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Review

CD34+ stromal cells/fibroblasts/fibrocytes/ telocytes as a tissue reserve and a principal source of mesenchymal cells. Location, morphology, function and role in pathology

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Summary. We review the morphofunctional characteristics of CD34+ stromal fibroblastic/fibrocytic cells (CD34+ SFCs) and report our observations. We consider the following aspects of CD34+ SFCs: A) The confusing terms applied to this cell type, often combining the prefix CD34 with numerous names, including fibroblasts, fibrocytes, dendrocytes, keratocytes, telocytes and stromal, dendritic, adventitial, supraadventitial, perivascular, paravascular and delimiting cells; B) Changes in their immunophenotype, e.g., loss of CD34 expression and gain of other markers, such as those defining mesenchymal and derivate cells (myofibroblasts, osteoblasts, chondroblasts, adipocytes); C) Morphology (elongated or triangular cell body and thin, moniliform, bipolar or multipolar cytoplasmic processes), immunohistochemistry (co-expression of and changes in molecular expression) and structure (characteristics of nucleus and cytoplasmic organelles, and points of contact and junctions in quiescent and activated stages by light and electron microscopy); D) Location and distribution in the vessels (adventitia or external layer), in the tissues (connective, adipose, blood, muscle and nervous) and in the organs and systems (skin, oral cavity and oropharynx, respiratory, digestive, urinary, male, female, endocrine and lymphoid systems, serosal and synovial membranes, heart, eye and meninges); E) Origin from the mesoderm and cranial neural crest in the embryo, and from stem cells (themselves or other cells) and/or peripheral blood pluripotent stem cells (circulating progenitor cells) in post-natal life; F) Functions, such as synthesis of different molecules, progenitor of mesenchymal cells, immunomodulation, parenchymal regulation (growth, maturation and differentiation of adjacent cells), induction of angiogenesis, scaffolding support of other cells and phagocytic properties. Since CD34+ SFCs are the main reservoir of tissue mesenchymal cells (great mesenchymal potential, probably higher than that proposed for pericytes and other stromal cells), we dedicate a broad section to explain their *in vivo* behaviour during proliferation and differentiation in different physiologic and pathologic conditions, in addition to their characteristics in the human tissues of origin (adult stem cell niches); G) Involvement in pathological processes, e.g., repair (regeneration and repair through granulation tissue), fibrosis, tumour stroma formation and possible CD34+ SFC-derived tumours (e.g., solitary fibrous tumour, dermatofibrosarcoma protuberans, giant cell fibroblastoma, nuchal-type fibroma, mammary and extramammary myofibroblastoma, spindle and pleomorphic cell lipoma, and elastofibroma) and H) Clinical and therapeutic implications.

Key words: Microscopy, Immunohistochemistry, Origin

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Definition and approach

CD34+ stromal fibroblastic/fibrocytic cells (CD34+ SFCs) (CD34+ stromal cells, CD34+ fibroblasts, CD34+ fibrocytes, telocytes) are a subset of fibroblasts located

in both perivascular and stromal positions in the connective tissue of multiple anatomical sites. CD34+ SFCs display an oval nucleus and slender, elongated bi or multipolar processes and, in addition to having the general functions of fibroblasts, behave as native mesenchymal stem cell progenitors (after losing CD34 expression), regulate the growth, maturation and differentiation of adjacent cells, and participate in immunomodulation (Yamazaki and Eyden, 1995, 1996a,b, 1997; Nakayama et al., 2000; Cummings et al., 2001; Papadas et al., 2001; Barth et al., 2002 a-c; Lin and Lue, 2013).

Therefore, the prefix CD34+, in conjunction with the aforementioned terms and others coined by different authors (see the next section), is used for a specific type of connective tissue cell, whose terminology, characteristics, evolution, morphology, immunochemistry, structure, location, distribution, origin, functions (including its ability to self-renew and its multipotentiality, to which we will give particular attention) and participation in pathology will be outlined below.

Criticism of terminology, choosing a name and historical overview of CD34+SFCs

As we have seen above, authors have coined numerous names for these cells, leading to confusion. Indeed, in a review of this scenario, Barth and Westhoff (2007) opined that "*probably, the authors were unaware of the fact that the cell populations they investigated and described were identical*". Depending on cell characteristics, arrangement, location and derivatives, some names applied to CD34+ SFCs are as follows: CD34+ fibroblasts, CD34+ fibrocytes (including tissue resident CD34+ fibrocytes and circulating CD34+ cells or circulating fibrocytes), CD34+ dendritic cells (or CD34+ dendritic interstitial cells or dendrocytes), CD34+ spindle cells (or CD34+ spindle-shaped cells), interstitial Cajal-like cells, telocytes, CD34+ reticular network cells, adventitial cells (adventitial fibroblastic cells, adventitial progenitor cells, vascular stem cells), supraadventitial cells (supraadventitial adipose stromal cells - SA-ASC), perivascular cells (perivascular ancestors, perivascular multi-lineage progenitor cells, perivascular multipotent progenitor cells, vascular stem cells), paravascular cells, delimiting cells, keratocytes and adventitial stromal cell-like cells (ADSC). Moreover, there are several names for CD34+ tissue-precursors of mesenchymal stem cells (which lose CD34 expression in descendent cells). Most of these names are important, albeit disputed, and cannot be excluded, since they are currently in use. It is not our intention to add a new name but to summarize the most commonly used. We therefore refer to these cells as CD34+ stromal fibroblastic/fibrocytic cells (CD34+ SFCs). In any case, irrespective of the term used, the most important concept is that the prefix CD34+ followed by one of these names defines a specific subset of fibroblasts. Here, we develop this topic as an analysis of the terms used in the literature, thereby enabling us to offer a historical view of the authors and of the issues concerning these cells.

CD34+ fibroblast is a commonly used term (Yamazaki and Eyden, 1995, 1996b; Silverman and Tamsen, 1996, 1997, 1998a-c; Silverman and Dana, 1997; Streutker et al., 2003; Fisher, 2004; Yazhou et al., 2004; Kuroda et al., 2008; Epivatianos et al., 2008; Tardio and Granados, 2010). The generic name "fibroblast" has been criticized by several authors who consider "fibrocyte" to be more appropriate, since "blast" entails a progenitor capacity or an activated cell stage. This terminology is also applied to other differentiated mesenchymal cells, such as chondrocytes or osteocytes (Boor and Floege, 2012). However, CD34+ fibroblasts may pass to an activated stage (myofibroblasts) and may behave as adult stem/progenitor cells (see below). The term CD34+ fibroblast may therefore be used, as it refers to a subpopulation of quiescent-slow-cycling resident cells, with the ability to self-renew and to originate daughter cells. Similar behaviour occurs with other resident quiescent cells, such as endothelial cells (ECs), pericytes or vascular smooth muscle cells (SMC) (Díaz-Flores et al., 1994, 2009a).

The term CD34+ fibrocyte is also commonly used (Barth et al., 2002a-c; 2004, 2005a; Ramaswamy et al., 2003; Ebrahimsade et al., 2007; Barth and Westhoff, 2007; Nimphius et al., 2007; Wessel et al., 2008; Douglas et al., 2010; Frances et al., 2011; Mills et al., 2011; Smith et al., 2011). Nevertheless, it is equally applied to a circulating progenitor of fibroblasts and myofibroblasts (Boor and Floege, 2012), and it may be questioned for the same reasons outlined above. Indeed, Bucala et al. (1994) defined a new leukocyte subpopulation (CD34+), suggesting the name "fibrocyte" by analogy with other circulating cell types (leukocyte, monocyte and erythrocyte). Currently, the term "circulating fibrocyte" identifies circulating mesenchymal progenitors (Bucala et al., 1994; Zvaifler et al., 2000; Schmidt et al., 2003; Quan et al., 2004, 2006), which express the stem cell antigen CD34 and may enter sites of tissue injury and contribute to repair (Aiba and Tagami, 1997; Chesney et al., 1998; Abe et al., 2001; Hartlapp et al., 2001; Yang et al., 2002; Pilling et al., 2003, 2006; Direkze et al., 2004, 2006; Phillips et al., 2004; Postlethwaite et al., 2004; Strieter et al., 2007). Therefore, in order to avoid confusion, the name "tissue resident CD34+ fibrocyte" would be more accurate to distinguish it from "Bucala's circulating CD34+ fibrocyte" (see below). In any case, if we consider the blood as a tissue, circulating fibrocytes may also be included within the subject of this review.

The term "CD34+ stromal cell", initially simplified as stromal cell (Kirchmann et al., 1994; Lindenmayer and Miettinen, 1995), has also been frequently used (Yamazaki and Eyden 1995, 1996a,b, 1997; Pursley et al., 1998; Nakayama et al., 2000, 2001, 2002a,b; 2003; Sakai and Matsuyama, 2002; Toti et al., 2002; Kuroda et

al., 2004a-c, 2005a-c; Kojc et al., 2005). Though broad and non-specific, it encompasses all possible denominations. Moreover, authors often use this name to indicate tissue-precursors of mesenchymal stem cells, which is true for CD34+ SFCs.

The term "CD34+ dendritic (dendritic interstitial, dermal dendritic, stromal dendritic, dendrocyte) cell" (Regezi et al., 1992; Skobieranda and Helm, 1995; Narvaez et al., 1996; Koizumi et al., 1999; Ruelas Villavicencio et al., 1999; Camacho et al., 2001; Soma et al., 2001; Papadas et al., 2001; Batistatou et al., 2002; Garcia Muret et al., 2002; Ide et al., 2007; Erdag et al., 2008; Lambrechts et al., 2009; Petersson, 2011) has mainly been used in the skin (Erdag et al., 2008). In this location, at least two types of cells share the term dendritic: CD34+ dendritic cells (Nickoloff, 1991), which are the object of this study, and Factor XIIIa positive dendritic cells (Headington, 1986), which mainly function as antigen-presenting cells (Cerio et al., 1989; Nestle et al., 1993).

"CD34+ spindle cell" (CD34+ spindle-shaped cell) (Jimenez et al., 1994; Lindenmayer and Miettinen, 1995; Aiba and Tagami, 1997; Hayashi et al., 2001; Collins et al., 2002; Reis-Filho et al., 2002; Okon et al., 2003; McNiff et al., 2005; Imai et al., 2008; Olaleye et al., 2010) is a name that expresses the morphology of these cells in certain locations or in various lesions (e.g., in some spindle cell tumours).

Recently, the name telocyte (Popescu and Faussone-Pellegrini, 2010), formerly interstitial-like (Cajal-like) cells (Gherghiceanu and Popescu, 2005; Popescu et al., 2005, 2007; Popescu and Faussone-Pellegrini, 2010; Hinescu et al 2008), was coined to prevent further confusion with other interstitial/stromal cells (Popescu and Faussone-Pellegrini, 2010) and has been adopted by several laboratories. The name telocyte is appropriate and highly descriptive. It defines the distinctive prolongations in these cells that the authors refer to as telopodes, which adopt a branching pattern (dichotomous branching pattern) and a moniliform aspect, with dilated (podoms) and thin (podomeres) segments. These characteristics are shared with quiescent CD34+ SFCs in the connective tissue (Faussone-Pellegrini and Popescu, 2011; Díaz-Flores et al., 2013). Popescu et al's detailed description of these cells in different anatomical sites is particularly interesting (For review, see Popescu and Faussone-Pellegrini et al., 2010; Faussone-Pellegrini and Popescu, 2011, and for details, visit www.telocytes.com).

Adventitial cells (adventitial fibroblastic cells, adventitial progenitor cells, vascular stem cells) refer to fibroblasts (fibroblastic cells) in the outermost connective tissue layer (adventitia) of the vessels (Sartore et al., 2001; Stenmark et al., 2002; Hu et al., 2004; Nakayama et al., 2004a,b; Torsney et al., 2005; Mallawaarachchi et al., 2006; Xu et al., 2007a,b; Hoshino et al., 2008; Lin and Lue, 2013) and is a term commonly used to highlight their role as progenitor cells. Currently, these cells are considered CD34+ cells, that is, CD34+ SFCs.

Delimiting fibroblast was formerly used in some tissues and organs (e.g., breast and skin) to describe fibroblasts located on the periphery of glands and vessels (as occurs for adventitial cells) (Ozzello, 1970, 1974; Stirling and Chandler, 1976; Eyden et al., 1986). In these locations stromal cells have been described as being most abundant (see below). As in the vessels, expression of CD34 has also been demonstrated in delimiting cells in glands.

The term perivascular cell includes pericytes/vascular smooth muscle cells and fibroblasts. There is no terminological confusion between CD34+ SFCs and vascular smooth muscle cells, but pericytes and perivascular fibroblasts (CD34+ SFCs) have been frequently assigned the same names, such as perivascular cells, adventitial cells, mural cells, pericapillary cells, periendothelial cells, undifferentiated cells and deep cells (Rouget, 1873; Krogh, 1919, 1929; Zimmermann, 1923; Farquhar and Hartmann, 1957; Battig and Low, 1961; Cogan and Kuwabara, 1967; Kuwabara and Cogan, 1963; Ashton and De Oliveira, 1966). This confusion extends to some pathologic processes. Thus, in 1942, Stout and Murray postulated a pericytic origin for a type of tumour, which they named haemangiopericytoma. This criterion was followed by many authors for a considerable time. Currently, conceptual changes have included most cases of haemangiopericytoma as solitary fibrous tumours, with a CD34+ fibroblastic (CD34+ SFCs) origin (Suster et al., 1995; Mentzel et al., 1997; Nielsen et al., 1997; Vallat-Decouvelaere, 1998; Brunnemann et al., 1999).

CD34+ keratocyte (Espana et al., 2004) is an example of a name for CD34+ SFCs in a specific location. Indeed, the term keratocyte has traditionally been used for corneal stromal cells.

The term CD34+ reticular network cells has been used for describing a reticulum composed largely of CD34+ "undifferentiated smooth-muscle cells" (in the Fallopian tube in combination with mononuclear cells), suggesting participation in immune surveillance (Yamazaki and Eyden, 1996b).

Recently, native CD34+ SFCs have been considered as tissue-precursors of mesenchymal stromal cells, which lose CD34 expression. These native cells have been given much attention (e.g., for tissue engineering) and different denominations, depending on the original tissue, post-isolation interval and culture passages (e.g., freshly isolated human adipose tissue-derived stromal vascular fraction cells and stromal cells from lipoaspirate, adventitial stromal cell-like cells-ADSCs, adipose derived stromal cells or adherent stromal/stem cell population-ASCs).

Characteristics, expression, and loss and gain of defining molecule CD34 in CD34+ SFCs (phenotype changes)

CD34 is a 110 KDa transmembrane cell surface

glycoprotein encoded by a gene located on chromosome 1 (Molgaard et al., 1989) (in region 1q 32 of chromosome 1). The CD34 family of cell-surface transmembrane protein comprises podocalyxin (hematopoietic progenitor cell antigen CD34), thrombomucin and endoglycan, which have an O-glycosylated and sialylated extracellular domain, characterizing them as a subfamily of the sialomucins. CD34 is expressed in hematopoietic progenitor cells of myeloid and lymphoid lineage (Civin et al., 1984), endothelial cells (Fina et al., 1990) and stromal cells in several organs (Van de Rijn et al., 1994). It is also described in mast cells, eosinophils, muscle satellite cells, hair follicle stem cells and neurons (Nielsen and McNagny, 2008). The potential functions of the CD34 family include enhancing proliferation (replicative capacity) and blocking differentiation of stem or progenitor cells (maintenance of the undifferentiated progenitor/stem-cell phenotype - immaturity or stemness of the cell - Krause et al., 1996; Suga et al., 2009), promoting or blocking cellular adhesion (e.g., lymphocyte adhesion to vascular endothelium in lymphoid tissue), trafficking of hematopoietic cells and cell morphogenesis (For review, see Lanza et al., 2001; Nielsen and McNagny, 2008).

As mentioned above, the phenotype and abilities of cells, including CD34 expression, may vary between *in vitro* and *in vivo* settings (Espana et al., 2004; Sengenes et al., 2005; Mitchell et al., 2006; Suga et al., 2009; Tarnok et al., 2010; Braun et al., 2013; Lin et al., 2013; Zimmerlin et al., 2013), as well as in some physiological or pathological processes *in vivo* or during *in vitro* passages. Thus, some authors pointed out that CD34 is a sometimes-on-sometimes-off molecule (Lin et al., 2013). The differences *in vitro* depend on the stages of isolation, passage and culture conditions (Sengenes et al., 2005; Traktuev et al., 2006; Lin et al., 2008; Suga et al., 2009; Tarnok et al., 2010; Braun et al., 2013; Zimmerlin et al., 2013). For example, between freshly isolated human adipose tissue-derived stromal vascular fraction cells in relation to serial-passaged adipose-derived stem cells (Sengenes et al., 2005; Mitchell et al., 2006; Traktuev et al., 2006; Suga et al., 2009; Tarnok et al., 2010; Lin et al., 2008; Maumus et al., 2011; Braun et al., 2013; Zimmerlin et al., 2013). The immuno-phenotype differences include progressive loss of CD34 expression with cell cycling (negatively correlated with cell expansion *in vitro*) (Fina et al., 1990; Delia et al., 1993; Maumus et al., 2011), occurring at peak levels in the adipose tissue-derived stromal fraction cells and early passage, and very reduced levels throughout the culture period (Mitchell et al., 2006). Thus, Maumus et al. (2011) pointed out that the heterogenous cell population in adipose tissue stromal vascular fraction included CD45+ leukocytes (about 30%) and a population of CD34+/CD45- cells (about 40%). In the initial adhesion phase (day 2), the CD34+ leukocyte population decreased with a concomitant increase of cells expressing CD34 (80%), as well as CD73 and CD13 (standard mesenchymal stromal cell markers). When CD34+ cells were cultured in α-MEM medium supplemented with fetal calf serum (10%), as cell numbers increased (from day 4 onwards), the quantity of CD34+ cells and the expression of CD34 protein diminished. Likewise, the expression of CD13, CD29, CD73 and CD90 increased. Recently, Braun et al., 2013 have demonstrated that, by day 4 of culture, a CD34+, CD146 negative, CD31 negative adventitial stromal cell subset obtained from the adipose tissue stromal vascular fraction upregulated CD105, CD146 and CD271, and downregulated CD34. Therefore, after processing lipoaspirates, the adherent fibroblastoid cell population (adipose-derived stem cells) only expresses CD34 at early passages (Bassi et al., 2012). Conversely, CD34 expression can be maintained under adipogenic culture conditions (Sengenes et al., 2005). *In vivo*, CD34+ expression can also be changed. Thus, in repair and in some invasive epithelial tumours, stromal cell remodelling occurs with loss of CD34 expression (loss of CD34+ stromal cells) and subsequent gain of αSMA expression (gain of myofibroblasts) (Barth et al., 2002a,b; 2004, 2005a,b; Barth and Westhoff, 2007) (See below).

These temporal changes in the immunophenotype explain the following circumstances: a) that the criteria established to define cultured multipotent mesenchymal stem cells include nonexpression of CD34 (Dominici et al., 2006 – see below), when the cells are CD34+ in the tissue of origin, b) that CD34+ cells obtained from different tissues were considered CD34 negative and c) that the characterizations of the CD34+ stromal cell-derived population vary according to laboratory.

Morphology, immunohistochemistry and structure of CD34+ SFCs

Morphology

In histological sections, CD34+ SFCs show a cellular body (nuclear or somatic region) and thin, bipolar (spindle-shaped) or multipolar (dendritic-like) cytoplasmic processes (Fig. 1). The cellular body presents either elongated or triangular morphology and contains an elongated, ovoid and creased nucleus (Fig. 1D), and a thin layer of cytoplasm (somatic cytoplasm). The cytoplasmic processes communicate with those of neighbouring CD34+ SFCs (Fig. 2). They are initially thin, may bifurcate, occasionally overlap (forming a labyrinthine system) and have a moniliform (thin segments and dilated portions) or hooked (hooks that partially envelope extracellular matrix components) aspect (Figs. 1, 2A,B). Regardless of the fusiform or dendritic morphology, CD34+ SFCs are flat cells (lamellar or velamentous cells), with their planes arranged on one or several axes, so that, in profile, their cell body and processes appear very thin (they can be as thin as 480Å and not ordinarily visible under light microscopy – Ozzello, 1970). In random sections, the

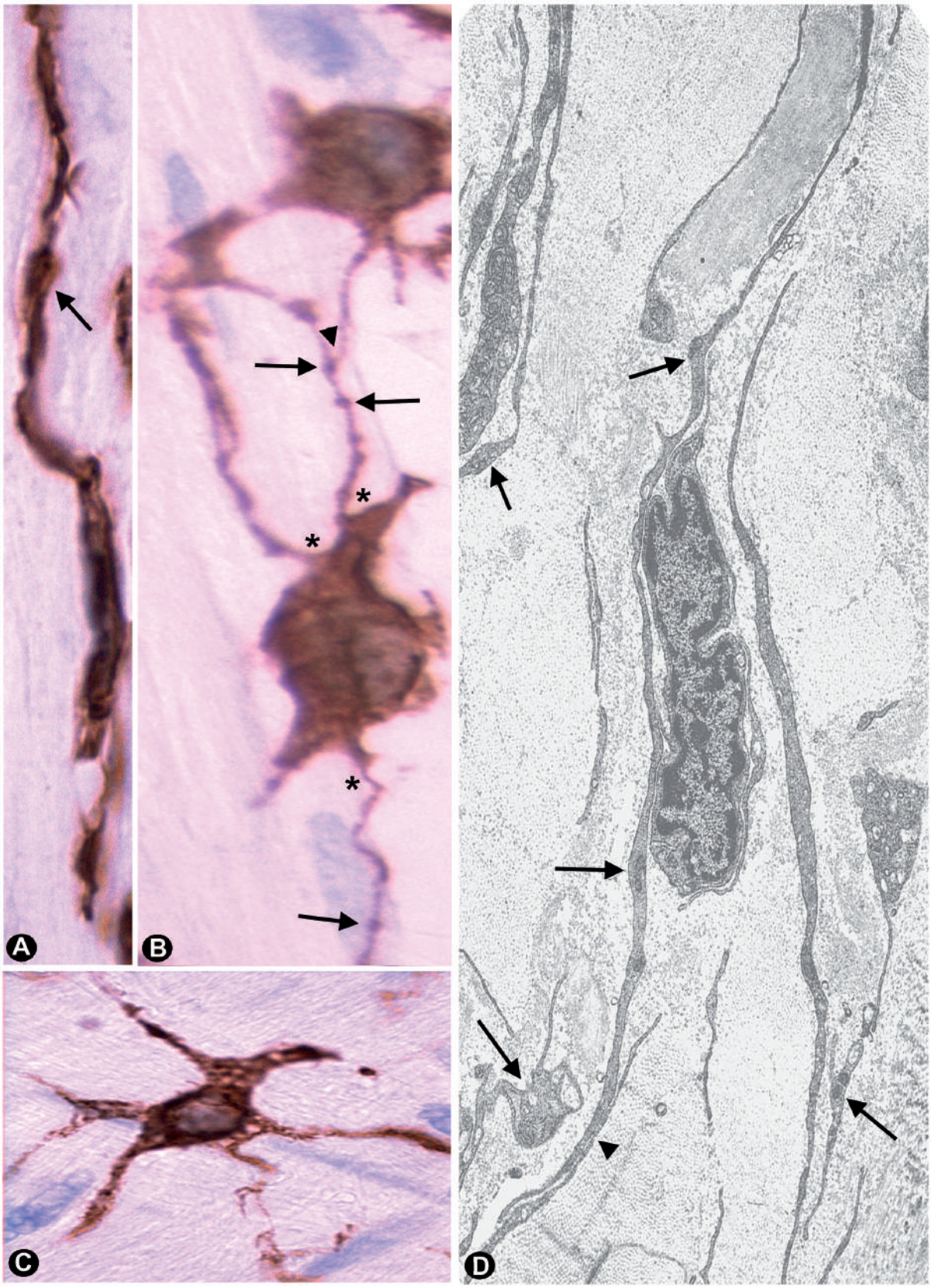

Fig. 1. Morphology and ultrastructural characteristics of CD34+ SFCs. Features of telocytes, with bipolar **(A)** or multipolar **(B and C)** cytoplasmic processes (telopodes) are observed. The cytoplasmic processes are initially thin (**B**, asterisks), communicate with those of neighbouring CD34+ SFCs (**B and D**, arrowhead) and have a moniliform aspect (thin segments-podomers- and dilated portions –podoms; **A, B and D**, arrows). The nucleus is indented, showing patches of heterochromatin near the nuclear membrane **(D)**. A, B, C, x 680; D, Uranyl acetate and lead citrate, x 12,000

flat surface of the cell will only be fully observed in the exceptional case of its orientation coinciding with the section plane (Fig. 2C,D). CD34+ stromal cells tend to be arranged in close proximity to collagen fibre bundles. The description of particular morphology and arrangement of CD34+ SFCs will be more extensive in the sections describing location, distribution and pathology.

Immunohistochemistry

By definition these cells are CD34+, enabling us to demonstrate the morphology outlined above (Figs 1, 2), although they may temporarily downregulate this marker (changes of expression - see above). CD34+ SFCs also express or can change (acquiring or losing) expression of vimentin, CD10, bcl2, CD117, CD99, EMA, S100 protein, desmin and cytokeratins (Chilosi et al., 1997; Suster et al., 1998b; Moore and Lee, 2001). The co-expression and changes of expression are variable, depending on cell regulation according to CD34+ SFC location, temporal activity and participation in pathological processes. For example, we have observed that, among other markers, CD34+ SFCs also express CD10 in vocal folds (Fig. 3A) (Díaz-Flores et al., 2014) and in neuromuscular spindles, and S100 protein and bcl2 in the papillae of hair follicles (unpublished observations; see CD34+ SFCs in the skin). Co-expression differences are very marked in soft tissue tumours expressing CD34 (see below). Examples of changes in the expression of the markers in CD34+ SFCs are the phenomena during repair and stromal tumour formation, in which these cells can downregulate CD34 and acquire expression of αSMA, with myofibroblast differentiation (Fig. 3B-D).

Structure

Semithin and ultrathin sections of non-activated SFCs reveal general characteristics typical of native, quiescent, fixed cells of connective tissue (Figs. 1D, 3). The major modifications of these cells when activated will be outlined in the next section. An extensive description of the ultrastructure of these quiescent cells has been undertaken in different anatomical sites, using the term "telocytes" (see Popescu et al., www.telocytes.com). As we have seen above, the nucleus is often slightly indented and relatively large in relation to the small content of cytoplasm in the cell body, showing patches of heterochromatin, particularly near the nuclear membrane (Figs. 1D, 4B). The nucleolus is inconspicuous; mitoses are only present in activated cells.

In the somatic body, there is a thin cytoplasmic layer, which contains polysomes, scarce cisternae of rough and smooth endoplasmic reticulum, few mitochondria, a small Golgi apparatus and centrioles. In the processes, the cytoplasm has few organelles, which slightly increase in number in the dilated portions, wherein mitochondria, endoplasmic reticulum and some caveolae may be observed (Fig. 1E). The narrow emergence from the cellular body and the networks of processes as a result of overlapping is also observed under electron microscopy (Fig. 4B,C) (Popescu et al., 2011). Points of contact and junctions are present between the processes (named small dense structures, manubria adherentia and puncta adherentia – Popescu et al., 2011) and the cellular surfaces have no basement membrane (Figs. 1B, 4B,C). The changes in CD34+ SFCs when activated will be outlined below.

Location and distribution of CD34+ SFCs

General considerations

The connective tissue of different anatomical sites harbours scattered CD34+ SFCs (Barth and Westhoff et al., 2007), which have been reported in capsules, septa, fibrous tracts and interstitial reticular networks. The distribution and characteristics of CD34+ SFCs depend on connective tissue components and location. Thus, the highest number of CD34+ SFCs is observed in the periphery of vessels (the main cellular constituent of the vessel adventitia) and around glands, nerves and skin annexes. For example, surrounding mammary acini (Yamazaki and Eyden, 1995), salivary gland acini (Yamazaki and Eyden, 1996b), thyroid follicles (Yamazaki and Eyden, 1997), hair follicles (Nickoloff, 1991), sweat glands (Narvaez et al., 1996), and endocervical and deep endometrial glands of the uterus (Lindenmayer and Miettinen, 1995). Conversely, CD34+ SFCs are not observed in some connective tissue areas, in which the delimiting cells of small vessels and glands are not CD34+ SFCs (e.g., lamina propria of the intestinal mucosa, in which there are only myofibroblasts). Likewise, CD34+ SFCs may be the only cell component of a fibroblast/myofibroblastic population in a specific location (e.g., in the intestinal submucosa) or may be associated with another subset of fibroblasts/myofibroblasts (e.g., epineurium, testicular capsule, etc, in which CD34+ SFCs are associated with αSMA+ myofibroblasts). Below, we consider the location and distribution of CD34+ SFCs in the vessels, in the tissues (including the blood as a tissue), and briefly in the organs and systems, which will enable us to understand and develop the origin and role of these cells.

CD34+ SFCs in vessels and vascular connective tissue

The cells in the vessel wall are endothelial cells (intimal layer), pericytes/smooth muscle cells (medial layer) and fibroblasts (adventitial or external layer). The major fibroblastic cell components are CD34+ SFCs, which concentrate and form the CD34-stained vascular adventitial layer of arteries and veins (these adventitial cells are considered MSC progenitors, typified as CD34+, CD31-, CD146-, CD45- — Corselli et al., 2012.

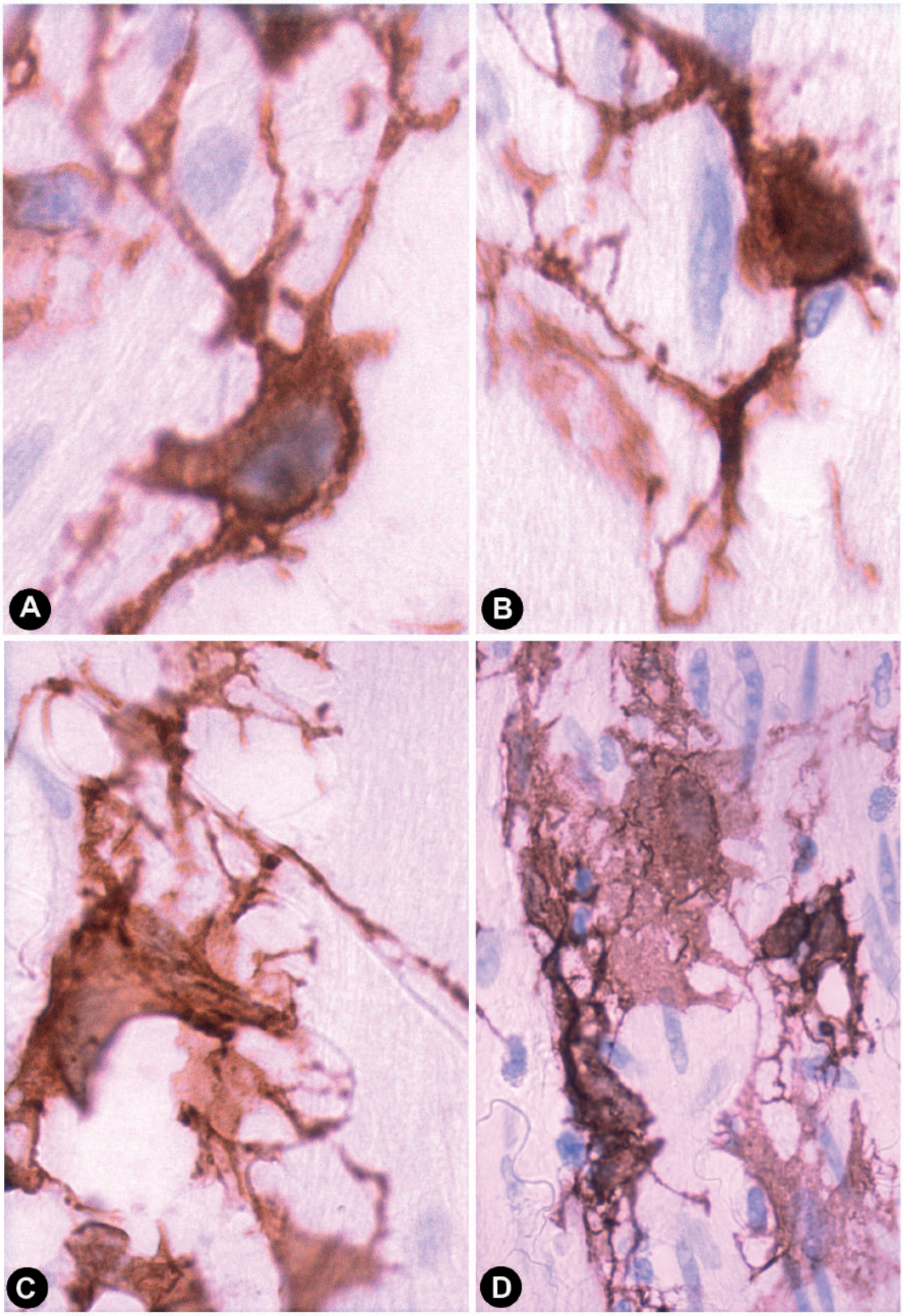

Fig. 2. CD34+ SFCs. The cytoplasmic processes communicate with those of neighbouring CD34+ SFCs, showing a moniliform aspect. The flat surface of these cells is only demonstrated when the orientation of this flat surface coincides with the section plane **(C and D)**, x 680

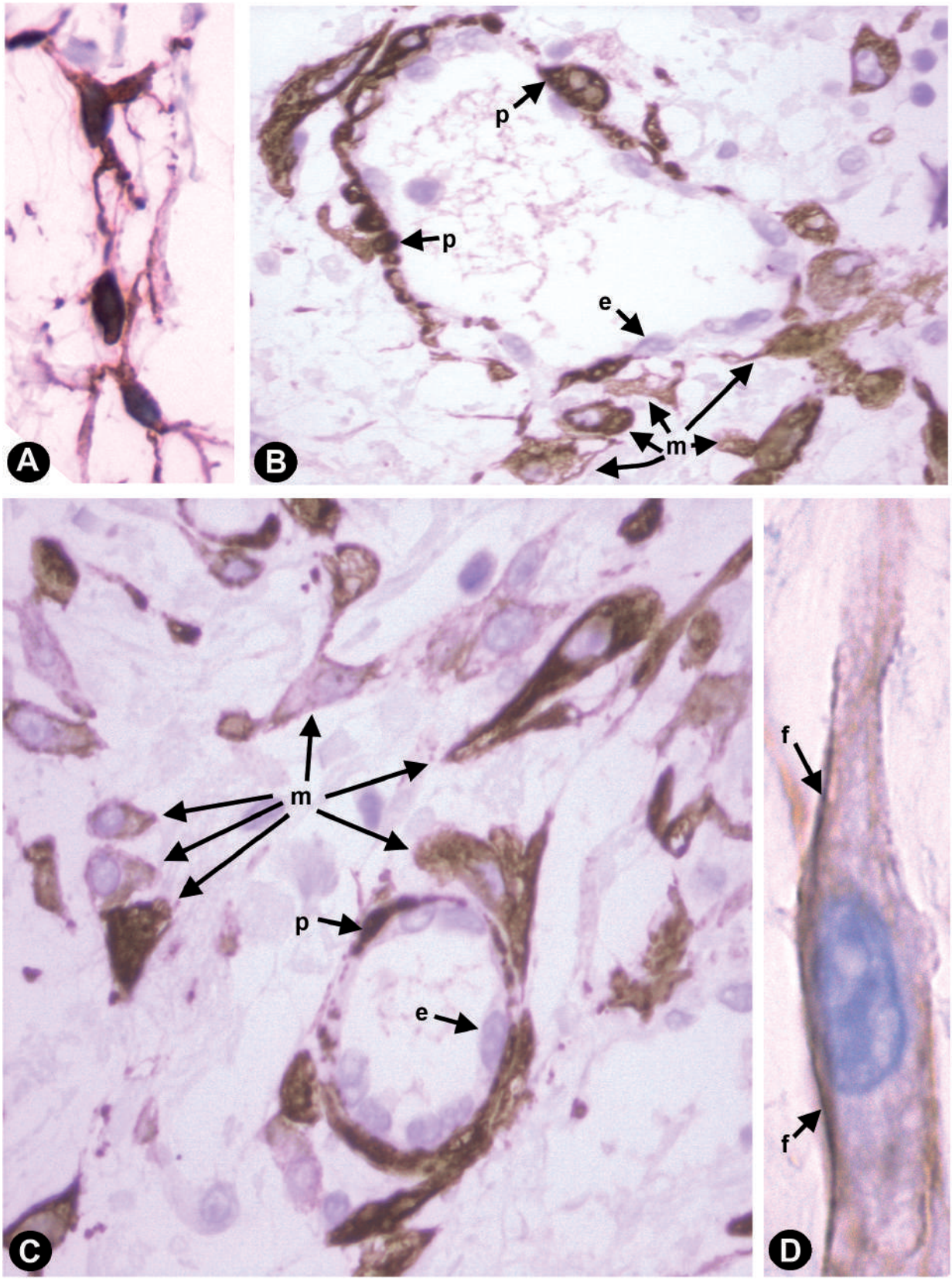

Fig. 3. Immunohistochemical co-expression and changes of expression of CD34+ SFCs. CD34+ SFCs expressing CD10 in vocal folds **(A)**. Changes of expression of CD34+ SFCs around vessels during repair with downregulation of CD34 and expression of αSMA (myofibroblast differentiation) **(B-D)**. e: endothelial cells, p: pericytes, m: myofibroblasts. A, CD10 staining. B, C and D, αSMA staining. A, B and C, x 320; D, x 680

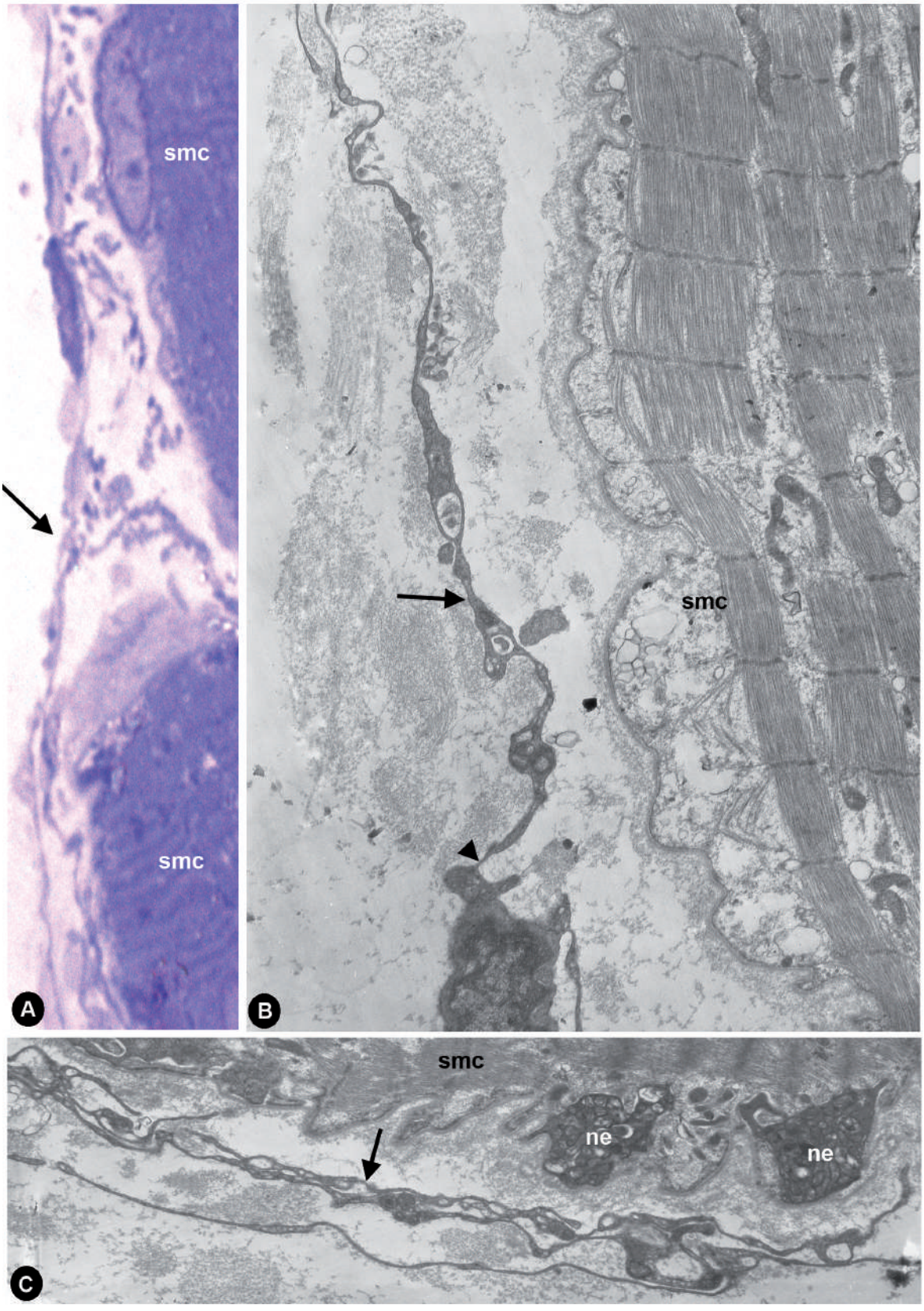

Fig. 4. Characteristics of non-activated SFCs in semithin **(A)** and ultrathin **(B and C)** sections, with features of telocytes bordering closely intrafusal striated muscle cells (smc) of neuromuscular spindles. Thin moniliform processes (telopodes) (arrows) with narrow emergence from the cellular body (arrowhead) are observed. Occasionally overlapping processes (probably belonging to different telocytes) are present (**C**, arrow). Nerve endings: ne. A, Toluidine blue, x 720; B, C, Uranyl acetate and lead citrate, x 20,000

See T*he adventitia of the large and medium sized vessel as a stem cell niche)*, and of the microcirculation of some regions (Fig. 5A-C). Some authors point out that the microcirculation does not contain adventitial CD34+ fibroblasts (they consider the co-existence of two separate perivascular mesenchymal stem cell progenitors: pericytes in microvessels and adventitial cells around larger vessels). However, CD34+ SFCs extend continuously through most of the vascular system (therefore, a very thin rudimentary adventitia is found in several microvessels) (Fig. 5A-C) (CD34+, CD31-, SMA-, CD140b- vascular stem cells of Lin and Lue, 2013) except for some small vessels in certain locations. Examples of microvessels with adventitial CD34+ SFCs are those of the reticular dermis and submucosa, muscular propria and serosa of the intestinal wall (Fig. 5D,E), and examples of microvessels without CD34+ fibroblasts are those of the papillary dermis and the intestinal mucosa (Fig. 5F). The presence of these "delimiting fibroblasts" around small vessels is easily demonstrated by electron microscopy (Fig. 5G). In the adventitia of large vessels, CD34+ SFCs appear in several layers (Fig. 5A), which decrease in number as vessel size reduces (Figs. 5B,C). In the capillaries, they are arranged in a single layer (Figs. 5C,E,G). Although CD34 is also intensely expressed in endothelial cells, both types of cells (ECs and CD34+ SFCs) are easily distinguished by this different response to CD31 (anti-CD31 stains endothelial cells but not CD34+ SFCs), and by their characteristics and respective locations in the vessel wall. Pericytes and SMCs are positive for anti-αSMA and negative for anti-CD34. Since CD34 is expressed in fibroblasts of the adventitia and in ECs of the tunica intima, the CD34-stained vessels show a double ring appearance (endothelium- and adventitia-stained), owing to two concentric circles “sandwiching” the unstained media layer (smooth muscle or pericytic layer) (Pusztaszeri et al., 2006; Lin et al., 2008, 2010) (Fig. 5A-F). Some CD34+ SFCs in the vascular wall may extend their processes into surrounding tissues and vice versa (Fig. 6A-C). Frequently these extensions associate with other tissue cells (native or recruited) (Fig. 6A-C).

CD34+ SFCs in the interstitium of the vascular connective tissue vary in number and morphology (e.g., fusiform or stellate). In the following sections, these particular characteristics will be outlined in different normal tissues and organs, and in pathology.

CD34+ SFCs in the adipose tissue

In adipose tissue, CD34+ SFCs appear widely distributed, without expressing pericytic markers (Maumus et al., 2011), and form a well-organized delicate network that surrounds lobes and lobules, predominantly in an annular fashion around the vasculature (in the adventitia) (Fig. 6D,E), and extends alongside adipocytes and their microvascularization (Fig. 6F-H) (Lin et al., 2008). CD34+ SFC cytoplasmic bodies and processes are closely associated with microvessels and adipocytes, and the attenuated portion of cytoplasm of the processes is not ordinarily visible in H&E stained sections. However, it can be observed in anti-CD34 stained sections, in semithin sections or by electron microscopy (Fig. 6F-H). Therefore, in normal white adipose tissue, the resident cells, excluding adipocytes, leukocytes or some cells of peripheral nerves, can be classified as follows: CD34+ SFCs (CD34+, CD31-ßαSMA-), blood vessel endothelial cells (CD34+, CD31+, αSMA-), lymphatic vessel endothelial cells (CD34-, CD31+, αSMA-) and pericytes/vascular SMCs (CD34-, CD31-, αSMA+). A freshly isolated fraction may be obtained by mechanical and enzymatic digestion of the adipose tissue (Zuk et al., 2001; Zimmerlin et al., 2010). This fraction is called adipose tissue-derived vascular stromal fraction (SVF), which contains a heterogeneous population, including adipose-derived stromal cells (ASCs) (Zuk et al., 2002; Gimble et al., 2007). Numerous authors have studied the immunophenotype of the different cell components of this stromal vascular fraction. These cell components have been separated and classified using varied terminology. Thus, Li et al., 2011, obtained four cell populations in the SVF, which they classified as follows: a) candidate preadipocytes (CD34+, CD31-, CD90+, CD146-), b) mature endothelial cells (CD34+, CD31-), c) immature endothelial cells (CD34-, CD31+) and d) candidate perivascular cells (pericytes) (CD34-, CD31-, CD146+). These cell populations seem to coincide with those described above in adipose tissue (excluding adipocytes, leukocytes and some cells of peripheral nerves). Some cells tentatively designated as immature endothelial cells (Li et al., 2011) may correspond to lymphatic vessel endothelial cells. Likewise, Braun et al., 2013, obtained three major cell subsets in the heterogeneous population of cells in this fraction: a) adventitial stromal cell-like cells (AdSC) or adipose tissue-derived stromal (stem) cells (ASCs) (CD34+, CD146-, CD271+/-), b) pericyte-like cells (PCs) (CD34-, CD146+, CD271+/-) and c) endothelial cells (CD34+, CD31+, CD146+). Therefore, cell precursors of ASCs are found in the CD34+ stroma vascular fraction of adipose tissue (Maumus et al., 2011). These native precursors of ASCs do not express pericytic, hematopoietic (CD14, CD45) or endothelial markers (CD31) and can give rise to adipocytes, osteoblasts and chondrocytes (Zuk et al., 2002; Cowan et al., 2004). In this respect, Bourin et al., 2013, have established a minimal definition of stromal cells as an uncultured vascular fraction (SVF: CD45-, CD235a-, CD31- and CD34+; expression of surface antigen CD13, CD63, CD90 and CD105 has added identification value) and as an adherent stromal/stem cell population (ASCs: markers in common with other mesenchymal stromal cells-MSCs, including CD90+, CD73+, CD105+, CD44+, and CD45- and CD31-). ASCs are distinguished from bone marrow-derived mesenchymal cells by their negativity for CD106 and their positivity for CD36. Cell identification is completed by differentiation assays, including selection of specific gene lineage or protein

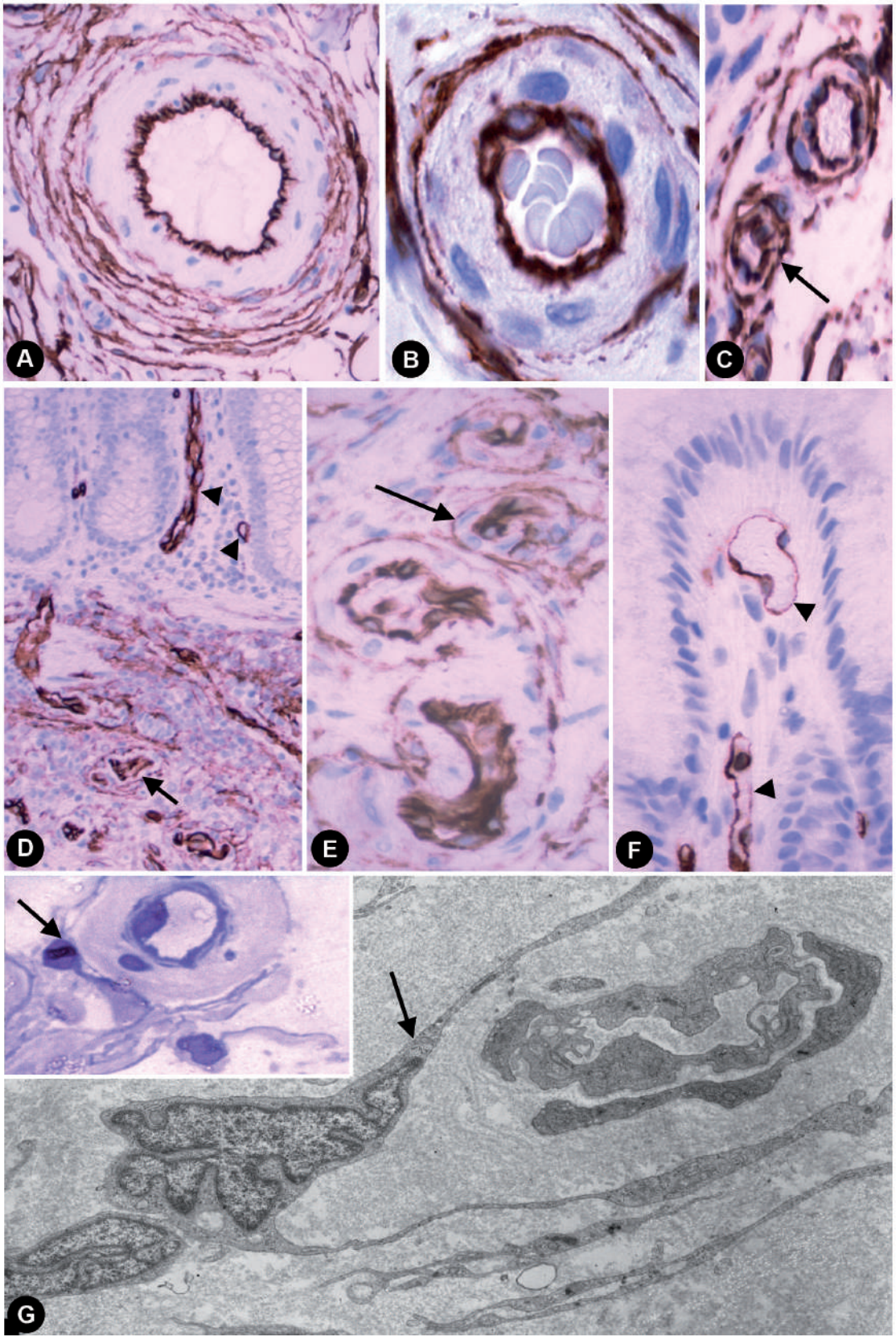

Fig. 5. Presence of CD34+ SFCs in the adventitia of medium- and small-sized vessels. CD34-stained vessels show a double ring appearance (endothelium and adventitia are both stained, sandwiching the unstained media layer) **(A, B and C)**. CD34+ SFCs may extend to the microcirculation **(C, D and E)** (arrows), as occurs in the intestinal submucosa **(D and E)**. In some regions, microvessels do not show CD34+ SFCs **(F)**, as in the intestinal mucosae **(D and F)** (arrowhead). These delimiting fibroblasts (with characteristics of telocytes) around small vessels are demonstrated in semithin and ultrathin sections **(G)** (Insert of G, vessel in semithin section). A, x 120; B, C, x 380; D, x 90; E, F, x 320; G, Uranyl acetate and lead citrate, x 12,000; Insert, Toluidine blue, x 380

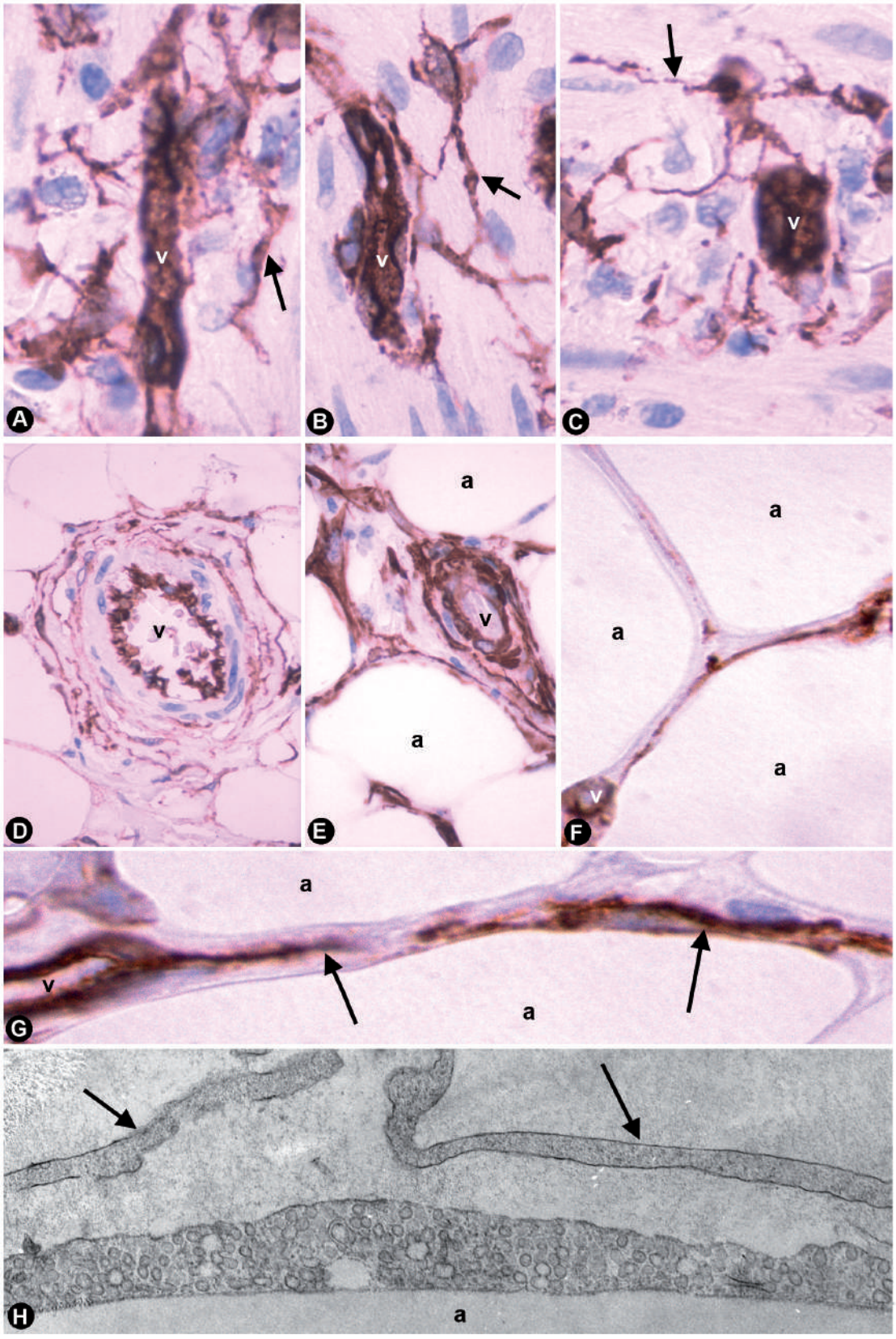

Fig. 6. Characteristics of CD34+ SFCs around vessels (v) and adipocytes (a). CD34+ SFCs extending their processes into surrounding tissue (**A to C**, arrows). CD34+ SFCs are shown around vessels in the connective tissue that surrounds lobes and lobules of adipose tissue **(D and E)**. Note processes of CD34+ SFCs closely associated with microvessels and adipocytes (**F and G**, arrows). In **H**, ultrastructural demonstration of SFC processes (telopodes) (arrows) near an adipocyte. A, B, C, E, x 320; D, x 280; F, G, x 680; H, Uranyl acetate and lead citrate, x 15,000

marker, demonstrating adipocytic (adiponectin, leptin, fatty acid binding protein 4, peroxisome proliferator activated receptor γ, glycerol 3 phosphate dehydrogenase), chondroblastic (aggrecan, collagen type II, Sox9) and osteoblastic (alkaline phosphatase, osteocalcin, osterix, runx2 and bone sialoprotein) markers. In the section "Characteristics, expression, and loss and gain of defining molecule CD34 (phenotype changes)", we have considered the immunophenotype changes in adipose tissue stromal cells and their derivatives, and in the section "Mesenchymal stromal progenitor/stem cell capacity (Multipotent mesenchymal stromal cell capacity) of CD34+ stromal cells", we will take into account these considerations to support this concept.

CD34+ fibrocytes in the blood (circulating CD34+ fibrocytes)

In the blood (the largest tissue in the body), circulating fibrocytes were identified two decades ago and defined as a new leukocyte subpopulation (comprising approximately 0.5% of non-erythrocytic cells) that mediates tissue repair (Bucala et al., 1994; Blakaj and Bucala, 2012). They derive from circulating CD14+ monocytes (Barth and Westhoff, 2007) and rapidly enter sites of tissue injury. Adherent cultured fibrocytes develop a spindle-shaped morphology (Bucala et al., 1994), and immunohistochemical characteristics of these cells have been described as follows (Bucala et al., 1994; Chesney et al., 1997; Quan et al., 2004; Bellini and Mattoli, 2007): expression of CD34, CD105, CD11a, CD11b, CD13, CD18, CD32, CD64, CD45 and LSP1. When cultured, they express MHC, class II, and co-stimulatory molecules (CD80 and CD86), and with acquired myofibroblast-like differentiation, α smooth muscle actin (Abe et al., 2001). Fibrocytes produce collagen I and III, fibronectin and MMP9, and therefore express hematopoietic stem cell/progenitor antigens (CD34), leukocyte markers (CD45), monocyte lineage markers (CD14) and fibroblast products (vimentin, collagen I, collagen III). The chemokine receptors on the surface of fibrocytes include CCR4, CCR5 and CCR7 (Abe et al., 2001), which act in fibrocyte signalling and a trafficking pathway, e.g., in response to secondary lymphoid chemokine (CCR7). Therefore, they are distinct from monocytes, dendritic cells, Langerhans cells, T lymphocytes and endothelial cells, and are unique in their expression of hematopoietic and monocyte lineage markers and extracellular proteins (Bucala, 2012). Fibrocytes secrete numerous cytokines, present antigen *in vitro* and *in vivo* (Chesney et al., 1997, 1998; Chesney and Bucala, 1997; Grab et al., 1999), 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, FGFß and PDGF (Hartlapp et al., 2001), and intervene in the development of fibrotic lesions, connective tissue disease, atherosclerosis and in tumour stroma formation.

CD34+ SFCs in the muscle

A network of CD34+ SFCs is observed between muscle cells in both striated (Fig. 7A) and smooth (Figs. 2, 7B) muscle. Furthermore, these cells are associated with vessels (adventitial cells) and nerves present in this location. In our opinion, most cells termed telocytes in the striated muscle and muscle spindles (Popescu et al., 2011; Suciu et al., 2012; Díaz-Flores et al., 2013) are CD34+ SFCs. Greater numbers of these cells are observed during muscle development and in some adult muscles, such as intrinsic muscle of the larynx (e.g., thyroarytenoid muscle) (Fig. 7A).

In the striated muscle, the satellite cells can express CD34, but CD34+ SFCs are located outside the satellite cell niche. CD34+ SFCs in this location have been excluded as endothelial cells or pericytes because they do not express either CD31 or NG2, respectively (Dupas et al 2011). Different CD34+ subsets have been purified from fetal muscle, including the following populations: 1) CD34+, CD31-, CD45-, SCA1- (79%), located in the muscle interstitium, with the ability to express myogenic-specific genes (myogenic lineage), 2) CD34+, CD31-, CD45-, SCA1+ (18%), restricted to the muscle epimysium and with the capacity to display adipogenic differentiation (adipogenic lineage), 3) CD34+, CD31+, CD45- (1%), with endothelial phenotype and capable of forming microvessels (angiogenic lineage), 4) CD34+, CD31-, CD45+ (2%), non-adherent and without the ability to differentiate into angiogenic, myogenic or adipogenic lineages (Dupas et al., 2011). Fetal mouse muscle therefore contains CD34+ progenitors with myogenic, adipogenic and angiogenic capacity, which appear committed to each of these specific lineages. Furthermore, 2% of the CD34+ cells are not included among these progenitors (Dupas et al., 2011). CD34+ cells isolated from fetal mouse muscle, presumably associated with vessels, can be a source of myogenic progenitors, which may have potential for treating muscular dystrophy (Le Grand et al., 2004; Auda-Boucher et al., 2007).

In smooth muscle (e.g., the tunica muscularis of urogenital and gastrointestinal tract), intercommunicating processes of CD34+ SFCs surround fascicles of SMCs, forming a dense reticular network with a particular spatial arrangement (Fig. 7B).

CD34+ SFCs in the nerve

CD34+ SFCs are present in nerves predominantly in the endoneurium and around the perineurium (Figs. 7C-E). They show spindle and stellate morphology and are well identified in longitudinal sections, in which they are observed as bipolar cells, while in transverse sections they show small oval nuclei and attenuated dendritic cytoplasmic processes (Weiss and Nickoloff, 1993). These cells are different from Schwann cells, since no dual CD34 and S100 immunoreactivity has been observed (Khalifa et al., 2000; Hirose et al., 2003). Weiss and Nickoloff, 1993, indicate that these cells

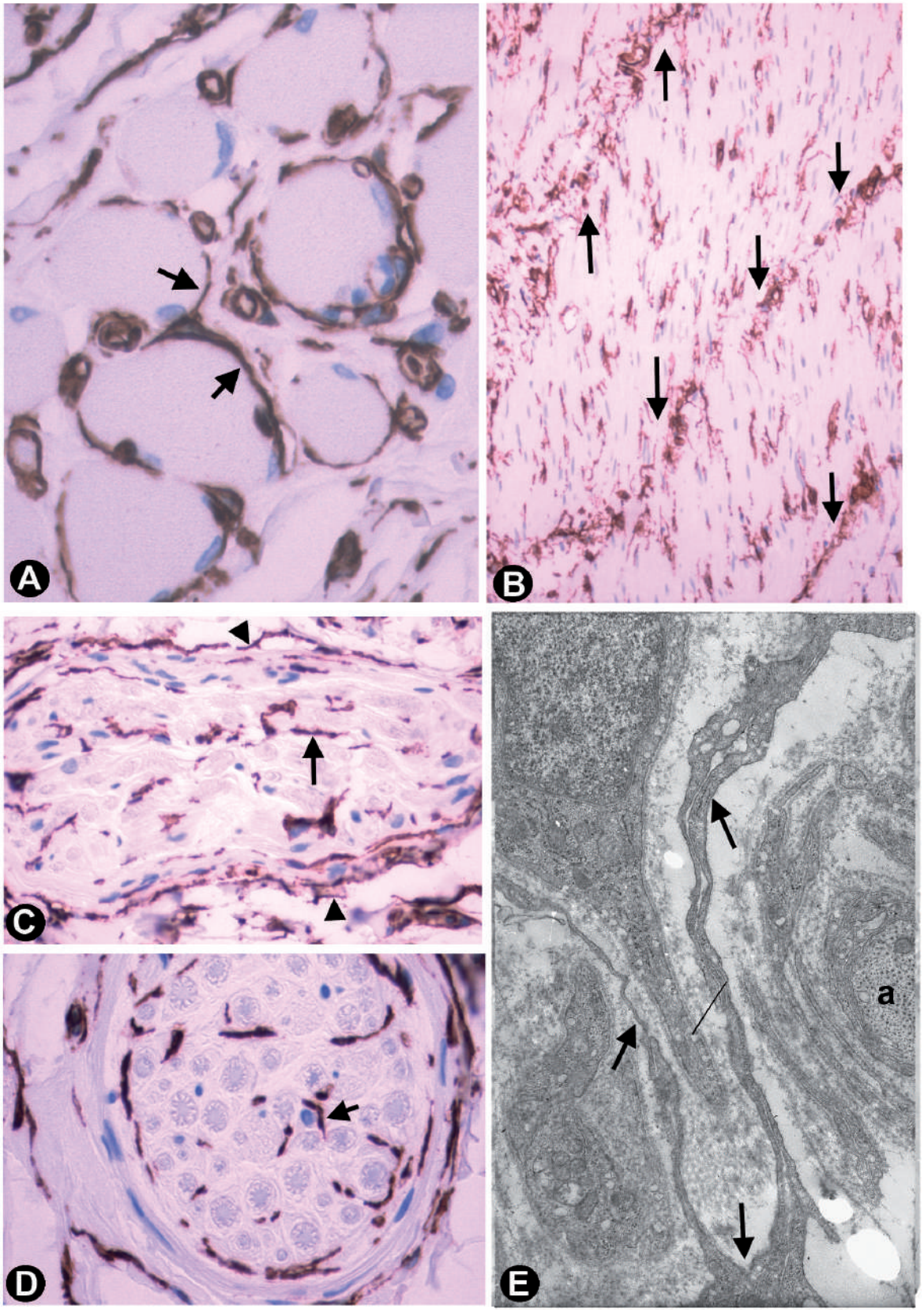

Fig. 7. Characteristics of CD34+ SFCs in the muscle and nerve. Abundant CD34+ SFCs around the thyroarytenoid muscle cells (**A**, arrows). A dense reticular network of CD34+ SFCs, with a particular spatial arrangement, is observed in the smooth muscle of the gastrointestinal tract (**B**, arrows). CD34+ SFCs are observed around perineurium (arrowhead) and in endoneurium (**C and D**, arrows). In **E**, ultrastructural characteristic of a fibroblastic endoneurial cell (telopodes - arrows). A, x 430; B, x 90; C, D, x 290; E, Uranyl acetate and lead citrate, x 14,000

occasionally appear condensed outside the perineurium; however, we have frequently observed them in this location, together with myofibroblasts (αSMA+ myofibroblasts). For some authors, CD34+ SFCs may play a supportive role for Schwann cells (Weiss and Nickoloff, 1993).

CD34+ SFCs in sensory receptors

We have demonstrated the presence of CD34+ SFCs (using the name telocyte) in neuromuscular spindles (NMSs) (Díaz-Flores et al., 2013) (Fig. 4). These cells were highly developed in NMSs, which provide an ideal microanatomical structure for their study. CD34+ SFCs in NMSs were characterized ultrastructurally by very long, initially thin, moniliform prolongations, in which thin segments alternated with dilations (Fig. 4B,C). CD34+ SFCs formed the innermost and (partially) the outermost layers of the external NMS capsule (similar to the capsule of the taste buds – Ciges et al., 1976) and the entire NMS internal capsule. In the latter, the prolongations were organized in a dense network, which surrounded intrafusal striated muscle cells (Fig. 4), nerve fibres and vessels, suggesting a passive and active role in controlling NMS activity, including their participation in cell-to-cell signalling. In human fetus (22-23 weeks of gestational age), CD34+ SFCs together with perineural cells formed a sheath, serving as an interconnection guide for the intrafusal structures. In pathological conditions, the number of CD34+ SFCs increased in residual NMSs between infiltrative musculo-aponeurotic fibromatosis and varied in NMSs surrounded by lymphocytic infiltrate in inflammatory myopathy.

CD34+ SFCs in the skin

In the normal skin, CD34+ SFCs are scarce or absent in the papillary dermis but numerous in the reticular dermis (Fig. 8A), where they adopt a spindle or dendritic morphology. The highest number of CD34+ SFCs are observed around vessels, and surrounding secretory coils of the eccrine sweat glands and hair follicles, mainly around their mid-portion, close to the bulge (Nickoloff, 1991; Kirchmann et al., 1994; Narvaez et al., 1996; Poblet et al., 2006; Erdag et al., 2007; Wessel et al., 2008) (Fig. 8B,C). In these locations, CD34+ SFCs form a reticular network (Wessel et al., 2008). The bipolar processes of the spindle-shaped cells in the reticular dermis are interposed between the collagen bundles and arranged parallel to the epidermis (Wessel et al., 2008). Strong CD34 reactivity is also found in endothelial cells of the blood vessels and in the epithelia of the external root sheath of the anagen hair follicles (below the bulge zone) (Fig. 8B). In cells of dermal papilla of some hair bulbs, we have observed CD34 and S100 protein expression (Fig. 8C,D); αSMA positive stromal cells are absent from the stromal dermis (Nickoloff, 1991; Narvaez et al 1996; Poblet et al., 2006; Wessel et al., 2008).

CD34+ SFCs in oral cavity and oropharynx

CD34+ SFCs are observed in the corion, encircling vessels and submucosal glands. Conversely, αSMA positive stromal cells are absent in the stroma (Barth et al., 2004).

CD34+ SFCs in respiratory tract

The majority of stromal cells in the laryngeal mucosa, including vocal folds, are CD34+ SFCs, which show bipolar or multipolar cytoplasmic processes (Fig. 8F). Conversely, there are no αSMA+ stromal cells (Barth et al., 2004; Kojc et al., 2005, Díaz-Flores et al., 2014). CD34+ SFCs in the normal laryngeal mucosa express TGF-ß1 receptors (Kojc et al., 2005). A dense reticular network of CD34+ SFCs is observed around striated muscle cells in the laryngeal muscle layer (non-published observations) (Fig. 7A).

In the lung, CD34+ SFCs are present in the connective tissue adjacent to the bronchial and bronchiolar epithelium (Nakayama et al., 2003) (Fig. 8G). Circulating fibrocytes have been considered precursors of bronchial myofibroblasts in asthma (Schmidt et al., 2003) and of cells that mediate lung fibrosis (Phillips et al., 2004).

In the submesothelial visceral pleura, CD34+ SFCs and CD34- fibroblasts are observed mainly in reactive pleural processes and in the pseudo capsular fibrous tissue surrounding pleural solitary fibrous tumours. These cells express progesterone receptor (androgen and estrogen are not expressed) and appear embedded in dense collagen bundles or located around the walls of vessels. At higher magnification the submesothelial CD34+ SFCs show slender, long cytoplasmic projections (Westra et al., 1994; Bongiovanni et al., 2002).

CD34+ SFCs in digestive tract

In the normal gastric wall CD34+ SFCs are present in muscularis mucosae, submucosa, muscular propria and subserosa, with a higher number around vessels (Kim et al., 2000; Nakayama et al., 2001, 2002a,b, 2004a,b). These locations are also observed during fetal life (Fig. 8H). Their distribution and characteristics are similar to the intestinal wall and will therefore be considered with more detail in the next paragraph.

In normal intestinal wall, CD34+ SFCs are always observed in the muscularis mucosae, submucosa (Fig. 5D), muscular propria and subserosa. In these layers, myofibroblasts are not detected. CD34+ SFCs are absent in the lamina propria of the mucosa (except in some of its deep regions adjacent to the muscularis mucosae) and in an area immediately underlying the mesothelium, in which αSMA+ myofibroblasts are observed. When present in deep regions of lamina propria, CD34+ SFCs line the bases of intestinal crypts (Fig. 8I), nerve bundles and smooth muscle cell fascicles of muscularis mucosae. The presence of CD34+ SFCs and myofibroblasts in the intestinal wall is therefore contrastive (Kuroda et al.,

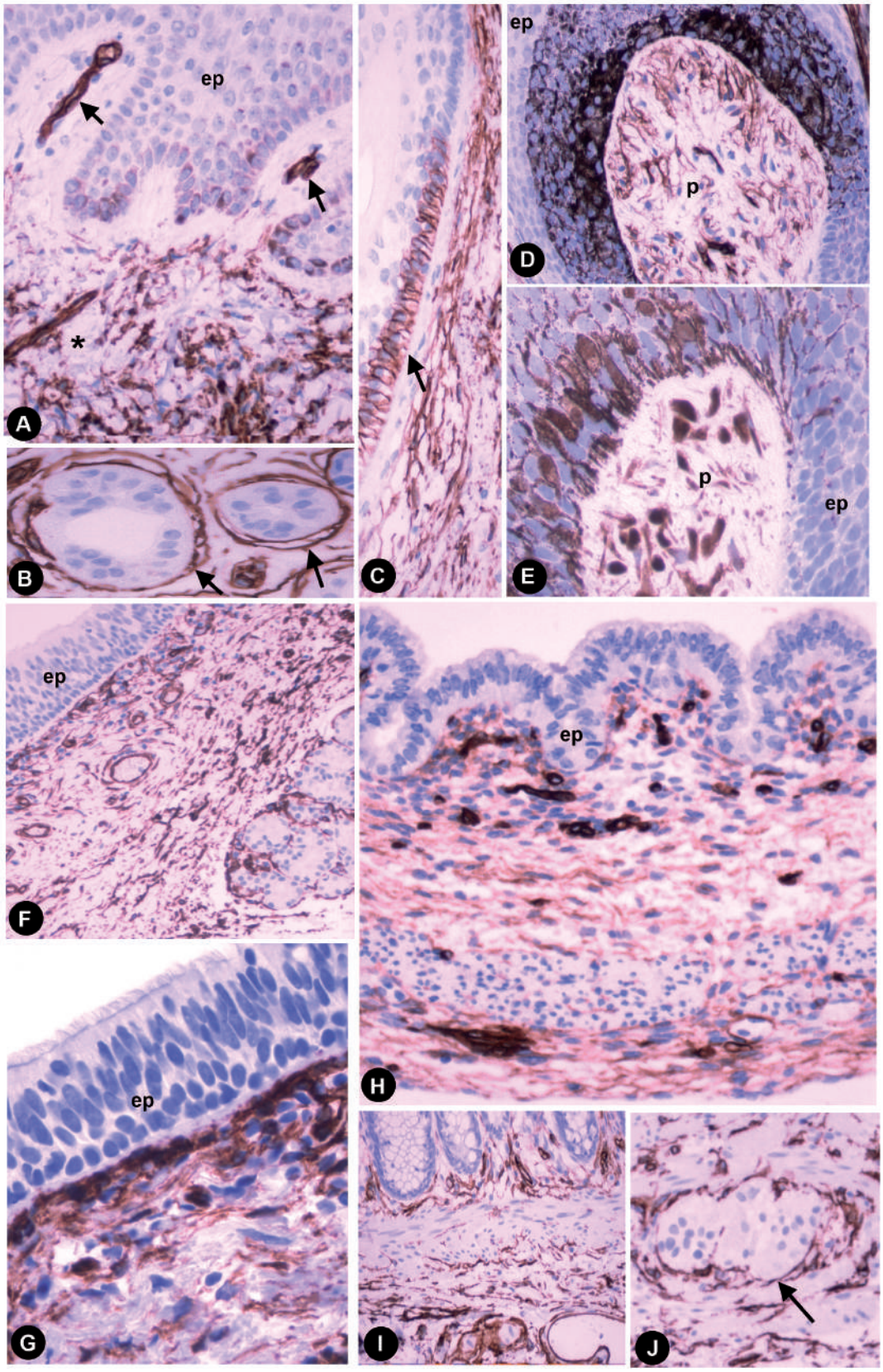

Fig. 8. CD34+ SFCs in skin, and in respiratory and digestive tracts. Numerous CD34+ SFCs in reticular dermis **(A)** (vessels of the papillary dermis without CD34+ SFCs cover: **A**, arrows), surrounding sweat glands (**B**, arrows) and a hair follicle **(C)** (CD34-positive cells are also located in the outer root sheath of the anagen follicle: **C**, arrow), and in a dermal papillae (p) of hair bulbs **(D)**. CD34+ SFCs in dermal papilla also express S100 protein **(E)**. CD34+ SFCs in laryngeal mucosa **(F)** and in the connective tissue adjacent to the bronchial epithelium **(G)**. CD34+ SFCs in the fetal gastric wall **(H)** and in the adult intestinal wall **(I)**, including their location around an Auerbach's plexus (J, arrow). (epithelium: ep). A, C, D, E, H, x 160; B, G, J, x 240; F, I, x 110

2005a), since myofibroblasts are present where CD34+ SFCs are absent, and vice versa. In all locations where CD34+ SFCs are present, they predominate in perivascular sites, organizing a network throughout the vascular system (in the vascular adventitia). CD34+ SFCs around (Fig. 8J) and between Auerbach's plexus ganglia are associated with CD117+ interstitial Cajal cells (Robinson et al., 2000). CD34+ SFCs are negative for CD117 (c-kit) and are therefore distinct from interstitial Cajal cells (Vanderwinden et al., 1999, 2000). However, a subset of cells surrounding Auerbach's plexus and within the circular muscle layer is positive for both CD117 and CD34 (Robinson et al., 2000). This finding explains the existence of gastrointestinal stromal tumours (GISTs) with the c-kit+ and CD34+ phenotype, which may arise from the subpopulation of CD34+ and c-kit+ interstitial Cajal cells (Robinson et al., 2000) (see below). CD34+ SFCs are also found around and in the peripheral areas of groups of immune cells.

CD34+ SFCs in salivary glands

CD34+ SFCs appear densely arranged around acini and ducts (Yamazaki and Eyden, 1996b; Soma et al., 2001). Ultrastructurally, these cells show long slender processes, which associate with other SFCs by means of gap junctions (Yamazaki and Eyden, 1996b).

CD34+ SFCs in pancreas

CD34+ SFCs are observed around acinar cells and pancreatic ducts, but mainly around the former, and focally in islets of Langerhans (Kuroda et al., 2004a). Myofibroblasts (expressing αSMA) are mainly present in periductal areas but also in the periacinar area and focally within islets of Langerhans (Kuroda et al., 2004a).

CD34+ SFCs in urinary tract

We have observed CD34+ SFCs in the kidney capsule and around vessels, glomerular Bowman's capsule and tubules (Fig. 9A,B). αSMA+ cells are also present. In general, CD34+ SFCs show a small nucleus, inconspicuous cytoplasm and thin, mostly bipolar (multipolar in a small subpopulation) cytoplasmic processes, communicating with those of neighbouring CD34+ SFCs. In the kidney capsule, CD34+ SFCs and αSMA+ cells are arranged parallel to the kidney surface. The bipolar cells of the deeper capsule are αSMA+ and CD34 negative, whereas the cells in the most superficial capsule, which form a greater number of layers, are CD34+ (Fig. 9A) and αSMA negative. In the Bowman's capsule, CD34+ SFCs and αSMA+ cells form a thin layer covering the thick basal lamina of the attenuated parietal epithelial cells (Fig. 9B).

In normal pelvis and ureter, CD34+ SFCs are present in the deep area of lamina propria, in the muscular layer and in the adventitia, predominantly in the latter (Kuroda et al., 2006). No myofibroblasts are observed (Kuroda et al., 2006).

In the lamina propria of the urinary bladder there are two distinct populations of stromal cells: CD34+ SFCs and αSMA myofibroblasts (Nimphius et al., 2007). CD34+ SFCs are located in the deeper lamina propria (Fig. 9C) and αSMA myofibroblasts in the superficial layer. Conversely, superficial lamina propria contains no CD34+ SFCs and αSMA+ myofibroblasts are absent in the deeper lamina propria. The projections of these cells are bipolar (especially myofibroblasts) or multipolar/dendritic-like (especially CD34+ SFCs arranged in the interstitial areas of lamina propria). Myofibroblasts are arranged parallel to the mucosa surface, and CD34+ SFCs encircle vessels. Cells with dual expression of CD34 and αSMA are not found (Nimphius et al., 2007). In the tunica muscularis, densely packed CD34+ SFCs are observed encircling fascicles of smooth muscle (Nimphius et al., 2007).

CD34+ SFCs in the male reproductive system

Stromal cells in the testes include myoid (contractile) cells and CD34+ fibroblasts. The myoid cells consist of smooth muscle cells and myofibroblasts (Ross and Long, 1966; Langford and Heller, 1973; de Kretser et al., 1975; Bustos-Obregon, 1976; Furuya et al., 1977; Toyama, 1977; Johnson et al., 1986; Virtanen et al., 1986; Christl, 1990; Davidoff et al., 1990; Holstein et al., 1996; Arenas et al., 1997; Middendorff et al., 2002; Kuroda et al., 2004c). CD34+ SFCs are present in the tunica albuginea, around and between seminiferous tubules, and in a reticular network surrounding Leydig cells (Kuroda et al., 2004c) (Fig. 9D). CD34+ SFCs occur focally in tunica albuginea, where numerous myofibroblasts are present. CD34+ SFCs and myofibroblasts are observed around seminiferous tubules, forming two layers: external and internal, respectively (Kuroda et al., 2004c).

CD34+ SFCs in the female reproductive system

A dense reticular network of the bi- or multipolar CD34+ SFCs is present in the normal cervical stroma (mainly bipolar and arranged in parallel) (Lindenmayer and Miettinen, 1995; Barth et al., 2002a). These cells predominate in perivascular and subepithelial sites and decrease in number at the most distant sites. The subepithelial stroma is free of αSMA+ myofibroblasts (Barth et al., 2002a). Fascicles of smooth muscle in deep cervix are surrounded by CD34+ SFCs.

A reticular network of CD34+ SFCs has been described in the normal endometrium (Kuroda et al., 2004b). Conversely, only a few αSMA+ cells are focally present (Kuroda et al., 2004b). Neither CD34+ nor αSMA+ stromal cells are observed during pregnancy. Abundant CD34+ SFCs are present in the myometrium (Lee et al., 2006).

CD34+ SFCs are observed in the Fallopian tube. In the mucosa (Yamazaki and Eyden, 1996a), these cells appear in a small to moderate number, but form a dense

reticular network around the smooth muscle layer (Kuroda et al., 2004b). In the ampular mucosa, CD34+ SFCs frequently adhere to mononuclear cells, and show lipid-rich residual bodies, solitary cilia and simple intercellular junctions (Yamazaki and Eyden, 1996a). A population of cells expressing both CD34 and αSMA has also been described in the lamina propria and submucosa layer of normal Fallopian tubes (Kuroda et al., 2004b), suggesting that these cells share a common origin.

In the ovary, CD34+ SFCs are observed in the albuginea, ovarian hilus (mainly around vessels) and surrounding the teca of follicles (Fig. 9E,F). Zhang et al. (2011) did not identify αSMA positivity in the stromal cells of the normal ovary, except for vascular pericytes. However, in epithelial ovarian cancer almost all fibroblasts were αSMA-positive, whereas a weak expression of stroma αSMA was detected in 30% of benign and borderline ovarian tumours (Zhang et al., 2011).

CD34+ SFCs in the breast

The stroma of normal mammary gland contains many CD34+ SFCs with a stronger density in the intralobular stroma (Yamazaki and Edyen, 1995; Moore and Lee, 2001; Barth et al., 2002b; Chauhan et al., 2003; Ramaswamy et al., 2003; Cimpean et al., 2005; Ebrahimsade et al., 2007). Thus, the lobular stroma show densely packed CD34+ SFCs, encircling intralobular ducts and acini. In the extralobular stroma, CD34+ SFCs are located mainly around vessels (particularly surrounding thick-walled, muscularized arteries and arterioles) and are scarce in areas distant from glandular and vascular structures. The stroma of the normal breast is free of αSMA+ myofibroblasts. However, myoepithelial cells and vascular mural cells (pericytes/vascular SMCs) show strong reactivity to αSMA. Vascular endothelial cells are reactive to CD34. No CD34 reactivity is observed in epithelial cells.

CD34+ SFCs in lymph nodes and tonsils

In lymph nodes, CD34+ SFCs are observed in the capsule, hilus and branches of the connective tissue that extends into the nodes (Fig. 9G). CD34+ SFCs are more numerous around vessels present in these regions (Fig. 9G). Interestingly, the vessels into the lymph node parenchyma are not surrounded by CD34+ SFCs (Fig. 9G). αSMA+ cells are also located in the regions where CD34+ SFCs are observed and around the vessels inside the parenchyma. In the tonsils, CD34+ SFCs are located at the periphery and in surrounding capsules (Papadas et al., 2001).

CD34+ SFCs in the thymus

CD34+ SFCs are observed in the capsule, subcapsule and trabecullae between the thymic lobules (Fig. 9H), mainly around vessels. With age, CD34+ SFCs are also abundant between adipocytes, and perilobular and trabecular lymphoid cells, where they form a network. In the capsula, CD34+ SFCs are spindle-shaped, with thin cytoplasmic processes that form several concentric and parallel layers (Fig. 9H).

CD34+ SFCs in stromal lymphocytic infiltrations

CD34+ SFCs are observed in the periphery of lymphatic infiltrations (e.g., in intestinal walls) (Fig. 9I), but are scarce or absent within (Barth et al., 2004).

CD34+ SFCs in the thyroid gland

Thyroid CD34+ SFCs can be identified in situ in normal thyroid tissue or in tissue from donors with Graves' disease and Hashimoto's thyroiditis (Yamazaki and Eyden, 1997). In normal thyroid, CD34+ SFCs are arranged around the follicles, showing bipolar projections (Fig. 9J). Thyroid fibroblasts cultured from these glands express a CD34-phenotype (unlike orbital fibroblasts and circulating fibrocytes). When treated with TSH, thyroid fibroblasts generate IL-6 and IL-8. When treated with TGF beta or rosiglitazone, they differentiate into myofibrocytes or adipocytes, respectively (Smith et al., 2011; Yamazaki and Eyden, 1997).

CD34+ SFCs in synovia

CD34+ SFCs have been observed in the underlying tissue of synovia (subintimal location) (Athanasou and Quinn, 1991).

CD34+ SFCs in the meniscus

CD34+ SFCs are observed in the superficial zone of the meniscus, but are absent in the inner part (Declercq et al., 2012). The presence of αSMA+ cells in normal meniscus is discussed (Ahluwalia et al., 2001; Declercq et al., 2012). Three distinct populations of CD34+ cells in the outer vascular portion of the meniscus body have been described (Verdonk et al., 2005): two CD34+/CD31- populations (CD34+ SFCs), located in the synovial sublining and superficial zone of the meniscus body, respectively, and a third distinct CD34+/CD31+ population, corresponding to endothelial cells.

CD34+ SFCs in serosal membranes

CD34+ SFCs are present in submesothelial tissues (Westra et al., 1994; Bongiovanni et al., 2002; Lee et al., 2006; Jimenez-Heffermann et al., 2004). The pleura and all peritoneal tissues, including subserosa of uterus, salpinx, ovary, ligament, colon, appendix, recto-vaginal cul de sac, urinary bladder and omentum contain large numbers of CD34+ SFCs (Lee et al., 2006; Jimenez-Hefferman et al., 2004). In the visceral and parietal pleura, dendritic CD34+ SFCs appear embedded in

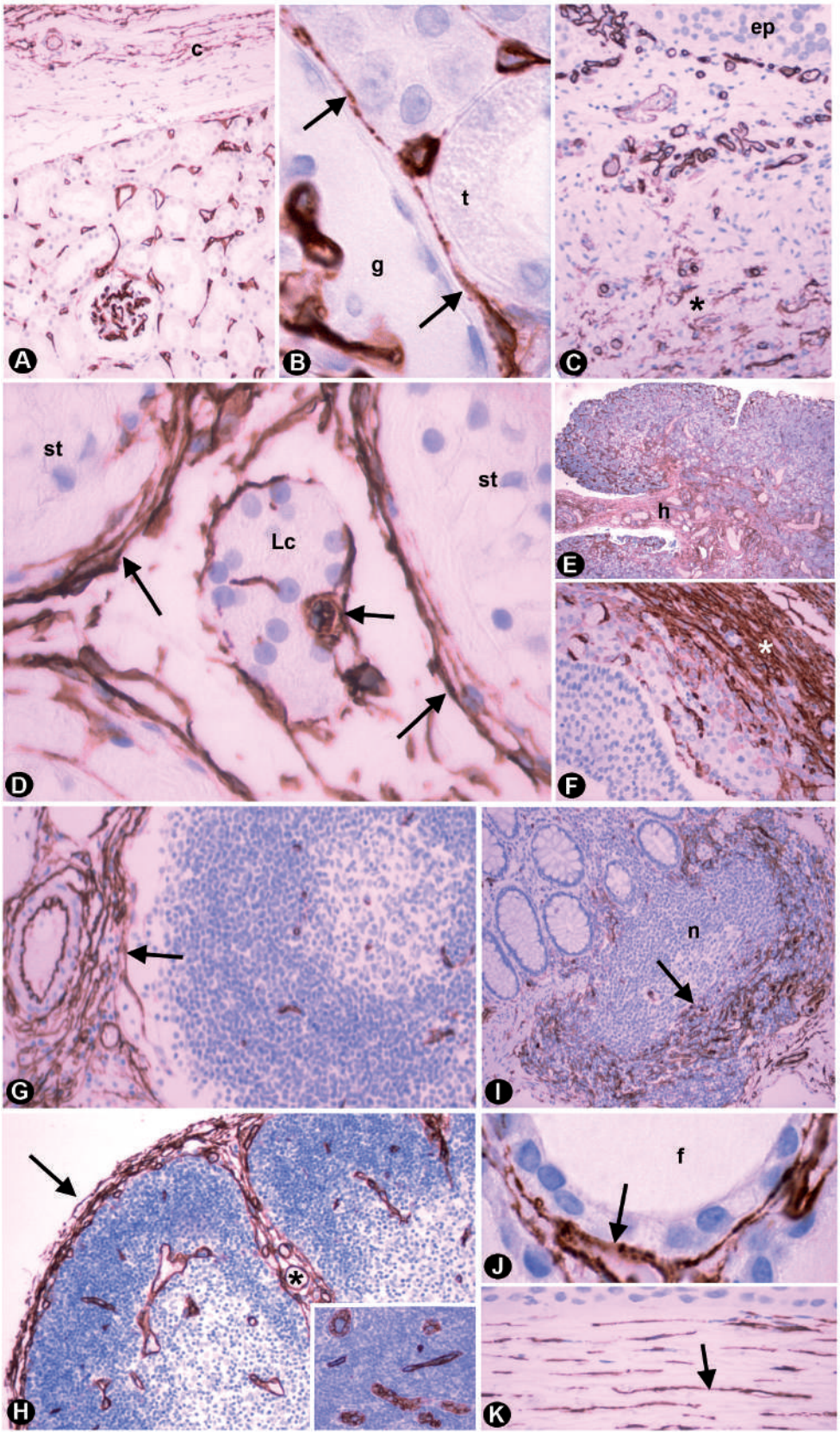

Fig. 9. CD34+ SFCs in urinary tract, male and female reproductive systems, lymph nodes and tonsils, thyroid and cornea. CD34+ SFCs are observed in the kidney capsule (**A,** c), and around vessels, glomerular Bowman capsule and tubules (arrows) (**B,** g: glomerulus; t: tubule). CD34+ SFCs in the deeper lamina propria of the urinary bladder (**G**; asterisk: deeper layer of the lamina propria; ep: epithelium). CD34+ SFCs (arrows) between seminiferous tubules and surrounding Leydig cells. (**D**; st: seminiferous tubules; Lc: Leydig cells). CD34+ SFCs in ovarian hilus (**E**, h) and surrounding the theca of a follicle (**F**, asterisk). CD34+ SFCs in the capsule of a lymphatic node (**G**, arrow) and thymus (**H**, arrow). A thymic trabecule with CD34+ SFCs is observed (**H**, asterisk). Detail of vessels without CD34+ SFC cover (**H**, insert). CD34+ SFCs (arrows) in the periphery of an intestinal lymphatic node (**I**, n); around thyroid follicles (**J**, f) and in corneal stroma (**K**). A, C, F, I, K, x 90; B, D, J, x 290; E, x 80; G, H, x 140

dense collagen (Bongiovanni et al., 2002). The long, slender cytoplasmic projections of CD34+ SFCs form a reticular network distributed throughout the stroma with condensation around vessels, and just below the mesothelial cell layer, creating the impression of a continuous layer (Jimenez-Hefferman et al., 2004). αSMA+ myofibroblasts appear in some areas of nonlesional peritoneal tissue and omentum, increasing in number in areas of inflammation and fibrosis (Lee et al., 2006).

CD34+ fibroblasts in the heart

CD34+ SFCs are the principal cellular component of the heart valve stroma in normal conditions. They have been reported (Barth et al., 2005a) in the spongiosa and fibrosa layers of the valves, showing elongated, slender, bipolar cytoplasmic processes arranged in a parallel fashion. Heart valve CD34+ SFCs are also positive for S100 protein, although less intensely than for CD34. Generally, CD34+ SFCs are more numerous in the spongiosa than in the fibrosa layer.

CD34+ SFCs in the eye

In the cornea, quiescent keratocytes express CD34 (Toti et al., 2002; Espana et al., 2004; Barbaro et al., 2009) (Fig. 9K), aldehyde dehydrogenase 3AI and keratan sulfate. These cells exhibit a bipolar or dendritic morphology and are arranged parallel to the corneal surface. Downregulation of CD34 expression and myofibroblastic differentiation are promoted by TGF ß1. When TGF signalling is supressed (e.g., keratocytes seeded on amniotic membrane matrix), CD34 expression is maintained (Espana et al., 2004).

CD34+ SFCs in meninges

In the dura mater, CD34+ SFCs are present and show long, tapering dendritic processes, arranged parallel to the long axis (Cummings et al., 2001). CD34+ SFCs are more prominent in the meningeal portion of the dura than in the periosteal dura. CD34+ SFCs are also present surrounding blood vessels. No CD34+ SFCs are observed in the leptomeninges (Cummings et al., 2001).

Origin of CD34+ SFCs

CD34+ SFCs may be considered descendent and/or progenitor cells (for the latter, see below). As descendent cells, they can first be detected by the tenth gestational week (with stellate morphology in loose connective tissue) (Barth and Westoff, 2007), and they originate in the embryo from mesenchymal stem cells (mesodermal origin) and from the neural crest, depending on location. The origin from the cranial neural crest (Takashima et al., 2007) explains expression of neural proteins in some progenitor cells in their basal state (Deng et al., 2006; Blondheim et al., 2006). In postnatal life, the source of CD34+ SFCs remains relatively unclear. Indeed, they may develop from tissue-derived stem cells (from themselves or other cells) and/or from peripheral blood pluripotent stem cells (circulating progenitor cells) (Bucala et al., 1994; Chesney et al., 1997; Zvaifler, 2000; Abe et al., 2001; Phillips et al., 2004; Direkze and Alison, 2006). Their origin from immature mesenchymal cells in the peripheral blood derived from bone marrow includes multipotent mesenchymal stromal cells and mesenchymal progenitors, termed fibrocytes. When we consider CD34+ SFCs as progenitor cells, we will discuss their self-generation, by outlining their modifications in the tissue of origin and in descendent cells. The source of CD34+ SFCs from other tissue progenitor cells has not been conclusively demonstrated.

Functions of CD34+ SFCs

The functional capacities of CD34+ SFCs, ubiquitously distributed throughout the body, include synthesis of different substances, as progenitors of mesenchymal cells, immunomodulation, parenchymal regulation, scaffolding support of other cells and phagocytic properties. Indeed, CD34+ SFCs are a subpopulation of fibroblasts and can therefore have the ability to synthesize and remodel the extracellular matrix. Their mesenchymal stem cell properties are currently the object of great interest. This capacity includes myofibroblastic, adipogenic, osteoblastic and chondrogenic differentiation, and extends beyond the mesenchymal lineage. Consequently, CD34+ SFCs play an important role in wound healing, tissue repair, fibrosis and tumour stroma formation. Moreover, they may participate in the functional heterogeneity of mesenchymal stem cells, which also includes immunomodulation (immunological tolerance), inhibition of monocyte differentiation into dendritic cells, parenchymal regulation and scaffolding support, and contribution to stem cell niches (survival, maintenance and differentiation of stem cells - Haniffa et al., 2007, 2009). First of all, we will address the general functions of CD34+ SFCs as a subset of fibroblasts. Subsequently, we will consider the participation of CD34+ SFCs as tissue progenitor/stem cells, particularly in findings that demonstrate this capacity and ensuing functions. Finally, we will add our own observations on these and other functional aspects.

General functions of CD34+ SFCs as a subset of fibroblasts

As a subset of fibroblasts, CD34+ SFCs are involved in their general functions, depending on their quiescent or activated stage. Indeed, in their quiescent state, fibroblasts normally act in the slow turnover of the extracellular matrix, including primary producers of type I, III and V collagen and fibronectin, and as contributors of the basement membrane by secretion of laminin and type IV collagen. Furthermore, CD34+ SFCs are a regulator of stromal collagen content (Barth and

Westhoff, 2007). In the activated stage, their remodelling capacity increases (see Mesenchymal capacity of CD34+ SFCs) by means of fibroblast-derived matrix metalloproteinases and can undergo phenotype changes to a proliferative, synthetic and contractile state. Cell-cell direct contact (e.g., adipose-derived stem cells promote human dermal fibroblast activation) and growth factors (e.g., PDGF, TGF ß1, insulin-like growth factor, bFGF, HGF and VEGF -Kim et al., 2007-) contribute to activate the fibroblasts. An example of fibroblast activation is what occurs during tissue repair, which includes a) increased proliferative capacity, originating new fibroblasts and myofibroblasts, b) temporal expression of αSMA in myofibroblasts (acquisition of contractibility - wound contraction - Bouissou et al., 1988; Darby et al., 1990; Clark, 2001), c) expression of other markers, such as endosialin and integrin receptors that bind fibronectin and fibrin on fibroblasts (McClain et al., 1996; Xu and Clark, 1997), d) stimulation of secretory activity of growth factors, chemotactic factors and extracellular matrix protein (Welch et al., 1990; Clark et al., 1995; Clark, 2001), e) activation of the fibroblast-derived proteolytic system (plasminogen activator, collagenases, gelatinase A and stromelysin – (Mignatti et al., 1996; Vaalamo et al., 1997), which contributes to fibroblast/myofibroblast migration and f) new interactions (e.g., dynamic cross-talk between activated fibroblasts and parenchyma cells).

Functions of CD34+ SFCs as precursors of mesenchymal cells (mesenchymal capacity)

Mesenchymal capacity of fibroblasts in general

It has long been discussed whether fibroblasts are precursor cells, capable of transforming into adipocytes, chondrocytes and osteoblasts (Díaz-Flores et al., 1992, 2006), or specialized cells, incapable of mesenchymal potential. Currently, there are interesting new contributions that partially solve the problem. For example, induced pluripotent stem cells (IPS cells) can be generated from adult human fibroblasts (Takahashi et al., 2007). Thus, 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 (Takahashi et al., 2007). In the following sections, we discuss the progenitor capacity of the CD34+ SFC subpopulation in particular.

Mesenchymal capacity of CD34+ SFCs in particular: CD34+ SFCs as progenitor cells, mesenchymal stromal progenitor/stem cell capacity, multipotent mesenchymal stromal cell capacity

Criteria proposed to define "Multipotent mesenchymal stromal cells". Variation of CD34 expression in descendent cells that modify these criteria. The International Society for Cellular Therapy recommends "multipotent mesenchymal stromal cells" as the most appropriate designation for cells with mesenchymal stromal progenitor/stem cell capacity (Horwitz et al., 2005). The criteria proposed to define these cells were as follows: 1) Adherence to plastic in standard culture conditions, 2) Specific immunophenotype, including expression of CD105, CD73, CD90, CD29, CD44, CD71, CD106, CD120a, CD166, Stro-1, ICAM-1, MHCI and non expression of CD34, among other markers (CD45, CD14, CD11, CD18, CD31, CD40, CD56, CD80, CD86, CD79a, CD19 or HLA-DR) (Chamberlain et al., 2007) and 3) Multipotent differentiation potential (*in vitro* differentiation into osteoblasts, adipocytes and chondroblasts) (Zuk et al., 2002; Dominici et al., 2006). These criteria therefore exclude CD34+ cells as multipotent mesenchymal stromal cells. However, the identity of these cells in their tissues of origin has remained unclear for some time, since their phenotype and abilities, including CD34 expression, may vary between the *in vitro* and *in vivo* settings (e.g., human adult adipose tissue, stromal vascular fraction and adipose tissue-derived stem/progenitor cells) (Augello et al., 2010) and the physiological processes of commitment and/or differentiation from immature status into specific lineages (Suga et al., 2009). These aspects will be discussed more extensively in the following section.

An example of phenotype variations of CD34+ SFCs according to observations in tissue of origin or derivatives: Human adult adipose tissue, stromal vascular fraction and adipose tissue-derived stem/progenitor cells. As discussed above, some tissues (adipose, blood and muscle) and their derivatives are substrates that help shed light on the mesenchymal capacity of CD34+ SFCs/fibrocytes. Immunophenotype differences between *in vivo* and *in vitro* settings in adipose tissue and its derivatives (stromal vascular fraction and adipose tissue-derived stem/progenitor cells) are a good example for the following reasons: a) Human adipose tissue is an abundant and easily procured source of multipotent stem/progenitor cells, enabling extraction of a large quantity (Zuk et al., 2002; Gimble and Guilak, 2003; Gimble et al., 2007), b) After removing adipocytes, the number of these cells is far greater than in bone marrow, and c) At present, numerous works already report the abundance of CD34+ stromal cells (CD34+ SFCs) in the adipose tissue and define their derived stem/progenitor cells in tissue and in culture (Lin et al., 2008, 2010; Gimble et al., 2007; Helder et al., 2007; Ning et al., 2006; Mitchell et al., 2006; Bassi et al., 2012; Braun et al., 2013). As stated in the section "Characteristics, expression, and loss and gain of defining molecule CD34 (Phenotype changes)", the expression of CD34 is quickly lost in cultured adipose tissue-derived stem/progenitor cells (with mesenchymal capacity) between the first passages (Lin et al., 2008, 2010; Gimble et al., 2007; Helder et al., 2007; Ning et al., 2006; Mitchell et al., 2006; Bassi et

al., 2012; Braun et al., 2013). Therefore, tissue adipose CD34+ adventitial stromal cell-like cells (to which the aforementioned terminology can be applied, including CD34+ SFCs) give rise to mesenchymal stromal cells (CD34-) under culture conditions (Braun et al., 2013); that is, tissue CD34+ SFCs have mesenchymal potential.

An example of phenotype variations of CD34+ SFCs during commitment from immature status to specific lineages in physiopathological processes. Following the behaviour of CD34+ SFCs during repair through granulation tissue in experimental conditions and in human pathology enabled us to confirm the mesenchymal capacity of these cells (non-published observations). Repair through granulation tissue involves coagulation, inflammation, angiogenesis, proliferation of mesenchymal cells, vascular involution and remodelling (Díaz-Flores et al., 2009a,b). In the first stages (1-72h after injury, with vasodilatation, serum extravasation/edematous spaces, leukocyte margination, and migration of PMNs and monocytes toward the interstitium), CD34+ SFCs are the first non-leukocyte cells to separate from the vascular wall and adipocytes, appearing in the edematous interstitium, within the extravasated serum (Fig. 10A-C) (99% of non-leukocyte-activated interstitial stromal cells express CD34, while the remaining 1% were αSMA+, from day two and three). Coinciding with tissue hydration, CD34+ SFCs increase in size and show abundant mitoses (Fig. 10D), high proliferative index (Ki67) and presence of some intracytoplasmic lipid droplets. Downregulation of CD34 and expression of αSMA (myofibroblast differentiation) occurs from day four onwards (Fig. 3B-D). Thus, from day seven onwards, whenever granulation tissue forms (with abundant newly-formed blood vessels and macrophage recruitment), stromal cells expressing CD34 are scarce (5%), while anti-αSMA+ cells are the predominant population (95%).

An example of the diversity of CD34+ SFC differentiation, depending on native location. CD34+ SFCs in different locations share many properties, including their multipotentiality and capacity to differentiate. However, such differentiation may occur more easily in one tissue or another, depending on the native source of CD34+ SFCs. Thus, bone marrow MSCs are more prone to differentiate into chondrocytes and osteocytes compared with ASCs. Conversely, ASCs have a greater tendency to differentiate into muscle cells than MSCs (Im et al., 2005; Huang et al., 2005). For Bourin et al. (2013), these features may depend on the different niches (microenvironment), where the cells reside in their native tissues, and on the protocols in *ex vivo*.

CD34+ SFCs in adult stem cell niches

As discussed above, CD34+ SFC niches may be present in different tissues, such as connective tissue (e.g., in dermis and hair follicle), adipose tissue, skeletal muscle, peripheral blood and, in particular, vessel walls. Below, we will focus on the microvasculature and on the large- and medium-sized vessels as stem cell niches of CD34+ SFCs.

The microvasculature as stem cell niche and transit point of precursor cells. Unitary hypothesis. The vasculature, above all the microvasculature (principally postcapillary venules and capillaries), has been considered an adult stem cell niche, which is a three-dimensional microenvironment, and the home of ECs, pericytes/SMCs and CD34+ SFCs. This specialized physical location includes extracellular matrix and basal lamina components. Furthermore, the microvasculature is the passing point or crossroads of transmigrating cells (Díaz-Flores et al., 2009a,b).

The microvasculature is relatively quiescent in normal conditions. Intima association and bidirectional interactions between CD34+ SFCs, pericytes/SMCs and ECs, along with microenvironmental influence, contribute to the maintenance of this vascular stability. When this complex mechanism is altered, the microvasculature quickly changes and becomes a substrate of a general inflammatory-reparative system (Díaz-Flores et al., 2009a). As outlined above an important phenomenon in the vessel wall is the activation of CD34+ SFCs, which are the first cells to separate from the vessel wall. This dissociation is followed by pericytes and ECs, and facilitated by the upregulation expression of genes involved in vessel formation, such as VEGF, angiopoietin 2 and nitric oxid synthetase, as well as by activation of metalloproteinases and suppression of their inhibitors. Hypoxia triggers this mechanism, which also leads to vessel dilation (nitric oxide), increased vascular permeability (VEGF), and the disintegration of vascular basal lamina and extracellular matrix (proteases). In such conditions, these cells rapidly pass from an associated, quiescent and stable state to a dissociated, mobile and proliferative one. In this transitory situation, there is initial formation of endothelial sprouts (angiopoietin 2) with continued migration of CD34+ SFCs and separation between pericytes and endothelial cells. Leaked plasma proteins serve as a provisional matrix where the cells continue their migration through interactions between integrins and a provisional matrix. Several factors intervene in this migration and proliferation. Descendent cells of the perivascular cells acquire the ability to differentiate into other pericytes, matrix-forming cells (fibroblasts, chondroblasts or osteoblasts), smooth muscle cells or adipocytes. The recruitment of pericytes and CD34+ SFCs, and the new association between these cells are facilitated by several signalling pathways, principally PDGF-ß/PDGFR-ß receptor, TGFß 1/ALK-5, SIP/EDG-1 and ANG/Tie 2 (Jain and Booth, 2003).

Diapedesis of leukocytes (neutrophils, macrophages and lymphocytes) precedes and accompanies angiogenesis during repair. The transmigration of these cells through blood vessel walls is not passive, since ECs, pericytes, CD34+ SFCs and migrating cells interact

by means of a cascade of signalling events, in different regulatory mechanisms. Thus, neutrophils are a source of VEGF-A and Interleukin-8 (Li et al., 2003; Ohki et al., 2005; Schruefer et al., 2006), macrophages for Interleukin-1, TNF α, PDGF-AB, TGF α and ß, FGF ß, VEGFß prostaglandin and reactive oxygen species (Polverini et al., 1977; DiPietro and Polverini, 1993; Moldovan and Moldovan, 2005). T-lymphocytes produce interferon gamma, Interleukin-1 and TNF-α. Moreover, platelets contribute with PDGF-AB, TGFß, epidermal growth factor (EGF)/TNF-α, tromboxane and insulin-like growth factor.

During the initial phase of angiogenesis, the migrating monocytes/macrophages may also contribute to the dissociation and detachment of the activated pericytes and CD34+ SFCs in parent vessels before vascular sprouts. Indeed, we have described morphologic associations between monocytes/macrophages and resident cells (pericytes and CD34+ SFCs) during this stage. These associations continue when the perivascular cells are partially detached from the vessel wall, and when they acquire transitional cell forms with myofibroblasts, suggesting interactive cooperation in migration, differentiation and functional activity (like a tug-macrophage towing a ship-perivascular cell-myofibroblast) (Díaz-Flores et al., 2009b).

Therefore, CD34+ SFCs and pericytes/SMCs in the microvessel wall and circulating fibrocytes crossing this transmigrating point may behave as precursors of other pericytes/SMCs, fibroblasts and myofibroblasts. A similar finding may occur for preexisting endothelial cells in the microvessel wall and circulating endothelial precursor cells (EPCs) (peripheral bone marrow endothelial precursor cells), which may originate other endothelial cells. In this way, a perivascular (periendothelial) niche for mesenchymal stem cells has been suggested, based on pericyte/SMC and CD34+ SFC plasticity and on the demonstration that mesenchymal stem cells, pericytes, CD34+ SFCs and myofibroblasts, in addition to changing their immunophenotype (see below), share the expression of several molecular markers at some point. Interest in this hypothesis has increased in recent years (Bianco et al., 2001; Helmbold et al., 2001; Zuk et al., 2001; Gronthos et al., 2003; Shi and Gronthos, 2003; Brachvogel et al., 2005, 2007; Djouad et al., 2007; Kolf et al., 2007; Sacchetti et al., 2007; Crisan et al., 2008; Covas et al., 2008; da Silva Meirelles et al., 2006; 2008; Khan et al., 2008; Tare et al., 2008; Zannettino et al., 2008; Arthur et al., 2009; Díaz-Flores et al., 2009a,b).

The adventitia of large- and medium-sized vessels as a stem cell (including CD34+ SFCs) niche. The arterial adventitia of large- and medium-sized vessels consists of connective tissue with small vessels (adventitial vessels), nerves, cells and extracellular matrix rich in collagen. Furthermore, in arteries with more than 30 layers of medial SMCs, the adventitial vessels originate small branches that penetrate the tunica media (generally the outer third of the media) to form the vasa-vasorum. It has been demonstrated that the adventitia of these vessels contains a cell population that has a strong ability to differentiate into mesenchymal lineages (Hu et al., 2004; Zengin et al., 2006; Pasquinelli et al., 2007; Hoshino et al., 2008; Passman et al., 2008). Indeed, adventitial cells exhibit myogenic induction (expression of αSMA and calponin) in response to TGF beta-1 and when cultured in appropriate media show osteogenic and adipogenic capacity (Hoshino et al., 2008). Furthermore, this capacity has been based on the fact that αSMA+ cells are mobilized from the arterial wall and assembled into endothelial sprouts (Zengin et al., 2006), and on the presence of Sca1(+) vascular progenitor cells in the vasculogenic zone of the arterial adventitia and are capable of differentiating into SMCs (Passman et al., 2008). Some authors separate two types of progenitor cells in the vessel wall: vascular wall-resident SMC progenitor cells (VW-SMCPCs) and vascular wall-resident mesenchymal stem cells (VW-MSCs) (Klein et al., 2010). The VW-MSCs reside in the vascular adventitia and in the subendothelial space (da Silva Meirelles et al., 2006; Zengin et al., 2006; Ergun et al., 2008). Therefore, the adventitia of large- and medium-sized vessels, in addition to contributing mesenchymal cells to the interstitium as occurs with smaller vessels, may participate in remodelling the vessel itself after injury, for example, in intimal thickening formation.

Indeed, the role of the adventitia as a source of cells and molecules that act on neointimal formation has been pointed out (Wilcox et al., 1997; Zalewski and Shi, 1997; Faggin et al., 1999; Gutterman, 1999; Li et al., 2000). This role may involve modification of the adventitia itself with release of factors that stimulate intimal thickening formation and/or a source of components of the intimal lesion. In the first case, in the adventitia surrounding injury sites, there is sequential recruitment of neutrophils, lymphocytes and monocyte/macrophages that release these stimulating factors of intimal thickening. For example, monocyte/macrophage produce superoxides, release cytokines (with myofibroblast proliferation) and enzymes that digest the extracellular matrix and facilitate adventitial cell migration (Smith et al., 1999; Wilcox et al., 2001; Díaz-Flores et al., 2009a). This response is similar to that of wound healing or stromal tumour formation (Smith et al., 1999; Wilcox et al., 2001; Díaz-Flores et al., 2009a). Wilcox et al., 1997 have hypothesized that vascular remodelling at the angioplasty site occurs when adventitial myofibroblasts constrict the vessel by forming a scar surrounding the injured artery, much as in healing skin wounds.

During development, mesoangioblasts are considered vessel-associated mesodermal stem cells (De Angelis et al., 1999; Minasi et al., 2002; Cossu and Bianco, 2003; Brunelli et al., 2004), which can be induced to differentiate into different cell types of the mesoderm, including smooth muscle cells, bone and cartilage (De Angelis et al., 1999; Minasi et al., 2002, Cossu and Bianco, 2003; Brunelli et al., 2004; Tagliafico

et al., 2004). Bianco and Cossu (1999) proposed that mesoangioblasts, originating from the dorsal aorta and accompanying the angiogenic vessels, leave the latter and adopt the fate of the tissue where the vessels enter. This concept provides further support for a perivascular niche hypothesis, since mesoangioblasts may represent ancestors of postnatal stem cells, and some vessel-associated progenitors (pericytes or a subset of pericytes) may remain undifferentiated and capable of differentiating during postnatal life (De Angelis et al., 1999; Minasi et al., 2002; Cossu and Bianco, 2003; Brunelli et al., 2004).

Role of CD34+ SFCs in immunological tolerance and in immunosuppression

As mentioned above, CD34+ SFCs meet the criteria of mesenchymal stem cells, which participate in immunological tolerance and have immunosuppressive properties. For instance, in immunotolerance, fibroblasts are involved in the recruitment and migration of T-cell precursors to fetal thymus (Liu et al., 2005; Gray et al., 2007) and promote peripheral T-cell tolerance (Lee et al., 2007). The immunosuppressive properties include inhibition of monocyte differentiation and function (Jiang et al., 2005; Nauta et al., 2006), NK cell function and T and B lymphocyte proliferation (Aggarwal and Pittenger, 2005; Gieseke et al., 2007; Sato et al., 2007). Moreover, the immunomodulatory properties of CD34+ SFCs in adipose tissue are similar to those of bone marrow mesenchymal stem cells (Puissant et al., 2005) and are applicable for the control of the graft-versus-host disease (Yañez et al., 2006).

Role of CD34+ SFCs in angiogenesis

CD34+ SFCs secrete VEGF, bFGF, PDGF-α and IL-8, which induce an angiogenic phenotype in cultured endothelial cells and promote angiogenesis *in vivo* (Hartlapp et al., 2001), in which several mechanisms participate (Díaz-Flores et al., 1994, 2009a). Thus, it has been pointed out that adipose derived stromal cells support postnatal neovascularization (Miranville et al., 2004).

CD34+ SFCs as phagocytic cells

CD34+ stromal cells have macrophage-like potentiality, as is shown in anti-CD34 and anti-CD68-stained sections, after "phagocytosis" of pigmented materials. Thus, CD34+ stromal cells that incorporate the pigment express CD34 (Fig. 10H) and are negative for anti-CD68, while macrophages express CD68 and are negative for anti-CD34. Furthermore, conventional techniques also distinguish phagocytosing CD34+ stromal cells from macrophages by their cell morphology and the characteristics of their inclusion bodies. For instance, after incorporation of melanin or other pigmented materials (iron, Indian ink, ..), CD34+ stromal cells conserve their spindle-shaped or elongated morphology, while macrophages have a large, ovoid cytoplasmic body (Fig. 10H). Likewise, the inclusion bodies in CD34+ stromal cells are smaller and more disperse than in macrophages (Fig. 10H).

Iron deposition in dermal fibrocytes is a useful tool for diagnosis of nephrogenic systemic fibrosis. The fibrocytes are often positive for CD34 and procollagen-I. 6 of 9 patients with nephrogenic systemic fibrosis showed positive iron staining in dermal fibrocytes. The amount of iron deposition correlated with apparent history of the use of gadolinium-based contrast agents.

CD34+ SFCs in pathology

CD34+ SFCs are involved in several processes, such as repair, inflammatory/immune lesions, fibrosis and tumours (including tumour stroma formation).

CD34+ SFCs in repair

As we have seen above, CD34+ SFCs are progenitor mesenchymal cells during repair (see Mesenchymal capacity of CD34+ SFCs). Repair includes two types of processes: regeneration and repair through granulation tissue. Regeneration occurs when dead, degenerated or damaged cells are replaced by other cells of the same type (e.g., parenchyma regeneration in which several factors may act - Arteaga et al., 2004). Repair through granulation tissue implies the following: I) formation of a provisional tissue (granulation tissue), with macrophage recruitment and proliferation of small blood vessels and fibroblasts-myofibroblasts, and II) posterior differentiation and remodelling towards a mature tissue. CD34+ SFCs are involved in several pathological repair processes, such as abnormal repair, atherosclerosis (e.g., role of adventitia), and tumour stroma (e.g., tumour stroma formation and cancer behaviour and metastasis). The expression of phenomena in repair is variable, including the stromal cell immunophenotype. Thus, several factors influencing CD34+ SFC behaviour after injury play an important role in the persistence of CD34+ SFCs in the lesion (without immunophenotypic transformation of CD34+ SFCs to myofibroblasts, mimicking a regenerative process) or in their transformation to myofibroblasts (anti-αSMA positivity and loss of CD34 expression, as occurs in repair through granulation tissue) (Fig. 3). For instance, the tissue around silicone prosthesis (non-published observation) or in some tumoral capsules (Díaz-Flores et al., 2011; 2012) shows abundant CD34+ SFCs (Fig. 11A-B). Conversely, in the stroma of some tumours and in skin scars (after reconstructive surgeries or excisions of malignant cutaneous neoplasms), CD34+ SFCs disappear (Erdag et al., 2007) (see below). A mixture of both types of cells (CD34+ SFCs and myofibroblasts) also occurs in some repair processes. During repair, circulating CD34+ fibrocytes leave the circulation (with participation of chemokines such as CXCL12 and expression of receptor, CCR2, CCR3, CXCR4, CCR5 and CCR7), increasing the number of resident CD34+

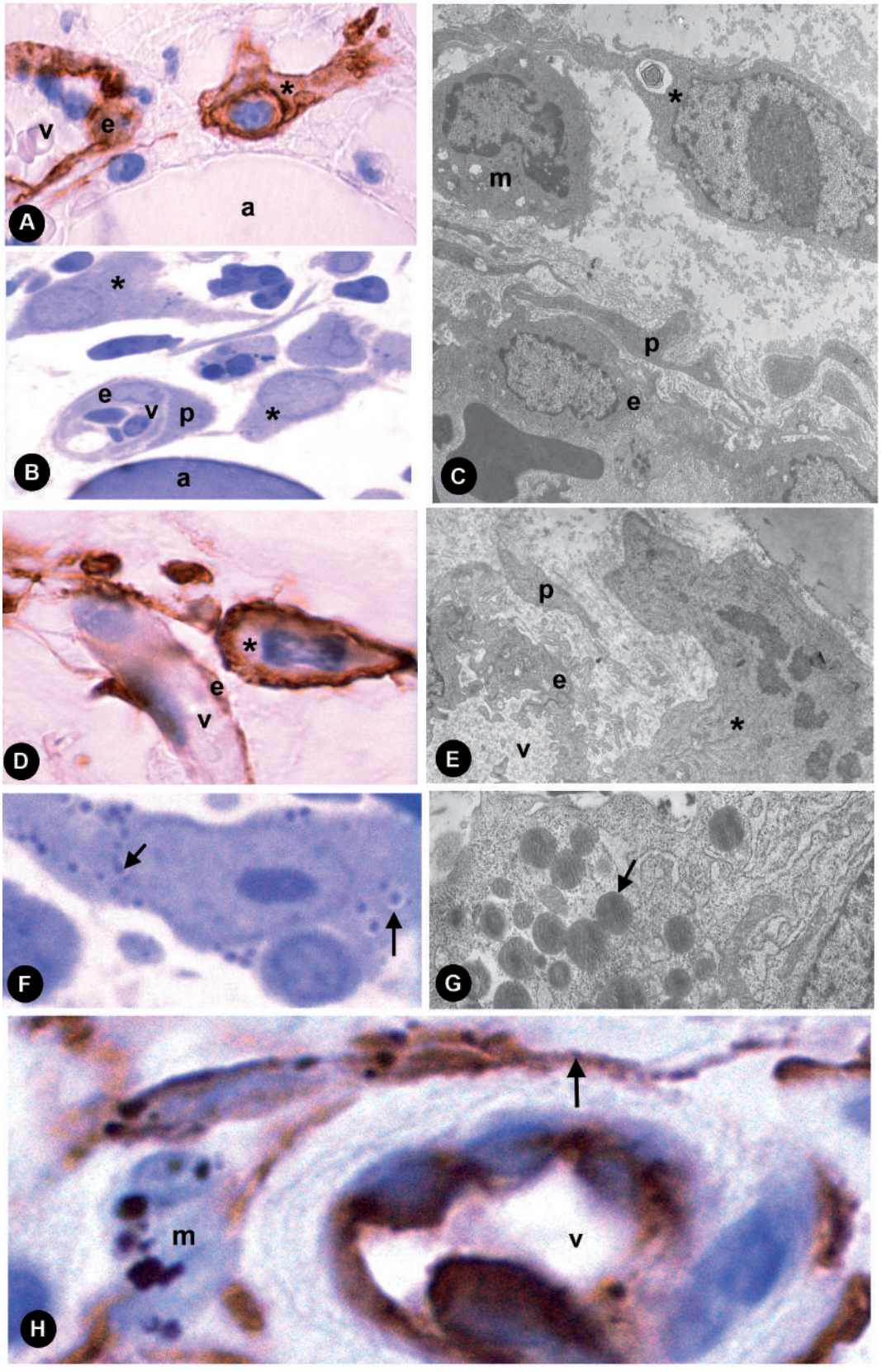

Fig. 10. CD34+ SFCs during repair in adipose tissue (**A-G**). In the first stages of repair through granulation tissue, CD34+ SFCs (asterisk) separate from the vessel wall (v) and adipocytes (a) (**A-C**) (e: endothelium; p: pericyte; m: macrophages). A CD34+ SFC in mitosis (asterisk) separating from a vessel (**D, E**). Intracytoplasmic lipid droplets (arrows) in CD34+ SFCs (**F, G**). Phagocytosis of pigment material in a macrophage (m) and in CD34+ SFCs (arrows) around a vessel (v). A, D, H, immunostaining with anti-CD34, x 380; B, F, semithin section, Toluidine blue, x 280 and x 820, respectively; C, E, G, ultrathin sections, uranyl acetate and lead citrate, x 15,000, 20,000 and 20,000, respectively.

fibrocytes when the latter are insufficient, and transform into myofibroblasts (Abe et al., 2001; Phillips et al., 2004; Moore et al., 2005). This phenomenon is inhibited by serum amyloid P (Pilling et al., 2003). *In vitro* fibrocytes express αSMA and contract collagen gel, thereby demonstrating their capacity to differentiate into myofibroblasts (Abe et al., 2001).

CD34+ SFCs in fibrosis

αSMA+ myofibroblasts play an important role in different types of fibrosis. Depending on immunohistochemical staining of their filaments, myofibroblasts may be classified as V-type (express only vimentin), VD-type (express vimentin and desmin), VAD-type (express vimentin, αSMA and desmin), VA-type (express vimentin and αSMA) and VM-type (express vimentin and myosin) (Powell et al., 1999a,b). The appearance of myofibroblasts is associated with loss of CD34 expression in CD34+ SFCs, for example, in skin scar and keloids (Aiba and Tagami, 1997; Erdag et al., 2007) and peritoneal dialysis-induced fibrosis (Jimenez-Hefferman et al., 2004). Likewise, circulating CD34+ fibrocytes may contribute to myofibroblasts in interstitial lung fibrosis (Schmidt et al., 2003; Phillips et al., 2004; Gomperts et al., 2006), systemic fibrosis (Quan et al., 2004) and nephrogenic fibrosing dermatopathy/nephrogenic systemic fibrosis (Quan et al., 2004; Daram et al., 2005). In the molecular mechanisms, TGF, and its receptor play an important role. Indeed, they are overexpressed. Numerous factors also promote proliferation and αSMA production, including PDGF, EGF, IGF-1 and 2, CTGF, IL-1, IL-13, endothelins, stem cell factor (SCF), ANG II, bFGF and PPARγ. Likewise, PDGF, IL-4 and IL-13 participate in the differentiation of CD14+ precursors to fibrocytes (Shao et al., 2008). T cells may have a role in the immunopathogenesis of fibrosis (Bucala, 2012).

CD34+ SFCs in tumours

CD34+ SFCs can participate in tumour stroma and/or form part of the tumour parenchyma.

CD34+ SFCs in the stroma of tumours

As outlined above, CD34+ SFCs and myofibroblasts play an important role in tumour stroma formation and progression (Nakayama et al., 2001; Barth et al., 2002a, 2005b; Ramaswamy et al., 2003; Kuroda et al 2005c; Ebrahimsade et al., 2007; Nimphius et al., 2007; Wessel et al., 2008). Though not always the case, many normal tissues and benign epithelial tumours contain CD34+ SFCs, whereas numerous malignant invasive epithelial tumours lose CD34 expression in the stromal cells and subsequently gain αSMA+ cells (myofibroblasts) (Fig. 11C) (Nakayama et al., 2000, 2001, 2003; Barth et al., 2002a-c, 2004, 2005b; Chauhan et al., 2003; Ramaswamy et al. 2003; Kuroda et al., 2005a,b; Ebrahimsade et al., 2007; Nimphius et al., 2007; Wessel et al., 2008). This phenotypic shift from CD34+, αSMA- fibroblasts towards CD34-, αSMA+ myofibroblasts has been considered an important prerequisite for tumour invasiveness (Barth et al., 2004, 2005b). However, this is not a constant fact; thus, CD34+ SFCs are preserved in some invasive tumours, as occurs in 2/3 of lobular carcinoma of the breast (Ebrahimsade et al., 2007). Some authors consider that circulating fibrocytes play an important role in contributing to tumour associated myofibroblasts and fibroblasts (Direkze et al., 2004, 2006).

We studied the phenotype of the stromal cells (CD34 fibroblasts and cells expressing αSMA) that may intervene through repair mechanisms to form the encapsulated or unencapsulated borders of 2 groups of tumours, depending on whether the tumoral cells express CD34 (e.g., solitary fibrous tumours) or αSMA (e.g., glomus tumours, myopericytomas and angioleiomyomas) (non-published observations). Our results show that the border of each group comprises stromal cells whose phenotype is opposite to that of the tumour: αSMA+ stromal cells for CD34+ tumours (Fig. 11D) and CD34+ stromal cells for αSMA+ tumours (Fig. 11B). An increased population of CD34+ SFCs was also observed in the peripheral areas of scars containing αSMA+ cells (Erdag et al., 2007).

CD34+ SFCs as a possible component of the tumour parenchyma (tumours partially or totally consisting of CD34+ SFCs)

Since CD34+ SFCs are considered to be progenitor cells with great mesenchymal potential (see CD34+ SFCs as progenitor cells: Mesenchymal stromal progenitor/stem cell capacity/Multipotent mesenchymal stromal capacity), they may participate (totally or partially) as tumour cells in several soft tissue tumours. In Table 1, we outline the mesenchymal tumours containing CD34+ SFCs. In some types of tumour, CD34 expression may occur in all or most cells, thereby contributing significantly to diagnosis. In other types of tumour, CD34 expression varies and yet in others is only demonstrated in scant cells. In most cases, co-expression of other markers is common. Other tumours expressing CD34 do not appear to be related to CD34+ SFCs and are therefore not included in the table.

Current concept of CD34+, SFCs as resident cells with mesenchymal potential, and clinical and therapeutic promise

CD34+ SFCs are considered a reservoir of tissue mesenchymal cells. Our observations of their characteristics in human adult stem cell niches in several tissues and organs, and of their *in vivo* behaviour during proliferation and differentiation in different physiologic and pathologic conditions suggest that their mesenchymal potential is, in all probability, higher than that proposed for pericytes and other stromal cells.

Since CD34+ SFCs and their derivatives (with loss

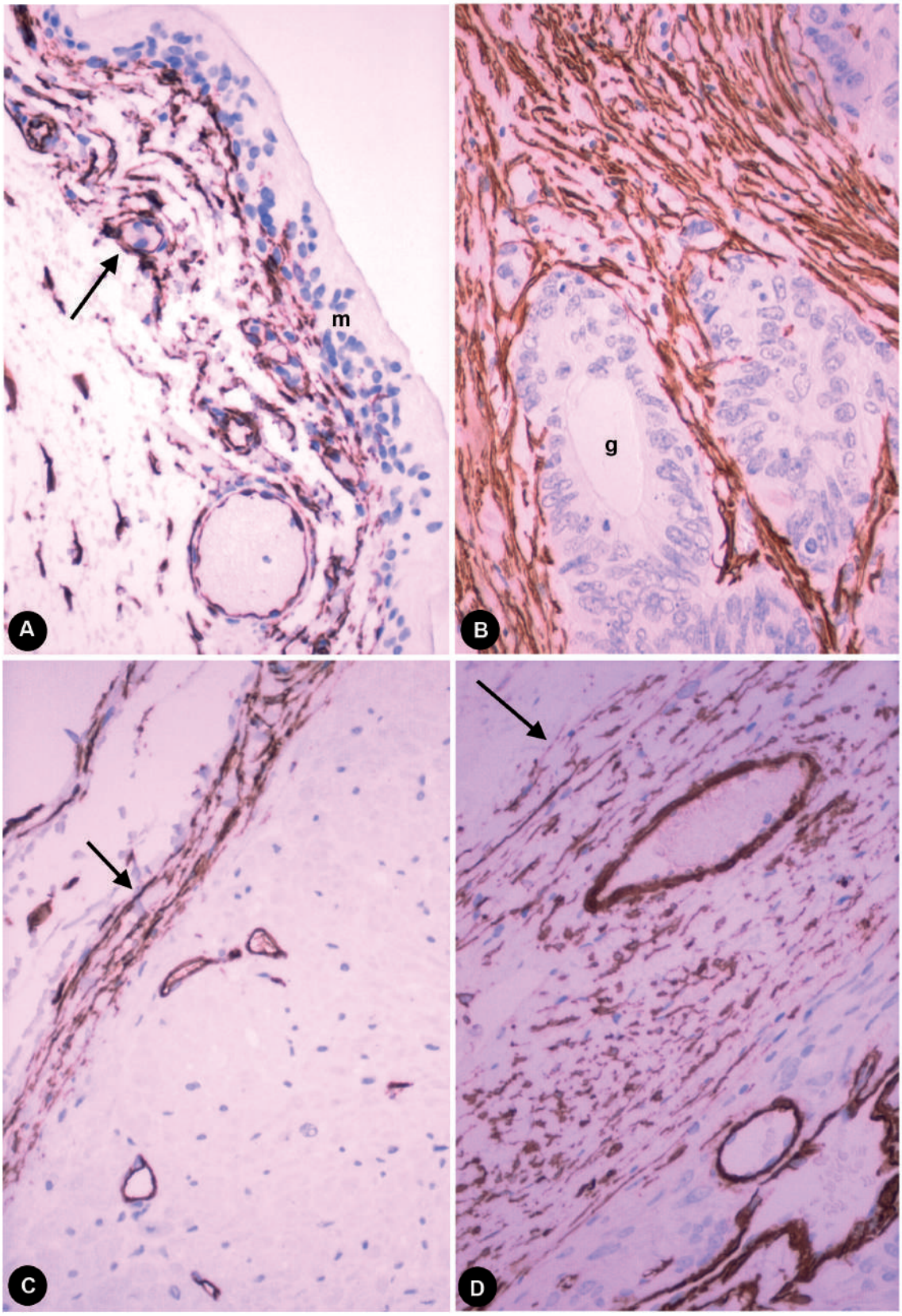

Fig. 11. Examples of reactive stroma with CD34+ SFCs or myofibroblasts. Macrophages (m) and CD34+ SFCs around silicone prosthesis **(A)**. Observe that macrophages form a continuous layer mimicking an epithelium and that CD34+ SFCs are located beneath this layer (arrow). A malignant invasive epithelial tumour (colon adenocarcinoma) in which the neoplastic glands (g) are surrounded by αSMA+ myofibroblasts **(B)**. CD34+ SFCs form the capsule (arrow) of an αSMA+ tumour (angioleiomyoma, in which αSMA positivity is not shown) **(C).** αSMA+ cells (myofibroblasts) form the capsule (arrow) of a CD34+ tumour (solitary fibrous tumour, in which CD34 positivity is not shown) **(D)**. Vascular endothelial cells in **C** also show positivity for CD34. Perivascular cells are also αSMA+ in **D**. A, C, x 140; B, D, x 230

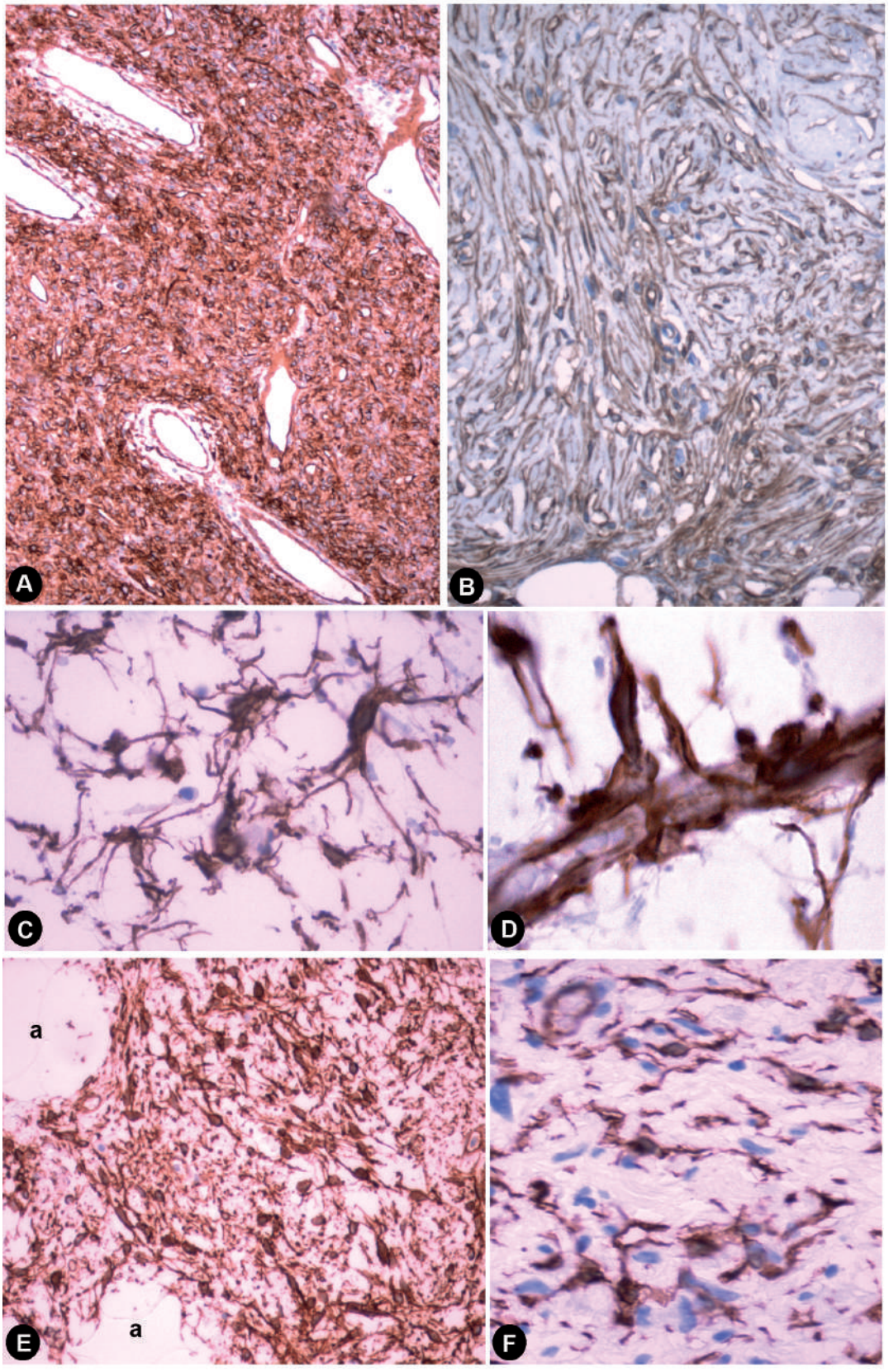

Fig. 12. Examples of soft tissue tumours in which CD34+ fibroblasts are an important component. Solitary fibrous tumour **(A).** Dermatofibrosarcoma protuberans **(B)**. Superficial angiomyxoma **(C)**. Some cells of angiomyxoma show processes ending in a vessel wall **(D)**. Spindle cell lipoma (a, adipocytes) **(E)**. Neurofibroma **(F)**. A, x 90; B, x 230; C, x 260; D, x 640; E, x 260; F, x 280

Table 1. Mesenchymal tumours containing CD34+ SFCs.

Tumour	Other immunophenotypic expression	References
Solitary fibrous tumour/Haemangiopericytoma	Vimentin (100%); bcl2 (65-70%); CD99 (40-70%); EMA (30%); SMA (15-30%)	Van de Rijn et al., 1994; Hanau and Miettinen, 1995; Suster et al., 1995; Nielsen et al., 1996; Fukunaga et al., 1997; Mentzel et al., 1997; Brunnemann et al., 1999; Heim-Hall and Yohe, 2008
Dermatofibrosarcoma protuberans	Apolipoprotein D, SMA in myoid nodules	Aiba et al., 1992; Mentzel et al., 1998a; West et al., 2004
Giant cell fibroblastoma	Vimentin, CD99, focal, Catenin	Terrier-Lacombe et al., 2003; Jha et al., 2007
Nuchal-type fibroma	Vimentin, CD99, focal, Catenin	Michal et al., 1999; Diwan et al., 2000; Zamecnik and Michal, 2001
Gardner fibroma	Vimentin, CD99, focal, Catenin	Diwan et al., 2000; Carlson and Fletcher, 2007
Mammary and extramammary types myofibroblastoma	Desmin, Estrogen-Progesteron, SMA (33%), bcl2, CD99 (variable)	McMenamin and Fletcher, 2001; Heim-Hall and Yohe, 2008; Beltran and Markiewicz, 2009
Acral fibromyxoma (superficial acral fibromyxoma/ cellular digital fibroma/ digital fibromyxoma)	Variable CD99, EMA, CD10	Fetsch et al., 2000, 2001; McNiff et al., 2005; Guitart et al., 2006; Al-Daraji and Miettinen, 2008; Prescott et al., 2008; Tardío et al., 2008; Luzar and Calonje, 2009
Superficial angiomixoma	SMA; S100; Factor XIIIa	Allen et al., 1988; Fetsch et al., 1997; Calonje et al., 1999
Cellular angiofibroma 30-60%	Desmin, Progesterone, Estrogen, variable SMA	Iwasa and Fletcher, 2004; Jha et al., 2007; McCluggage et al., 2004
Esclerotic fibroma (circunscribed storiform collagenoma; pleomorphic fibroma)	CD-99	Rudolph et al., 1999; Hanft et al., 2000; Mahmood et al., 2003
Elastofibroma	CD-133; factor XIIIa	Hisaoka and Hashimoto, 2006; Yamazaki, 2007
Plaque-like CD34+ dermal fibroma (medallon-like dermal dendrocyte hamartoma)		Kutzner et al., 2010; Rodríguez-Jurado et al., 2004; Shah et al., 2007
Spindle cell pleomorphic lipoma (Myxolipoma, dendritic fibromyxolipoma) Spindle cell hibernoma (+ in spindle cell component)	Occasionally S100, bcl2, Desmin (in spindle cell hibernoma, S100 + more frequent)	Templeton and Solomon, 1996; Suster and Fisher, 1997; Suster et al., 1998a,b; Graadt van Roggen et al., 1999; French et al., 2000 ; Furlong et al., 2001
Lipoblastoma	S100, desmin	Coffin et al., 2009
Lipofibromatosis and sclerotic lipomas (Variable)	Focal SMA, S100; CD-99; EMA	Zelger et al., 1997; Fetsch et al., 2001; Kabasawa et al., 2007
Well-differentiated liposarcoma (in spindle cells) and pleomorphic liposarcoma (focally +50%)	Occasionally S100, keratin, EMA, desmin, hmg2	Gebhard et al., 2002; Heim-Hall and Yohe, 2008
Hemosiderotic fibrolipomatous tumours	Calponin	Marshall-Taylor and Fanburg-Smith, 2000; Browne and Fletcher, 2006; Famburg-Smith et al., 2013
Neurofibroma (stromal cells)	S100 (40-50% cells)	Weiss and Nickoloff, 1993; Khalifa et al., 2000; Hirose et al., 2003
Perineurioma (60%)		Díaz-Flores et al., 1997; Hornick and Fletcher, 2005
Schwannoma (B Antoni)	S100	Weiss and Nickoloff, 1993; Khalifa et al., 2000; Hirose et al., 2003
Hybrid nerve sheath tumours		
Calcifying fibrous tumour	Occasional SMA and Desmin	Nascimento, 2013
Fibrous hamartoma of infancy (In sclerotic areas on angiomatoid spaces)		Fletcher et al., 1988; Groisman and Lichtig, 1991; Popek et al., 1994; Michal et al., 1999
Intramuscular myxoma	Desmin, SMA	Nielsen and Hogendorn, 2013
Pleomorphic hyalinizing angiectatic tumour of soft parts		Weiss and Dei Tos, 2013
Ischemic fasciitis (Atypical decubital fibroplasia) (50%)	SMA; CD-68	
Epithelial sarcoma (50%)	Keratins, EMA	Oda et al., 2013

of CD34 expression) have great mesenchymal potential, their clinical and future therapeutic implications are outlined in numerous studies for mesenchymal cells, including: a) in regenerative medicine and tissue engineering, b) in angiogenesis, by means of factors that promote destabilization or formation of a stable vasculature, c) in wound healing (topical cell application using mesenchymal cell delivery materials and hydrogels, such as fibrin sealants), based on stimulation of regenerative paracrine signalling, spreading proliferation and differentiation into resident cells, and on preventing apoptosis, d) in homeostatic mechanisms that maintain the hematopoiesis (bone marrow microenvironment), e) in the interaction (equipped to interact) with innate and adaptive immune system, (modulate the immune system, e.g., suppressing T cell proliferation), f) in adipose tissue during proliferation or differentiation of adipocyte progenitor cells (to prevent obesity), g) in cellular and molecular mediators of fibrosis in diverse tissue and organs (to prevent, reduce or reverse), and h) modulation of tumour stroma. Nevertheless, the difficulty of establishing appropriate procedures and protocols, together with the concurrence of adverse events (e.g., impair immune surveillance, promote tumour growth, metastasis and angiogenesis), indicate the need for further studies.

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