 2004; Ozerdem et al., 2005). Recently, Ozerdem et al. (2005) have indicated 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. Likewise, using mouse chimera in brain repair after ischemia, Kokovay et al. (2006) observed two populations of bone marrow-derived cells: 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. 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 α and β receptors. When cocultured in collagen with isolated endothelial cells, their transformed into pericytes (Howson et al., 2005).

Synovial membrane ASC

Multipotent mesenchymal AS cells have been enzymatically released from the human synovial membrane, and their ability to proliferate and to differentiate into the chondrocyte, osteocyte and adipocyte lineage has been demonstrated (De Bari et al., 2001).

Myogenic progenitors in adult skeletal and cardiac muscle

Traditionally, satellite cells have been considered tissue specific stem cells in skeletal muscle (Mauro, 1961; Beauchamp et al., 1990, 2000). These cells, situated beneath the basal lamina of muscle fibres and therefore defined positionally as sublaminar cells (Fig. 7A), are mitotically quiescent in normal conditions. During regeneration, they can proliferate and originate myoblasts, which fuse and contribute to multinucleated myotube formation. Thus, these cells are functionally defined by their capacity of myogenic differentiation (Morgan and Partridge, 2003). Indeed, the satellite cells may renew themselves (Beauchamp et al., 1999) or may derive from cell precursors, although the latter have not been isolated. In recent years, it has been shown that cells derived from bone marrow can contribute to regenerating skeletal muscle (Ferrari et al., 1998;

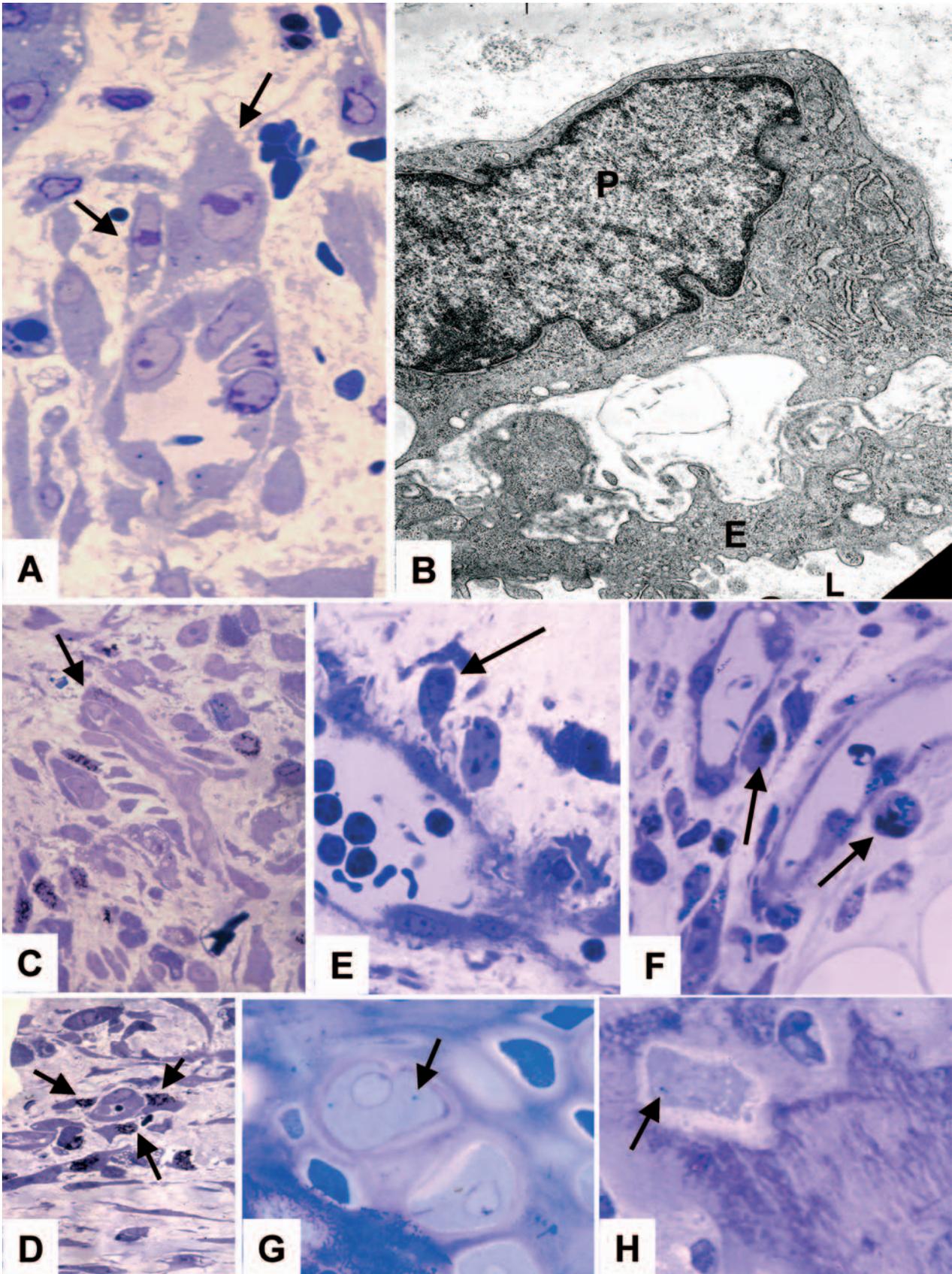


Fig. 6. A. Bulging and hypertrophied pericytes (arrows) in a postcapillary venule are observed after angiogenesis activation (Semithin sections, Toluidine blue, x 1,150). **B.** Transmission electron photomicrograph showing an “activated” pericyte (P) whose somatic volume was increased. E: endothelium; L: Lumen of postcapillary venule. (Uranyl acetate and lead citrate x 16.000). After chondrogenic and osteogenic stimulation, ^3H -labelled (**C,D**) and Monostral Blue labelled (**E,F**) activated pericytes (arrows) are shown. The Monostral Blue marker is subsequently present in chondrocytes (**G**, arrow) and osteoblasts (**H**, arrow) (Semithin sections, Toluidine blue, x 1,150)

Gussoni et al., 1999; LaBarge and Blau, 2002). Nevertheless, these studies have only demonstrated a low percentage of bone marrow-derived and hematopoietic stem cells-derived myofibres. In this way, Sherwood et al. (2004) pointed out that functional adult myogenic progenitors do not arise from hematopoietic or other bone marrow or circulating precursors. Indeed, although they confirmed the presence of bone marrow-derived cells located beneath the basal lamina in injured and regenerating smooth muscle, expressing some though not all satellite cell markers, they demonstrated that these cells displayed no intrinsic myogenicity. Human synovial membrane-derived mesenchymal ASC have been referred as having myogenic potential *in vitro* (De Bari et al., 2001) and with the capacity for skeletal muscle repair (De Bari et al., 2003).

In recent years, the possibility of regenerating contractile myocardial tissue by means of exogenous and resident cardiac regenerating cell transplantation has received much attention. Among these cardiac-regenerating cells are bone marrow ASC (Orlic et al., 2001; Strauer et al., 2002), mesenchymal ASC (Toma et al., 2002; Mangi et al., 2003), embryonic stem cells (Kehat et al., 2001; Laflamme et al., 2005; Menard et al., 2006) and intrinsic cardiac ASC (Beltrami et al., 2003 and Torella et al., 2006)

Nervous system ASC

Different neural stem cells and progenitor or precursor cells (Parker et al., 2005) have been considered in the adult central nervous system. Parker et al. (2005) have differentiated the concepts of stem cells and progenitor or precursor cells in the nervous system, comparing "neurogenesis" with "hematopoiesis". Indeed, a stem cell must meet the following conditions: multipotentiality, ability to populate or repopulate a neural region, capability of being serially transplanted, and capacity to produce daughter cells with identical properties and potential. On the contrary, a progenitor or precursor cell has a more restricted lineage commitment. In some regions of the adult brain, the generation of new neurons is evident (Seki and Arai, 1993; Kempermann and Gage, 1999; Temple and Alvarez-Buylla, 1999; Fuchs and Gould, 2000; Gage, 2000; Nottebohm, 2002; van Praag et al., 2002; Carleton et al., 2003; Schmidt-Hieber et al., 2004; Doetsch and Hen, 2005; Ming and Song, 2005). Thus, in the adult mammalian hippocampus, thousands of new granules are generated each day (Cameron and McKay, 2001). Likewise, the olfactory bulb presents a remarkable amount of neural turnover (Doetsch and Hen, 2005). As far as the hippocampus is concerned, the ASC niche that generates dentate gyrus granule neurons is in the subgranular zone, between the dentate gyrus itself and the hilus (Palmer et al., 2000; Seri et al., 2001), while the niche that originates granule and periglomerular neurons of the olfactory bulb is located in the subventricular zone (Fig. 7B), along the lateral wall of the lateral ventricle (Doetsch et al., 1997). Therefore, the cells born in the

subgranular zone require scant migration to reach the dentate gyrus, while cells located in the subventricular zone demand extensive migration through the rostral migratory stream to the olfactory bulb. The niche of the subgranular zone is constituted of astrocytes, immature dividing D cells and associated blood vessels (Palmer et al., 2000). In the subventricular zone, the niche shows neuroblasts, astrocytes, immature precursors and ependymal cells (Doetsch et al., 1997, Doetsch, 2003). An unexpected fact is that ASC show astrocyte characteristics (Doetsch et al., 1999; Laywell et al., 2000; Seri et al., 2001; Imura et al., 2003; Alvarez-Buylla 2004). A specialised basal lamina and a rich extracellular matrix are also present (Mercier et al., 2002; Doetsch, 2003), which, together with abundant cell-cell interactions, the closely associated vasculature and the growth factor signaling, form the regulatory system of the niche. In this way, they contribute morphogens and development signals, such as BMPs, Notch, Eph/ephins, Shh and Noggin. An enhanced synaptic plasticity has been described in the newly generated granule cells of the adult hippocampus (Schmidt-Hieber et al., 2004) and the newborn granule cells are tonically activated by ambient GABA before being sequentially innervated by GABA- and glutamate-mediated synaptic inputs (Ge et al., 2006), suggesting that newborn neurons may serve neuronal network activity through tonic and phasic GABA signals.

In the olfactory epithelium (Fig. 7C-G), progenitors of neurons and supporting cells, and human populations of mitotically active neural progenitors that form neurospheres *in vitro* have been described (Roisen et al., 2001; Winstead et al., 2005). This accessible location in the nasal cavity has been suggested to undertake autologous transplantation, providing populations for potential therapy after traumatic injury and neurodegenerative diseases (Marshall et al., 2006).

ASC and progenitor cells have been isolated from mammalian retina (for review, see Young, 2005) and epidermal growth factor is a neuronal differentiation factor for retinal ASC *in vitro* (Angenieux et al., 2006). After experimental transplantation, neural ASC have been shown transdifferentiating into myotubes (Galli et al., 2000) and hematopoietic cells (Bjornson et al., 1999).

Numerous studies *in vitro* and *in vivo* suggest that hematopoietic stem cells (HSC) can acquire neural cell fates (Eglitis and Mezey, 1997; Brazelton et al., 2000; Mezey et al., 2000, 2003; Sanchez-Ramos et al., 2000; Woodbury et al., 2000; Black and Woodbury, 2001; Priller et al., 2001; Kabos et al., 2002; Corti et al., 2002; Munoz-Elias et al., 2003, 2004; Takizawa, 2003; Torrente et al., 2002; Zhao et al., 2003; Cogle et al., 2004). On the contrary, recent observations (Massengale et al., 2005) question this hypothesis, suggesting that HSCs and their progeny maintain lineage fidelity in the brain and do not adopt neural cell fates, since the vast majority become microglia or exhibit other hematopoietic cell fates. Cuevas et al. (2002, 2004) point out that bone marrow stromal cells injected in a lesional

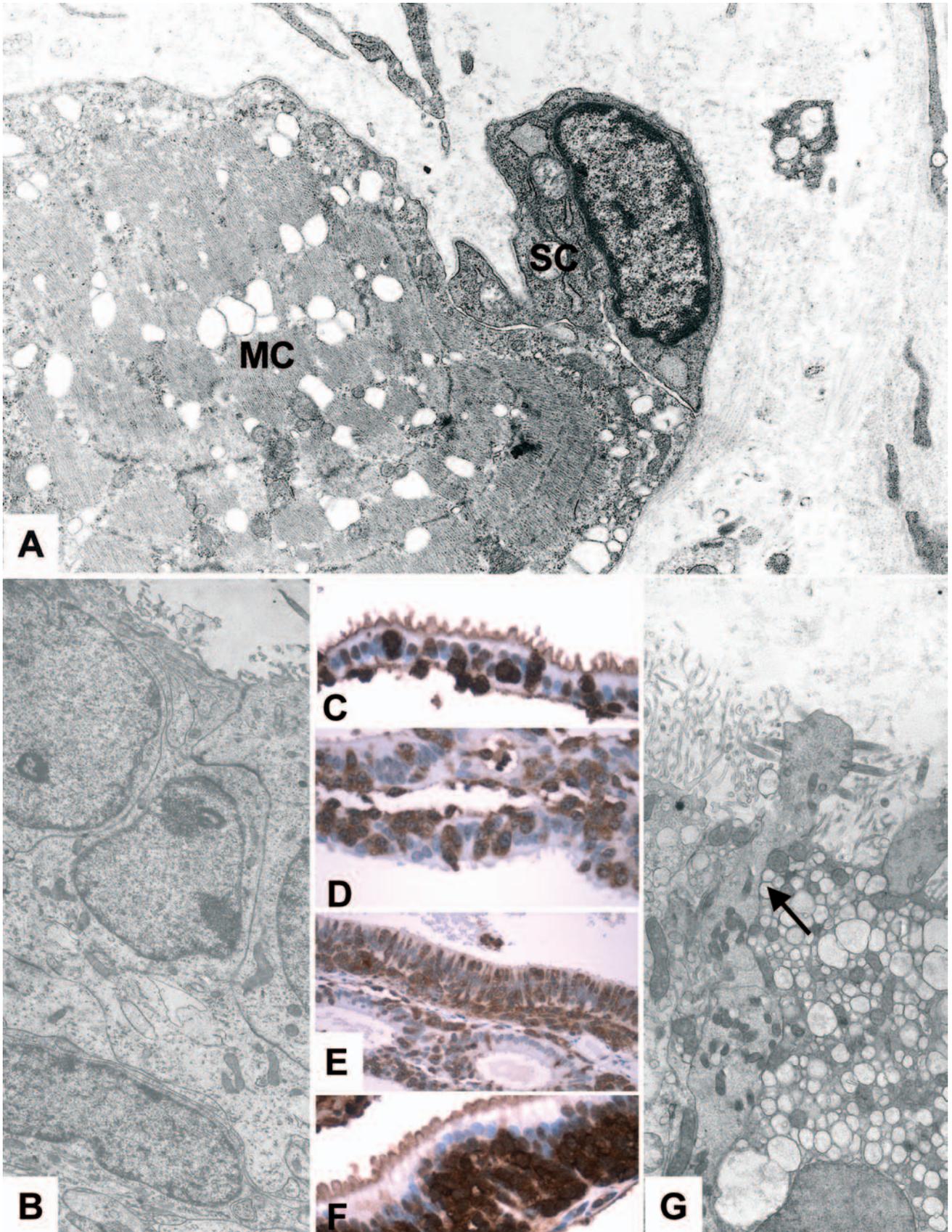


Fig. 7. Transmission electron photomicrographs showing a satellite cell (SC) situated beneath the basal lamina of a skeletal muscle cell (MC) (A) and a partial area of the subventricular zone in the nervous system (B) (Uranyl acetate and lead citrate x 10,000). Human basal cells, which give rise to the olfactory receptor cells, are observed in the olfactory epithelium next to a neuroblastoma, showing chromogranin and synaptophysin positivity (C-F, x 240 and x 120). Ultrastructural characteristics of the olfactory receptor cell (arrow) (G, x 10,000).

peripheral nerve can survive, migrate and differentiate into Schwann cells. Furthermore, they demonstrate a long-term efficacy. In this way, Keilhoff et al. (2006) confirm that bone marrow stromal cells may transdifferentiate into Schwann-like cells, and that their may benefit axonal regeneration after their implantation into a biogenic muscle graft to bridge a sciatic nerve gap.

Pituitary gland ASC

Recently, the presence of a small population of ASC has been demonstrated in mouse anterior pituitary, which may intervene in cell turnover and in regenerative processes (Chen et al., 2005).

Cancer ASC

Cancer stem cells are considered subpopulations of tumor cells with the capacity to form new tumors (Hamburger and Salmon, 1977; Miller et al., 2005; Soltysova et al., 2005; Zhang and Rosen, 2006). This cancer ASC hypothesis has been supported by an experimental study demonstrating that only a small proportion of human acute myeloid leukaemic cells were capable of transferring the leukaemia to immunodeficient mice and that these cells, with high self-renewal capacity, were stem cell CD34+ (Lapidot et al., 1994; Sutherland et al., 1996; Bonnet and Dick, 1997; Bonnet, 2005). Hematopoietic ASC through accumulated mutations and/or epigenetic changes could originate leukaemic ASC in which the self-renewal processes and the differentiation are not completely abolished. Nevertheless, it is also possible that transit-amplifying or differentiated cells may reacquire the self-renewal capacity (Brown et al., 1997; Cozzio et al., 2003; Jaiswal et al., 2003; Jamieson et al., 2004; Huntly et al., 2004; Weissman, 2005). Therefore, the cancer ASC could derive from transformation of ASC in the tissue of origin or from more committed progenitors (Cozzio et al., 2003; Huntly et al., 2004; Jamieson et al., 2004; Weissman, 2005). The ASC prolonged lifespan allows accumulation of genetic mutations and therefore predisposes the ASC to tumour formation (Morris, 2000). Zhang and Rosen (2006) have reviewed several properties shared by some ASC and cancer progenitor cells, pointed out by various authors. These properties include: a) negative regulation of both by the *Pten* tumor suppressor gene (Groszer et al., 2001); b) the fact that polycomb gene *Bmi1* is required for the maintenance of adult self-renewing hematopoietic stem cells; c) participation of signals that influence ASC quiescence and proliferation, such as mitogenic cytokines, WNT, Notch and Hh in cancer development (Beachy et al., 2004; Reya and Clevers, 2005); d) trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms, with a pivotal role of the stromal cell-derived factor CXC chemokine receptor 4 (Kucia et al., 2005); and e) Octamer 4 (Oct-4), a transcription factor, is expressed by immortalized human and cancer

stem cells. Several works have contributed evidence of the presence of neoplastic cells with stem cell properties, such as tumorigenic breast cancer cells (Al-Hajj et al., 2003), brain tumor initiating or stem cells (Singh et al., 2003, 2004), tumorigenic prostate cancer stem cells (Collins et al., 2005) and stem cells in lung cancer (Kim et al., 2005). For instance, in prostate cancer, it has been demonstrated that a small fraction of the total cells comprising the tumor, approximately 0.1%, express stem cell characteristics, CD44+ and CD33+. These cells self-renew, proliferate and differentiate to reacquire the phenotype of the tumor from which they were derived (Collins et al., 2005). In the genetic mutations that are associated with certain tumor development are those that contribute to the disruption of cellular differentiation by specific chromosomal translocations that give rise to fusion genes. In this way, pluripotent marrow-derived stromal cells have been considered as a likely candidate for the origin of Ewing tumors and EWS/ETS expression in these cells blocked differentiation along osteogenic and adipogenic lineages, in line with the undifferentiated appearance of Ewing tumors (Torchia et al., 2003). Recently, more data have been contributed to the development of Ewing's sarcoma from primary bone marrow-derived mesenchymal progenitor cells (Riggi et al., 2005). Indeed, bone marrow-derived mesenchymal progenitor cells display permissiveness for EWS-FLI-1 mediated transformation, which is the most common fusion that occurs in chromosomal translocations associated with Ewing family tumors, generating tumors that display hallmarks of Ewing's sarcoma. On the contrary, embryonic stem cells and spontaneously immortalized embryonic fibroblasts did not manifest permissiveness for EWS-FLI-1 mediated transformation (Riggi et al., 2005).

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