Histol Histopathol (2020) 35: 1083-1103

http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

Review

Intussusceptive angiogenesis and its counterpart intussusceptive lymphangiogenesis

L. Díaz-Flores[1], R. Gutiérrez[1], S. Gayoso[1], M.P. García[2], M. González-Gómez[1], L. Díaz-Flores Jr[1], R. Sánchez[3], J.L. Carrasco[1] and J.F. Madrid[4]

[1]Department of Basic Medical Sciences, Faculty of Medicine, University of La Laguna, [2]Department of Pathology, Eurofins® Megalab-Hospiten Hospitals, [3]Department of Internal Medicine, Dermatology and Psychiatry, Faculty of Medicine, University of La Laguna, Tenerife and [4]Department of Cell Biology and Histology, School of Medicine, Campus of International Excellence "Campus Mare Nostrum", IMIB-Arrixaca, University of Murcia, Murcia, Spain

Summary. Intussusceptive angiogenesis (IA) is currently considered an important alternative and complementary form of sprouting angiogenesis (SA). Conversely, intussusceptive lymphangiogenesis (IL) is in an initial phase of study. We compare their morphofunctional characteristics, since many can be shared by both processes. To that end, the following aspects are considered: A) The concept of IA and IL as the mechanism by which blood and lymphatic vessels split, expand and remodel through transluminal pillar formations (hallmarks of intussusception). B) Terminology and historical background, with particular reference to the group of Burri, including Djonov and Patan, who initiated and developed the vessel intussusceptive concept in blood vessels. C) Incidence in normal (e.g. in the sinuses of developing lymph nodes) and pathologic conditions, above all in vessel diseases, such as dilated veins in hemorrhoidal disease, intravascular papillary endothelial hyperplasia (IPEH), sinusoidal hemangioma, lobular capillary hemangioma, lymphangiomas/lymphatic malformations and vascular transformation of lymph nodes. D) Differences and complementarity between vessel sprouting and intussusception. E) Characteristics of the cover (endothelial cells) and core (connective tissue components) of pillars and requirements for pillar identification. F) Structures involved in pillar formation, including endothelial contacts of opposite vessel walls, interendothelial bridges, merged adjacent capillaries, vessel loops and spilt pillars. G) Structures resulting from pillars with intussusceptive microvascular growth, arborization, remodeling and segmentation (compartmentalization). H) Influence of intussusception in the morphogenesis of vessel tumors/ pseudotumors; and I) Hemodynamic and molecular control of vessel intussusception, including VEGF, PDGF BB, Hypoxia, Notch, Endoglobin and Nitric oxide.

Key words: Lymphangiogenesis, Intussusceptive angiogenesis

Offprint requests to: Lucio Díaz-Flores, Universidad de La Laguna, Facultad de Medicina, Departamento de Ciencias Médicas Básicas, Ofra-La Cuesta s/n, La Laguna, 38071 Tenerife, Islas Canarias, Spain. email: kayto54@gmail.com

DOI: 10.14670/HH-18-222

The concept of angiogenesis and lymphangiogenesis

Angiogenesis and lymphangiogenesis are the mechanisms by which blood and lymphatic vessels, respectively, develop from an established vasculature in the embryo, and in several normal and pathological conditions in postnatal life.

Sprouting angiogenesis (SA)/sprouting lymphangiogenesis (SL) and intussusceptive angiogenesis (IA)/intussusceptive lymphangiogenesis (IL) are the two principal types (sprouting and intussusceptive) of angiogenesis/lymphangiogenesis. Indeed, although the sprouting type has generally been identified with angiogenesis/lymphangiogenesis, the intussusceptive type is currently considered an important alternative or complementary form of SA/SL. Other types of neovascularization, such as vasculogenic mimicry or

vessel co-option (see Díaz-Flores et al., 2017a) will not be considered in this work.

The concept of intussusception in blood (IA) and lymphatic (IL) vessels

Intussusception (IA and IL) can be defined as the processes by which pre-existing blood and lymphatic vessels split, expand and remodel during development and post-natal life through the formation of transluminal tiny pillars/posts (diameter ≤2.5 μm), large/giant pillars (diameter >2.5 μm), and folds, which form pillars when spanning opposite vessel walls. The presence of these intravascular structures (hereinafter, pillars) is the principal indicator of IA and IL (pillars as hallmarks of intussusception), which form by extension of endothelial cellular processes, followed by collagen, vascular mural cells and other tissue connective cells into the vessel lumen. This process leads to expansion (intussusceptive microvascular growth: IMG), arborisation (intussusceptive arborisation: IAR), branching remodelling (intussusceptive branching remodelling: IBR) and/or segmentation (intussusceptive segmentation) of the vasculature (Caduff et al., 1986; Burri, 1990, 1992; Burri and Tarek, 1990; Patan et al., 1996a, 2001a,b; Djonov et al., 2000a,b, 2003; Augustin, 2001; Burri and Djonov, 2002; Burri et al., 2004; Makanya et al., 2009; Paku et al., 2011; Díaz-Flores et al., 2018a).

Nomenclature in IA and IL (Terminological questions)

In addition to intussusceptive angiogenesis (Burri, 1992; Djonov, 2000a; Burri and Djonov, 2002; Burri et al., 2004), different denominations have been used for this process in blood vessels, including vessel intussusception, intussusceptional angiogenesis (Caduff et al., 1986), in-itself vessel growth (Caduff et al., 1986), non-sprouting angiogenesis (Frontczak-Baniewicz and Walski, 2002; Kurz et al., 2008; Groppa et al., 2018), splitting angiogenesis (Ji et al., 2006; Williams et al., 2006a; Gianni-Barrera et al., 2011, 2018; Hussain et al., 2012) and inverse sprouting angiogenesis (Paku et al., 2011). Depending on the final results of the process, the terms intussusceptive microvascular growth, intussusceptive arborisation, intussusceptive branching and intussusceptive segmentation are also specifically used for the main forms of intussusceptive angiogenesis (Djonov, 2000b, 2001, 2002; Patan et al., 2001a,b; Burri and Djonov, 2002; Burri et al., 2004; Makanya et al., 2009; De Spiegelaere et al., 2012). Of these denominations, only the term intussusceptive lymphangiogenesis has been taken into account for this process in lymphatic vessels (Díaz-Flores et al., 2019a-c).

The findings described with the denominations intraluminal or internal splitting angiogenesis or longitudinal/luminal division, in which only intraluminal processes of ECs are formed, have raised the problem of whether they should be considered synonymous of intussusceptive angiogenesis or characteristics of another type of angiogenesis (Zhou et al., 1998; Williams et al., 2006b; Egginton, 2009). Even more, both processes (intussusceptive angiogenesis and longitudinal splitting/growth by division of existing vessels) have been jointly described (Groningen van et al., 1991). Gianni-Barrera et al. (2018) used the term vascular splitting for grouping both possibilities. In any case, the different opinions can be combined when considering the filopodial ridges (characteristics of longitudinal splitting) as structures involved in pillar formation (intraluminal endothelial bridges or nascent pillars) or remain as ridges (see section "structures involved in pillar formation…").

Historical background of IA and IL

IA has received considerable attention, whereas IL has been poorly studied. The concept of blood vessel growth by intussusception was introduced by Caduff et al. (1986). Using vascular corrosion casts and scanning electron microscopy to study rabbit postnatal pulmonary parenchyma, these authors proposed that tiny holes observed in a sheet-like region of the microvasculature of growing postnatal lung enlarge to form new capillary meshes (in-itself or intussusceptional growth). The holes in casts corresponded histologically to intravascular tissue pillars. Then, in studies in the postnatal lung and in chicken chorioallantoic membrane (CAM), the Burri group coined the term intussusceptive microvascular growth as a new mechanism of capillary network formation (Burri and Tarek, 1990; Burri, 1992; Djonov et al., 2000b), contributed the ultrastructure of the hole (terms used: interendothelial bridge/post/pillar) and the phases of pillar formation (Burri and Djonov, 2002; Burri et al., 2004). After the concept of intussusception was established, Burri and Djonov (2002) reviewed the literature and honestly indicated that minute intercapillary meshes had been described by Thoma (1893) and Clark (1918) and that Short (1950) had the merit of linking these meshes with growth. However, Burri, Djonov, Patan and collaborators (Burri and Tarek, 1990; Burri, 1992; Patan et al., 1992, 1993, 1996a,b, 1997, 2001a,b; Patan, 1998, 2000, 2004, 2008; Djonov et al., 2000a,b, 2002, 2003; Burri and Djonov, 2002; Burri et al., 2004; Djonov and Makanya, 2005) are the ones who truly started and developed the concept of blood vessel growth by intussusception. This mechanism of formation was later expanded (Burri and Djonov, 2002; Burri et al., 2004). Indeed, the use of the chicken chorioallantoic membrane (CAM) and other procedures contributed to the evidence and implementation of facets of intussusceptive pillar formation and their outcome, including IMG, IBR and IAR as a common alternative to capillary sprouting (Patan et al., 1992, 1993, 1996a; Djonov et al., 2000a,b; Burri and Djonov, 2002; Djonov et al., 2002, 2003;

Burri et al., 2004), as well as intussusceptive segmentation (Patan et al., 2001). Several authors have contributed to the incidence of IA in other locations (Groningen van et al., 1991; Hansen-Smith et al., 1996; Zhou et al., 1998; Macchiarelli et al., 2006; Andres and Djonov, 2010; De Spiegelaere et al., 2010, 2012; Kelly et al., 2017; Fidan et al., 2019), in pathological processes (Patan et al., 1996, 2001a,b; Djonov et al., 2001; Crivellato et al., 2003; Konerding et al., 2010; Nico et al., 2010; Van Steenkiste et al., 2010; Ribatti and Djonov, 2012) and in vessel diseases, including vessel tumors and pseudotumors (Díaz-Flores et al., 2016a, 2018a,b). Although the influence of hemodynamic conditions and molecular mechanisms in IA have not been fully resolved, there are numerous contributions to this issue (Williams et al., 2006a,b; Winnik et al., 2009; Baum et al., 2010; Taylor et al., 2010; Styp-Rekowska et al., 2011; Dimova et al., 2013, Gianni-Barrera et al., 2013; Belle et al., 2014; Gianni-Barrera et al., 2014; Mentzer and Konerding, 2014; Naylor et al., 2014; Packham et al., 2014; Hlushchuk et al., 2017; Logothetidou et al., 2017; Groppa et al., 2018; Vimalraj et al., 2018, 2019; D'Amico et al., 2019; Dimova et al., 2019; Esteban et al., 2019). Conversely, the concept of intussusception in lymphatic vessels is in an initial phase of study (Díaz-Flores et al., 2019a-c).

Incidence of IA and IL

IA and IL occur in developing tissues, in physiologic conditions and in several pathologic processes, including tumours. Thus, IA has been demonstrated in all the species, tissues and organs studied for this purpose. Indeed, IA has been described in lung of neonatal rat (Caduff et al., 1986; Burri and Tarek, 1990), developing chicken eye vasculature and in the chorioallantoic membrane (Patan et al., 1993, 1996a, 1997; Schlatter et al., 1997; Djonov et al., 2000b), kidney (Djonov et al., 2002; Makanya et al., 2005; Logothetidou et al., 2018), ovary, retina, bone and skeletal muscle (Hansen-Smith et al., 1996; Zhou et al., 1998), myocardium (Groningen van et al., 1991), placenta (Fidan et al., 2019), spleen (Kelly et al., 2017) among other tissues and organs (Macchiarelli et al., 2006; Andres and Djonov, 2010; De Spiegelaere et al., 2010, 2012), and experimentally in hypoxic and inflammatory processes (Konerding et al., 2010), as well as in liver cirrhosis (Van Steenkiste et al., 2010). Several tumours also show IA and IL (Ribatti and Djonov, 2012), including carcinomas of colon (Patan et al., 1996b, 2001b), kidney and mammary gland (Djonov et al., 2001), melanomas (Nico et al., 2010) and gliomas and lymphomas (Crivellato et al., 2003; Nico et al., 2010). Likewise, intussusception participates in vascular diseases, including hemorrhoidal dilated veins in hemorrhoidal disease and tumours and pseudotumors of blood and lymphatic vessels (Díaz-Flores et al., 2016a, 2018a,b, 2019a,c). IL has been described in the sinuses of developing lymph nodes, in transformation vascular of lymph nodes and in lymphangiomas/lymphatic malformations (Díaz-Flores et al., 2019a-c).

General differences between (SA/SL) and (IA/IL)

The differences between SA/SL and IA/IL include 1) the growth path of endothelial cells (ECs) from the pre-existing vessels: ECs growing toward the interstitium (outward growth) with abluminal morphogenic findings in SA/SL and ECs extending toward the lumen of the vessel itself (in-itself extension or intussusception) with intraluminal morphogenic findings in IA/IL (Zhan et al., 2018), 2) blood or lymph flow: SA/SL may occur with or without blood or lymph flow in the pre-existing vessels, while IA/IL need pre-existing vessels with blood or lymph flow, 3) EC proliferation: higher rate of EC proliferation in SA/SL (in stalk ECs) than in IA/IL, compensated in IA/IL with spreading and thinning of ECs (Kauffman et al., 1975; Schlatter et al., 1997; Djonov et al., 2000a,b, 2002, 2003; Kurz et al., 2003). EC-proliferation can occur after the IA phase, when the lumen of the divided vessels expands, 4) metabolic cost: higher in SA/SL than in IA/IL (IA/IL is more energy-efficient). Indeed, IA/IL is a more simple process, without EC proliferation or invasive behaviour, 5) duration time: a longer process in SA/IA (a few days) than in IA/IL with a rapid increase of the capillary network (minutes, hours) (Djonov et al., 2000a,b, 2002), 6) the behaviour of the interstitium: interstitial tissue degradation occurs in SA/SL, but is minimal in IA/IL, 7) perfusion of newly formed capillaries: sluggish in SA/SL (needs a certain time to integrate into the vascular system) and immediate (without interruption of the functionality during vessel formation) in IA/IL, 8) SA/SL and IA/IL are involved in vessel growth and expansion, but IA/IL also have other important roles, such as vessel remodelling (Burri and Tarek, 1990).

Specific differences between sprouting and intussusception depending on location: blood or lymphatic vessels

In addition to the aforementioned differences between SA/SL and IA/IL, the differences can also depend on whether these mechanisms of sprouting and intussusception occur in blood or lymphatic vessels, especially in associated conditions, formation of secondary structures and outcomes.

Sprouting in blood vessels (with vessel dilation, increased permeability and degradation of the basal membrane) can be associated with coagulation, inflammation and proliferation of mesenchymal cells. Indeed, the presence in the blood vessel walls (predominantly in the pericytic microvasculature) of cells with progenitor capacity, such as ECs, pericytes, perivascular fibroblasts/stromal cells/telocytes, and homing cells from the bone marrow (MSCs, monocytes-fibrocytes) form a niche and transit point of precursor cells (Díaz-Flores et al., 2009a,b, 2014, 2015a,b, 2016b-d). This niche is a common substrate of regulatory

mechanisms that include 1) control of quiescent and angiogenic stages (cell-cell contacts and soluble factors), 2) interactions between transmigrating cells and niche resident cells, and 3) regulation of cell recruitment, proliferation, and differentiation. Thus, sprouting angiogenesis plays an important role in tissue repair through granulation tissue (Díaz-Flores et al., 2009a) and tumor stroma formation, while intussusception in blood vessels facilitates neovascularization without modifying vascular permeability and without participating in the aforementioned processes. The participation of sprouting and intussusception in lymphatic vessels can be secondary or reactive to these processes.

Intussusception in blood and lymphatic vessels leads to the formation of new vessels and to other structures with a different functionality, such as vessel arborization, pruning, or compartmentalization and formation of an intra-vessel meshwork of processes with immunological functions. The intensity and characteristics of these processes can vary depending on whether they occur in blood or lymphatic vessels, including different size vessels (see below).

Complementarity between sprouting (SA/SL) and intussusception (IA/IL)

Sprouting and intussusception can be complementary mechanisms, with synergistic interaction (Djonov et al., 2000a; Hlushchuk et al., 2011b; Peebo et al., 2011; Konerding et al., 2012; Díaz-Flores et al., 2017b; Karthik et al., 2018). With regard to blood vessels, IA was shown to participate in capillary expansion or vessel remodelling following a SA phase. Experimental models were undertaken in the chick chorioallantoic membrane, developmental avian kidney, lung and zebrafish caudal vein plexus, and the rat femoral vein, among others (Djonov et al., 2000a,b; Burri and Djonov, 2002; Makanya et al., 2005, 2007; Gibney et al., 2012; Ackermann et al., 2014; Díaz-Flores et al., 2017b; Karthik et al., 2018). For example, in the rat femoral vein after PGE2 and glycerol perivenous administration, two overlapping phases occur: initial vein wall vascularization from vein ECs with predominance of SA, followed by IA with vessel loop and pillar formation and vein remodelling (Díaz-Flores et al., 2017b) (see below). Likewise, the development of zebrafish caudal vein plexus is initiated by SA, while subsequent growth and remodelling occurs mainly by IA (Karthik et al., 2018). An example of these complementary mechanisms in lymphatic vessels is their association during the formation of lymph node sinuses, in which SA participates in an initial phase by lymphatic sprouts, which grow toward the lymph node anlage and form a lymphatic sac around the LN anlage. When the lymph node sinuses emerge from the lymphatic sac, numerous intussusceptive pillars form, originating a meshwork of intra-sinusal processes between the opposite walls of the sinuses (Díaz-Flores et al., 2019b).

Characteristics of pillars in IA and IL. Requirements for pillar identification

In vascular corrosion casting, pillars appear as holes of round, oval or slit-like morphology (Caduff et al., 1986; Burri and Tarek, 1990; Burri, 1992; Patan, 1993, 1996a,b, 1997; Djonov et al., 2000a,b, 2002, 2003; Burri and Djonov, 2002; Burri et al., 2004; Djonov and Makanya, 2005). In light microscopy (including immunohistochemical techniques), confocal microscopy and transmission electron microscopy, intravascular pillars show a cover and a core. The pillar cover is formed by ECs, which are CD34+ (Fig. 1A,B), CD31+, podoplanin-, VEGFR3- and Prox-1- in blood vessels, and podoplanin+ (Fig. 1C,D), VEGFR3+, Prox1+, CD31+ and CD34- in lymphatic vessels. The pillar core content, formed by interstitial tissue structures (ITSs), depends on pillar size. In general, pillars contain a core of packed collagen fibres in both blood (Fig. 2A,B) and lymphatic (Fig. 2C,D) vessels. Processes of mural cells (pericytes or vascular SMCs) (Fig. 3A,B) and fibroblasts/myofibroblasts may be observed. In addition to these components, large pillars can contain other interstitial cells, varying-sized blood vessels (Fig. 3C) and, above all, giant pillars of lymphatic vessels in lymphangiomas/lymphatic malformations, other complex tissue structures, such as larger vessels (Fig. 3D), nerves, glands, cutaneous annexes or striated muscle (Fig. 3E) (Díaz-Flores et al., 2019a).

3D demonstration is required for the precise identification of pillars and to exclude vessel bifurcations or other structures that simulate pillars (Burri and Tarek, 1990; Djonov et al., 2000a,b, 2001; Burri and Djonov 2002; Djonov et al., 2002; Burri et al., 2004; Hlushchuk et al., 2008; De Spiegelaere et al., 2012; Díaz-Flores et al., 2019b,c). Procedures include a) vascular corrosion casting using scanning electron microscopy (recognition of holes), b) tissue sections immunostained with endothelial markers (to which collagen and pericyte markers, among others, can be added) using confocal laser scanning microscopy (Fig. 4), c) serial histological sections (semithin and ultrathin) with observation of the subsequent appearance, disappearance and contact changes of pillars and ITSs, and d) intravascular injection of a fluorescent dye and *in vivo* microscopic video analysis.

Structures involved in pillar formation (primary structures/pillar precursors). Characteristics and mechanisms

The structures that are involved in pillar formation (Fig. 5A-J) include: A) Endothelial contacts of opposite vessel walls. B) Endothelial ridges and transcapillary interendothelial bridges (nascent pillars), including the peg-like form. C) Merged adjacent capillaries with modified contacting walls. D) Vessel loops. E) Split pillars, (Patan et al., 2001a,b; Burri and Djonov, 2002; Burri et al., 2004; Díaz-Flores et al., 2018a,b, 2019a-c).

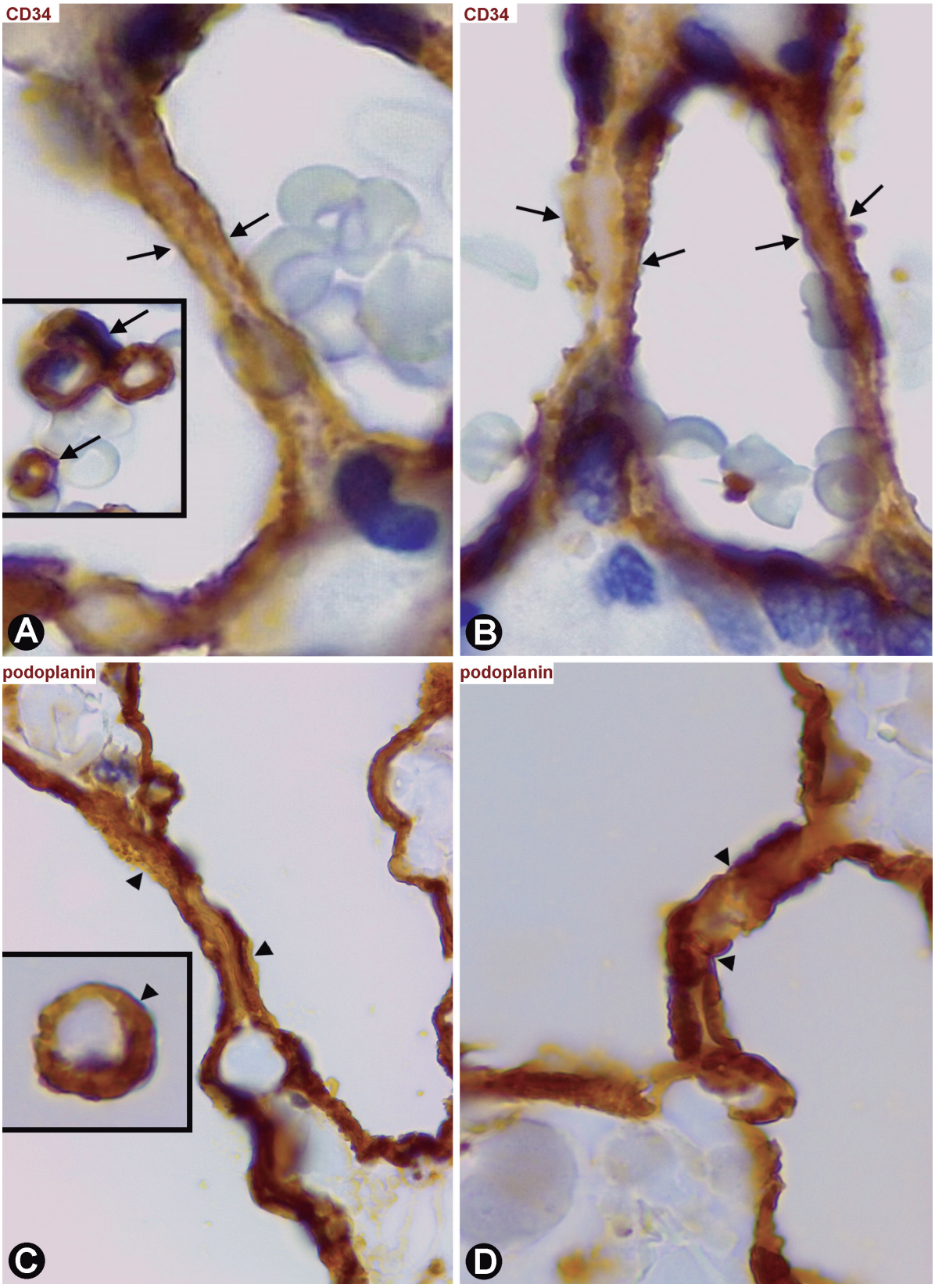

Fig. 1. Characteristics of pillars in longitudinal **(A-D)** and transversal sections (inserts in **A** and **C**) in blood **(A and B)** and lymphatic vessels **(C and D)** immunostained with anti-CD34 and anti-podoplanin, respectively. Note that the covers of pillars in blood vessels appear formed by anti-CD34+ ECs (arrows) **(A and B)** and in lymphatic vessels by anti-podoplanin+ LECs (arrowheads) **(C and D)**. A, B, × 760; C, D, × 600.

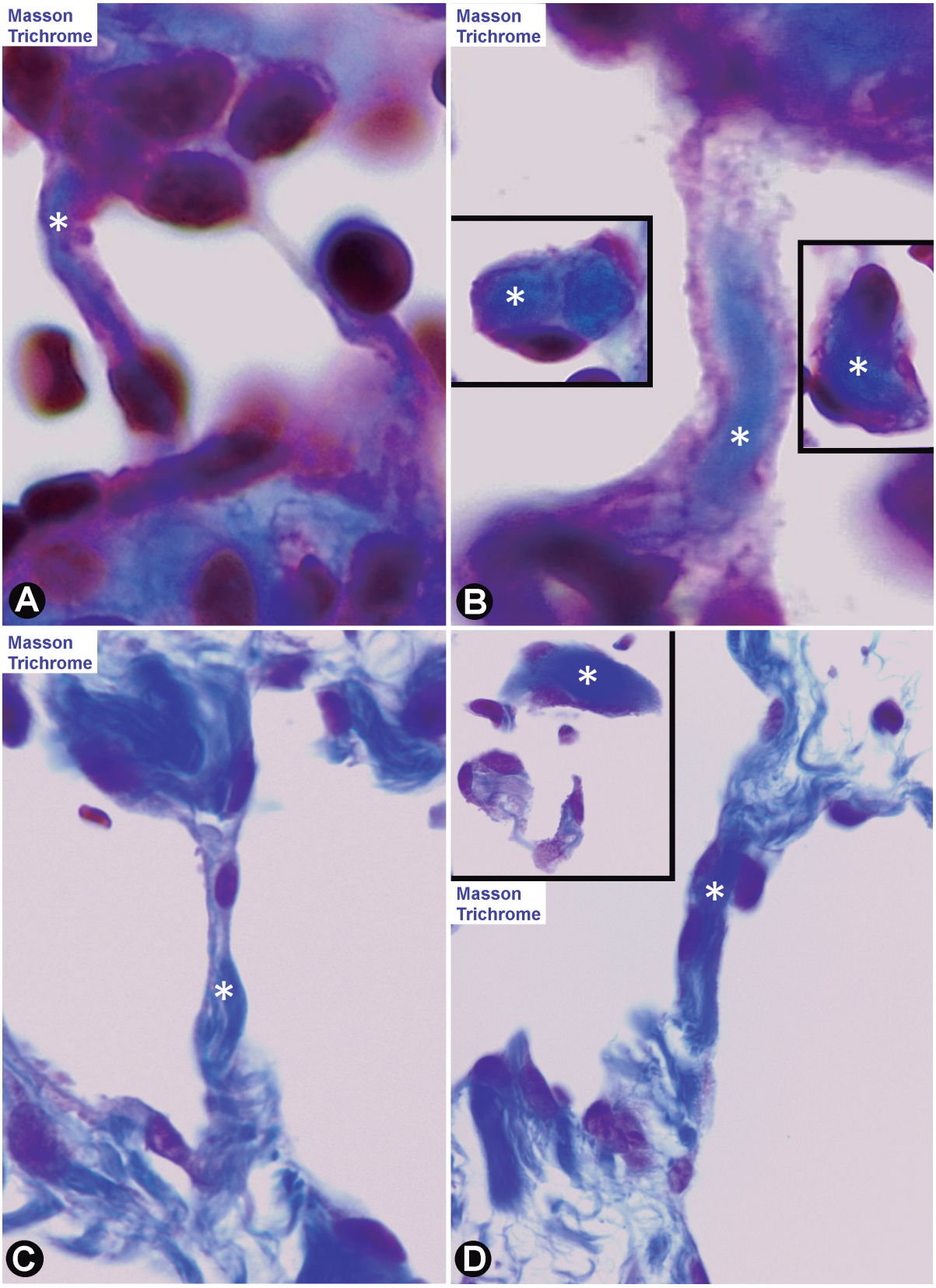

Fig. 2. Pillars in blood **(A and B)** and lymphatic vessels **(C and D)** stained with Masson trichrome, in longitudinal **(A-D)** and transversal sections (inserts in **B** and **D**). Note the presence of collagen (blue stained) in the pillar cores (asterisks). A, B, × 760; C, D, × 580.

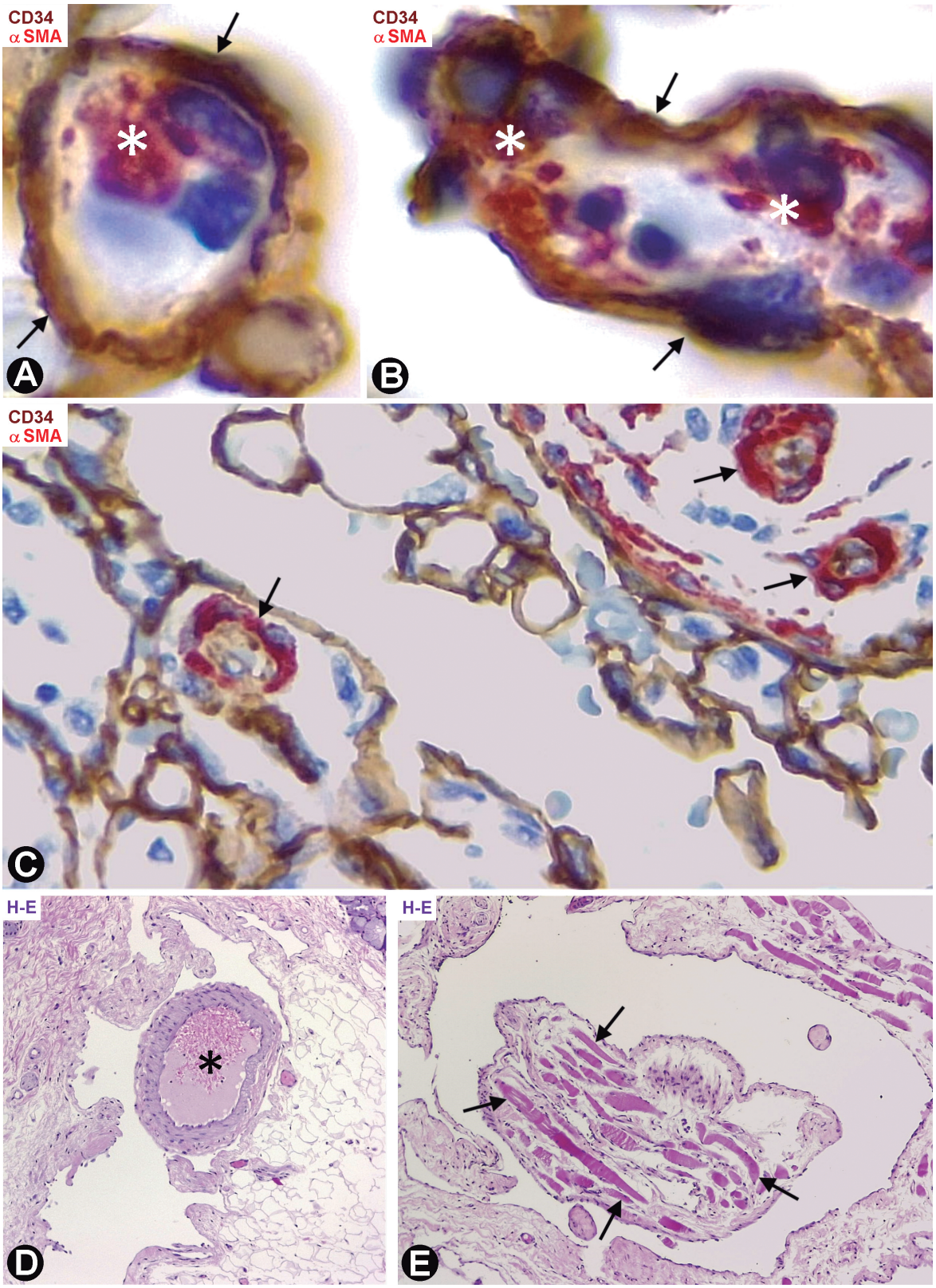

Fig. 3. Characteristics of pillar cores in sections double-immunostained with anti-CD 34 (brown) and anti-αSMA (red) **(A-C)**, and stained with HE **(D and E)**. Intravascular pillars, covered by CD34+ ECS (arrows), show αSMA+ cells (white asterisks) **(A and B)** and blood vessels (arrows) **(C)** in the pillar cores. Presence of a larger vessel (black asterisk) **(D)** and of striated muscle fibres (arrows) **(E)** in the core of giant pillars in lymphatic vessels. A, B, × 700; C, × 120; D, E, × 60.

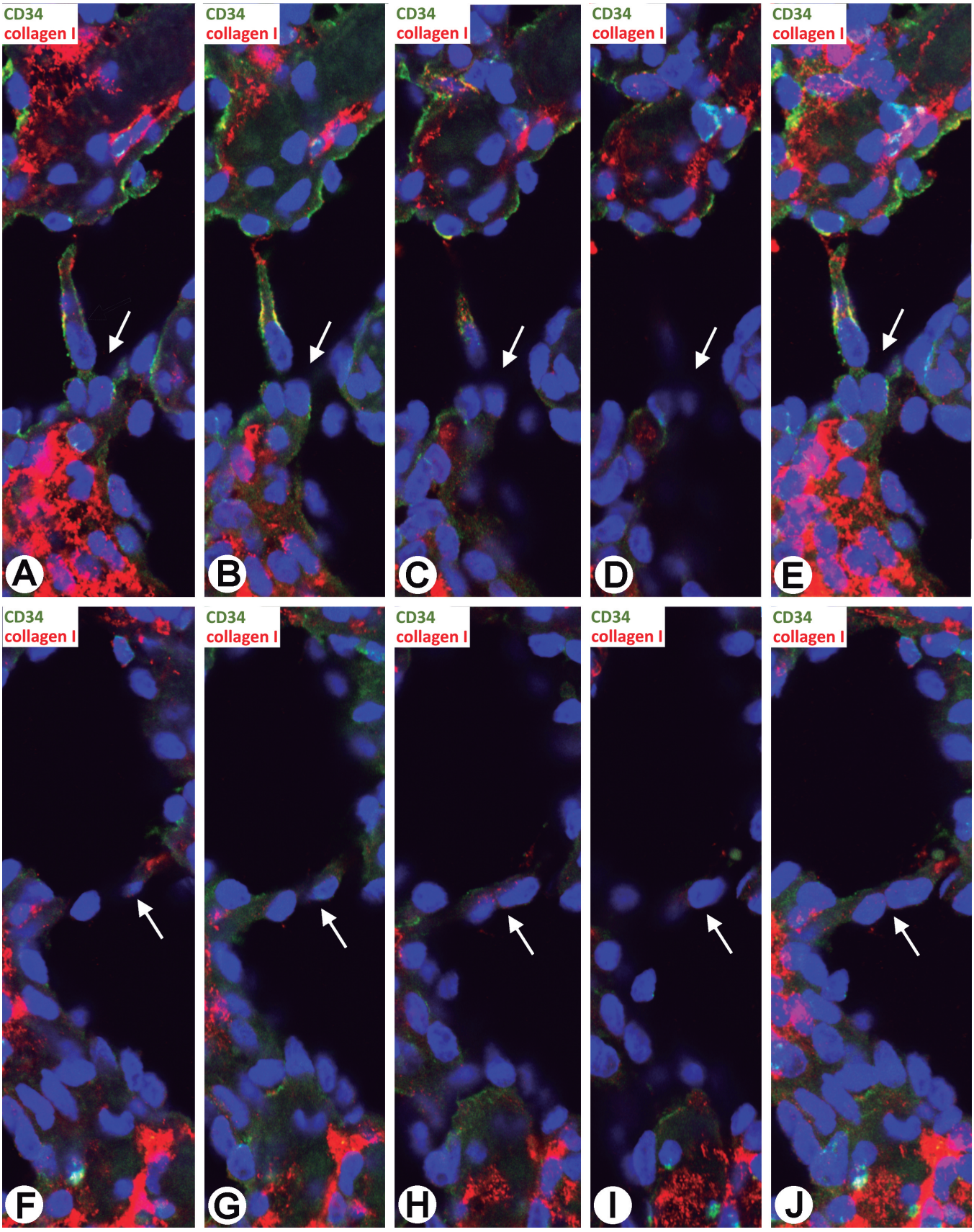

Fig. 4. Pillars (arrows) are observed at high magnification in confocal microscopy. Single **(A-D and F-I)** and whole-mount **(E and J)** views (6 μm) immunostained with anti-CD34 (green), anti-collagen I (red) and DAPI (blue). Note the cover of pillars (arrows) formed by endothelial cells and collagen I in the core. × 600.

During the formation of these structures, the vessel permeability and the basement membrane remain scantly modified or unmodified. Although some of these structures disappear quickly, being difficult to detect, they can persist and even be considered an exponent of specific forms of angiogenesis in some physiological and pathological conditions of the vessels. These issues are considered below.

A) The interendothelial contacts of the opposite vessel walls (Fig. 5A,B,E-H) form the first of four successive phases or stages proposed initially for pillar formation (stage I) (Burri and Tarek, 1990). The contacting ECs can be prominent (Fig. 5A,B) or planar (Fig. 5E,G,H) and the contacts symmetric (Fig. 5A) or asymmetric (Fig. 5B). The initial phase is followed by reorganization of EC junctions with EC bilayer arrangement and formation of a central virtual core (pillar perforation) (stage II) (Burri and Tarek, 1990). The third phase is characterized by incorporation in the central virtual core of pericytes (Kurz et al., 2008) (Fig. 5F), fibroblasts, myofibroblasts and collagen, as well as extracellular matrix formation, including newly formed collagen fibres (stage III). Finally, the pillar increases in size (mainly by greater extracellular matrix formation) and may merge with other pillars, which leads to the division of the vessel lumen (stage IV) (Burri 1990, 1992; Burri and Tarek, 1990; Djonov et al., 2000a,b, 2002, 2003; Patan et al., 2001a,b; Burri and Djonov, 2002; Burri et al., 2004). In this mechanism, the pressure exerted by pericytes or other interstitial cells can participate facilitating ECs contacts (Burri and Djonov, 2002). The denominations "endothelium independent intussusception" or "connective cell dependent intussusception" have been used for this possibility initiated by connective tissue cells that wrap ECs (Kilarski and Gerwins, 2009).

B) The formation of intraluminal endothelial bridges (nascent pillars) between the opposite vessel walls or between large/giant pillars is another important mechanism of pillar development, related with other forms of interendothelial contacts (Fig. 5C,D). Thus, nascent pillars are formed by EC filopodial ridges, some of which can be long and very thin (Fig. 5I). Therefore, the 1st stage of this process consists of intraluminal endothelial bridges, followed by the following stages (Paku et al., 2011): 2) Degradation of the basement membrane in the points in which the nascent pillars originate. 3) Attachment of ECs to collagen fascicles. 4) Pillar EC retraction and incorporation of collagen into the nascent pillars (formation of a pillar core) (Figs. 1, 2). A pulling force exerted by the actin cytoskeleton of ECs has been proposed as the mechanism that participates in the suction and subsequent transport of the collagen bundles in nascent pillars into and through the blood vessel lumen (Paku et al., 2011). 5) Recruitment of perivascular cells into the core and formation of a new extracellular matrix. For this mechanism the denominations "endothelium-dependent intussusception" and "inverse sprouting", have been proposed (Kilarski and Gerwins, 2009; Paku et al., 2011). A variant of these structural types is the peg-like contact, which is only established from one side of the vessel wall.

C) In the merged adjacent capillaries, two lateral EC contacts are established in the contacting walls, delimiting a non-contacting central zone. The non-contacting central zones detach from the lateral contacts and form pillars, which are often elongated and in which splitting may also occur. This mechanism is frequently observed in the adjacent lymphatic vessels that form the sinuses of developing lymph nodes (Fig. 5J).

D) Vessel loops formed by a bilayer of endothelial sheets arise from two points (two connecting segments) of pre-existing vessels and encircle an interstitial tissue structure (ITS: portion of the vessel wall with or without perivascular tissue) (Fig. 5A-D). In the loops formed by extension of ECs (Patan et al., 2001a,b) (mainly in granulation tissue) translocation may occur mediated by myofibroblast contraction (looping angiogenesis) (Kilarski and Gerwins, 2009). When the loop lumen is open and continuous with that of the pre-existing vessel, the pillars form and become intraluminal, presenting a cover (from the internal ECs of the loop) and a core (the ITS) (Fig. 6A-D). However, in serial sections or in 3D images, the ITS appears partially connected to the surrounding connective tissue (mainly at the ends of the pillar) from which the ITS was segregated. Complex loop systems are formed by the splitting of pillars or through new loops formed from other loops. The formation of pillars by vessel loops was described in the ovarian pedicle of nude mice after ovariectomy and human colon adenocarcinoma xenograft (Patan et al., 2001a,b), and in hemorrhoidal veins in hemorrhoidal disease (Díaz-Flores et al., 2018a). This process has frequently been observed in some blood and lymphatic vessel tumors/pseudotumors, including intravascular papillary endothelial hyperplasia (IPEH), sinusoidal hemangioma and sinusoidal hemangioma-like zones of IPEH, and in lymphangiomas/lymphatic malformations (Díaz-Flores et al., 2016a, 2018b, 2019a) (Fig. 5A-D). Likewise, vessel loops and pillars have been experimentally developed in the rat femoral vein by perivenous administration of PGE2 and glycerol (Díaz-Flores et al., 2017b) (see below). The designation "piecemeal form of intussusceptive angiogenesis" has been proposed for this process by which pillars are formed and transported toward the vessel lumen in blood vessel tumors and pseudotumors, in dilated hemorrhoidal veins and in experimental conditions developed in the femoral vein (Díaz-Flores et al., 2016a, 2017b, 2018a,b). When thrombosis occurs in vessels in which pillars develop, the ITSs may be initially formed by thrombotic components, mainly fibrin.

E) Formation of new pillars can occur by splitting of the larger pillars. This finding is frequently observed in certain pathological conditions of the vessels. Indeed, pillars with secondary pillars may be observed, resembling segmented cactus with rounded cladodes (Fig. 6D).

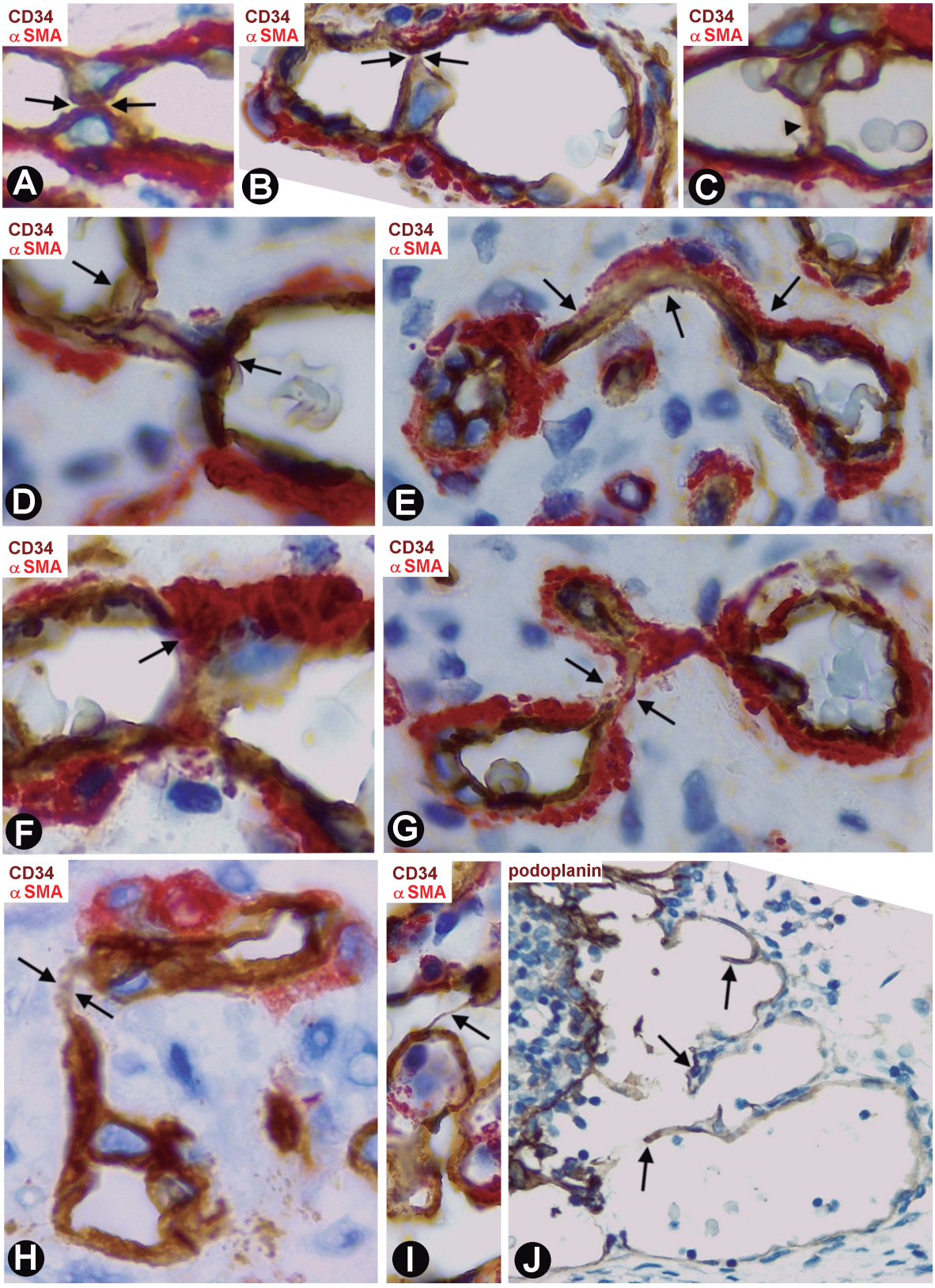

Fig. 5. Characteristics of the structures involved in pillar formation (pillar precursors/primary structures) observed in sections double-immunostained with anti-CD34 (brown) and anti-αSMA (red) **(A-H)**, and immunostained with anti-podoplanin **(I)**. Interendothelial contacts of the opposite vessel walls (**A-E**, arrows) and a nascent pillar (**C**, arrowhead) are observed in blood vessels. Note the different morphology (prominent in **A** and **B** or planar in **D** and **E**) and symmetry (symmetric in **A** and asymmetric in **B**) of the contacting ECs. Incorporation of a process of a pericyte is observed in a pillar (**F**, arrow). Two phases of perforation of planar contacts are seen between two splitting capillaries (**G** and **H**, arrows). A very thin nascent pillar is shown in **I** (arrow). Remaining pillars (arrows) after perforation of contacting walls of merged adjacent lymphatic vessels in a sinus of a developing lymphatic node **(J)**. A-H, × 300; I, × 260; J, × 120.

The aforementioned primary structures may appear in different stages of pillar formation, some of them (e.g. nascent pillars) joining pillars to vessel walls or other pillars.

Structures formed from pillars or pillar precursors (secondary structures)

Secondary structures are formed from pillars or pillar precursors. These secondary structures include newly formed vascular networks, those resulting from vessel arborisation, branching remodelling, pruning and compartmentalization, as well as pillar grouping, in which the pillars are arranged irregularly (Fig. 7A,B) or linearly (Fig. 7C,D). When the pillars are grouped linearly, they form intravascular septa (Fig. 7C). In addition, isolated pillars and pillar precursors may be present within and between pillar groups during and after the intussusceptive process.

Importantly, the higher expression of these structures is observed in some vessel diseases, mainly in vessel tumors/pseudotumors, which are therefore excellent substrates for studying intussusceptive phenomena in pathologic conditions. Indeed, examining these structures in some of the vessel lesions with numerous pillars will allow us to more easily establish their characteristics, mechanisms of formation and evolution (see the section Study of IA and IL in vessel lesions with numerous intussusceptive pillars).

Physiopathological relevance of IA/IL

Participation in capillary network formation (intussusceptive microvascular growth). Many capillary segments can be quickly formed from a capillary network, which expands simultaneously through intussusception without important functional changes in the pre-existing vessels (Burri and Djonov, 2002; Burri et al., 2004). In this process, the predominant precursor structures are interendothelial contacts from the opposite vessel walls and transcapillary interendothelial bridges (nascent pillars). Therefore, the continuous formation and enlargement of numerous pillars leads to the remodelling of pre-existing capillary networks and organ-specific vascularization, adapting to local nutrient and gas exchange needs. This process has been well studied in blood vessels and is termed intussusceptive microvascular growth (IMG) (Caduff et al., 1986; Burri and Tarek, 1990).

Participation in the formation of feeding and collecting vessels (vessel arborization: segregation of vessels for arterialization and venulization). Segregation of feeding vessels (future precapillary arterioles) and collecting vessels (future post-capillary venules) occurs by intussusception in an associated mechanism with capillary network formation. Thus, the blood arrival and return to/from the newly formed network is adjusted to the new requirements. In this process, rows of parallel and vertical pillars merge, change from round or oval to elongated (slit-like in vascular corrosion casting) morphology, and demarcate and segregate microvessels (Burri et al., 2004; Makanya et al., 2009; De Spiegelaere et al. 2012). Mechanisms of arteriolization or venulization occur simultaneously in the segregated vessels. This process has also been well studied in blood vessels and is termed intussusceptive arborization (IAR).

Participation in feeding and collecting vessel remodelling (optimization of blood supply and drainage). The optimization of blood supply and drainage (optimization of hemodynamic conditions) according to local requirements is based on the morphologic adaptation of branch bifurcations (of the branch geometry) and vascular pruning in the feeding and collecting vessels by intussusceptive transluminal pillars (Djonov et al., 2002, 2003; Burri et al., 2004; Makanya et al., 2009; De Spiegelaere, 2012; Mentzer and Konerding, 2014). In this process, pillar location (central or eccentric), size, shape and fusion influence the results, including relocation of vessel bifurcation angles (Kurz et al. 2003; Lee et al., 2010, 2011; Ackermann et al. 2013), modification of the daughter branch diameter and/or branch pruning (intussusceptive vascular pruning). This process is termed intussusceptive branching remodelling (IBR).

Participation in vessel compartmentalization (segmentation). Lumen compartmentalization occurs without complete division of the pre-existing vessel into new vessels. In this process, folds projecting from various locations of the vessel walls originate pillars, which can join longitudinally and form intraluminal and incomplete septa, meshworks and subunits. When septa formation occurs without vessel division, the process is known as segmentation (Patan et al., 2001a,b) or compartmentalization. In blood vessels, this process has been described in veins in hemorrhoidal disease, in sinusoidal hemangioma and in sinusoidal hemangioma-like zones of other vascular tumors/pseudotumors. In lymphatic vessels, segmentation has also been observed in the sinuses of developing human foetal lymph nodes, vascular transformation of lymph node sinuses and in lymphatic malformations/lymphangiomas (Díaz-Flores et al., 2019 a,b,c) (see below). Lymphatic intussusceptive segmentation is highly significant in certain locations, as occurs in lymph node sinuses. The latter originate from the lymphatic sac surrounding the primitive lymphatic anlage. An intraluminal meshwork is formed in these sinuses increasing the surface contact of the lymph and the duration of this contact (Moll et al., 2009). Thus, a new role can be assigned to vessel intussusception: formation of structures that participate in the filtering of fluids, interactions with lymphocytes, macrophages, antigen-presenting cells and metastatic cancer cells, as well as with numerous particles and molecules (important role in immunology and pathology) (Díaz-Flores et al., 2019b).

The phenomena that participate in the formation of capillary networks (IMG) and of feeding and collecting vessels (IAR), as well as in feeding and collecting vessel

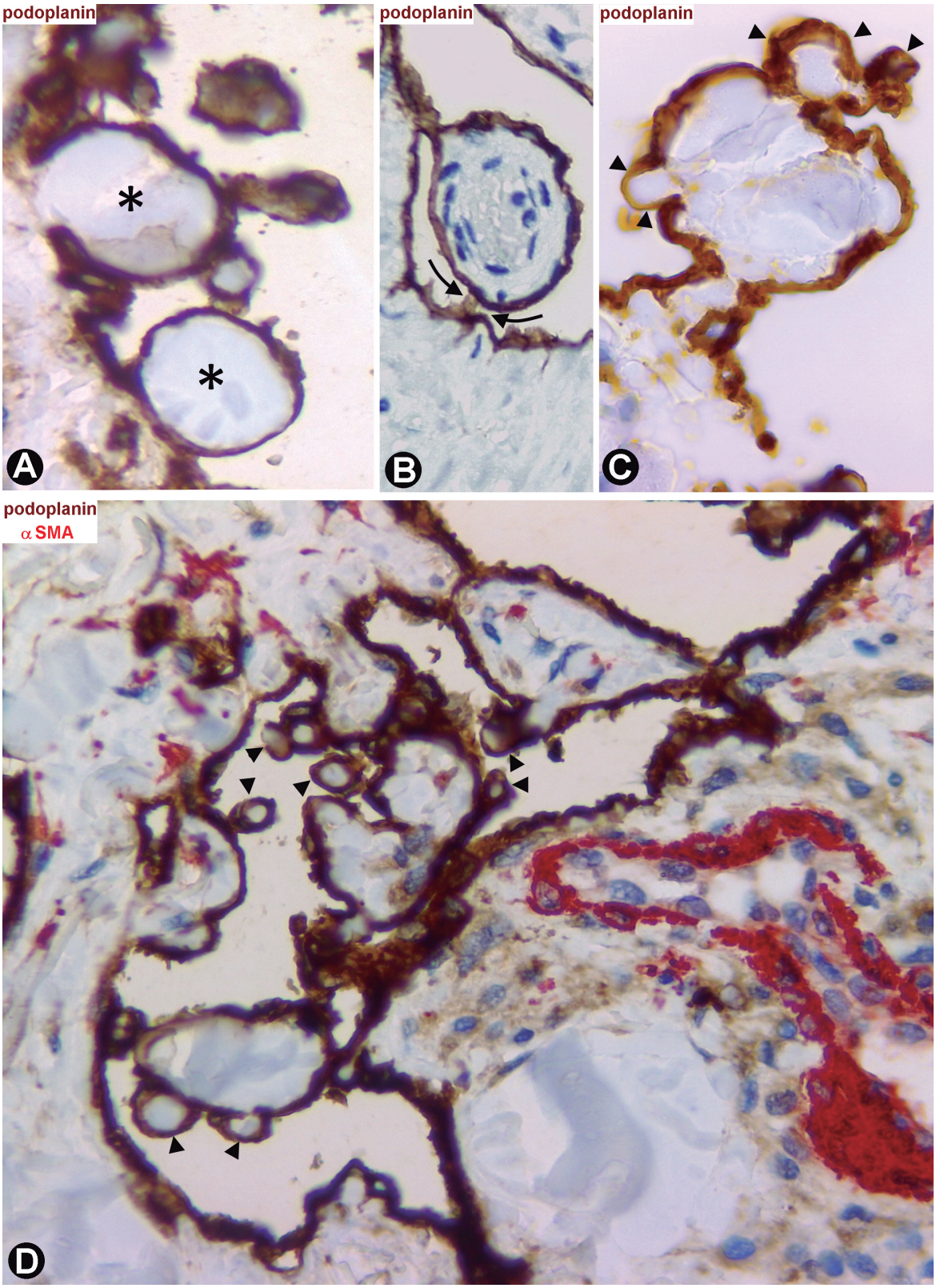

Fig. 6. Vessel loops and pillars in lymphatic vessels of a cystic lymphangioma. Sections double-stained with anti-podoplanin (brown) and anti-αSMA (red). **A.** Initial formation of two large pillars (asterisks) is observed in a region of a lymphatic vessel. Note endothelial sheets that form loops, which partially surround interstitial tissue structures (ITSs), originating the pillar cores. **B.** A large pillar partially connected to the surrounding connective tissue from which the ITS is segregated. Observe that the loop lumen is open (arrows) and the pillar becomes intraluminal, presenting a cover (CD 34+ cells) and a core (ITS). **C.** Two small pillars (arrowheads) are observed forming from the large pillar by the aforementioned procedure. **D.** Image of a lymphatic vessel in proximity to a blood vessel. The lymphatic vessel presents anti-podoplanin+ ECs and numerous pillars (arrowheads) in different stages of formation from the vessel wall or from other pillars. Note that groups of pillars connect opposite vessel walls. The blood vessel shows numerous α-SMA+ mural cells and podoplanin- ECs. A, × 760; B, D, × 220; C, × 600.

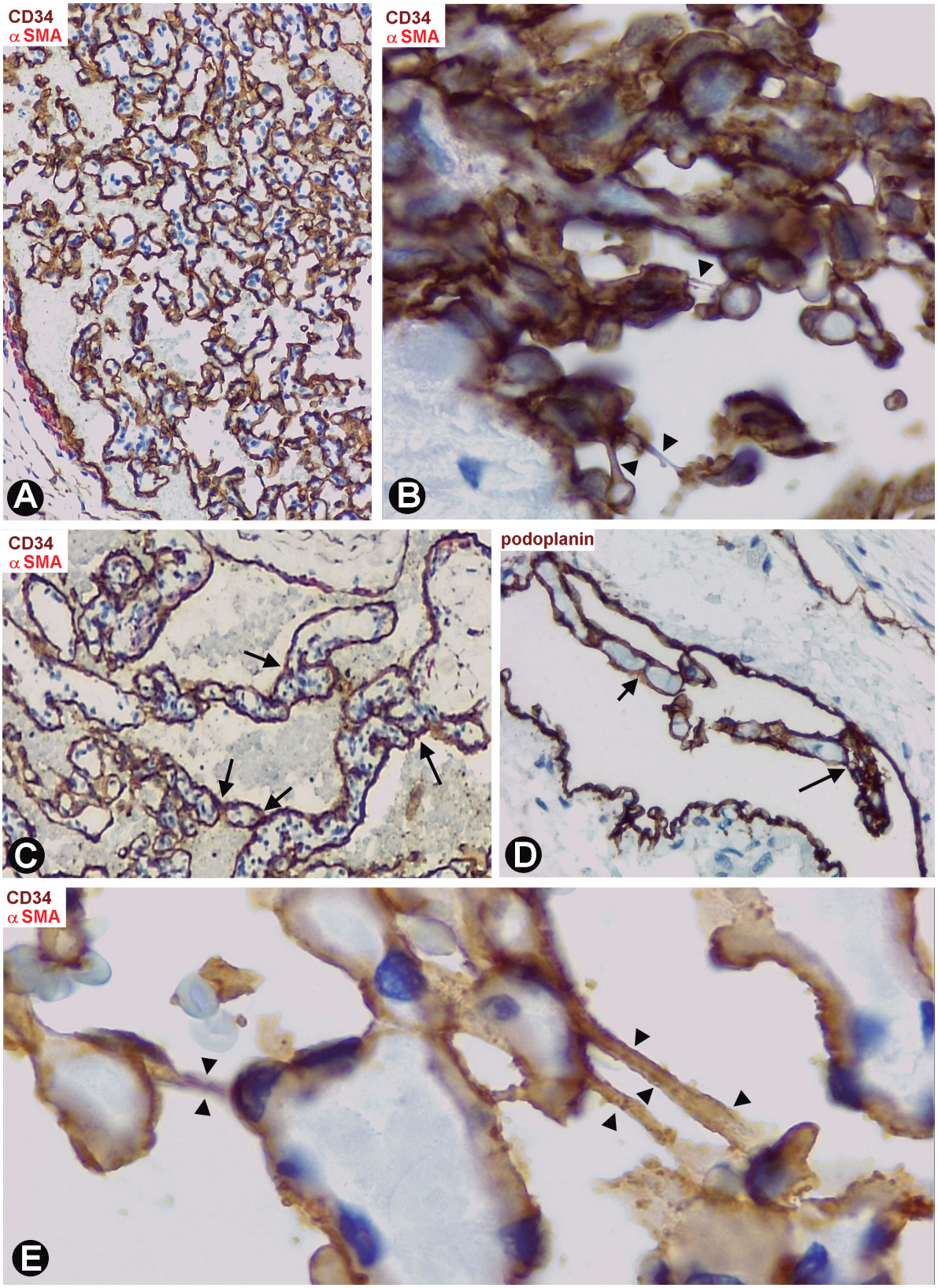

Fig. 7. Pillars in IPEH **(A, B, E)**, sinusoidal hemangioma **(C)** and cystic lymphangioma **(D)**. Sections stained with anti-CD34 and anti-SMA **(A-C and E)** and anti-podoplanin **(D)**. Note pillar connections by EC contacts **(A-D)**, core-to-core (arrows) **(A-D)** or by thin pillars (arrowheads) **(B and E)**. A, C, × 80; B, E, × 760; D, × 180.

remodelling (IBR) have been widely studied, mainly by vascular corrosion casting using scanning electron microscopy.

The aforementioned ability of IA/IL in the morphogenesis of vascularization is highly evident in vascular diseases. Indeed, the histogenesis of many of these pathological processes, including vascular tumors, can be explained by vessel intussusception mechanisms (see the section Influence of IA/IL on the morphogenesis of vascular tumors/pseudotumors).

Participation of IA in pathologic processes

Pathological vascular remodelling involves intussusception and splitting (Ali et al., 2019), including inflammatory processes (Konerding et al., 2010; Rossi-Schneider et al., 2010). Complex networks of tortuous and dilated capillaries with intussusceptive findings occur in florida microvascular angiogenesis of preterm lung (De Paepe et al., 2017), spleen in a murine model of Alzheimer disease (Kelly et al., 2017) and murine colitis (Konerding et al., 2010, 2012). Likewise, IA and alteration of the functional angioarchitecture of the brain cortex develop in a murine model of Krabbe disease (Giacomini et al., 2015)

IA has been described in human colon adenocarcinoma xenografts (Patan et al., 1996b; 2001a,b), mammary gland tumors (Djonov et al., 2001), B-cell non-Hodgkin's lymphomas (Crivellato et al., 2003), primary melanomas (Ribatti et al., 2005), and gliomas (Nico et al., 2010). In these tumors, vessel splitting occurred by IMG mechanisms in pre-existing and/or newly formed vessels by sprouting angiogenesis (association of sprouting and intussusceptive angiogenesis). IA participates in cancer ecosystems (Zuazo-Gaztelu et al., 2019) and an important fact is the formation of new vessels by IA and the growth of tumors after radiation or chemotherapy (transient switch from SA to IA) (Hlushchuk et al., 2008). Thus, the resistance to therapy (escape of the tumor to therapy) may be due to a low EC proliferation and unmodified vessel permeability in IA. Likewise, the consideration of the vessel behaviour depending on primary or metastatic tumors, including the tumor region and the type of angiogenesis is important for angiogenic therapy (Bugyik et al., 2016).

We have paid particular attention to pathological diseases of blood and lymphatic vessels, mainly vessel tumors/pseudotumors. Next, we consider vessel lesions with numerous intussusceptive pillars and the influence of IA/IL in the morphogenesis of vessel tumors/pseudotumors.

Study of IA and IL in vessel lesions with numerous intussusceptive pillars

Examples of lesions with numerous pillars are intravascular papillary endothelial hyperplasia (IPEH) in blood vessels and some lymphangiomas/lymphatic malformations in lymphatic vessels (Fig. 7A-E). The evolution of numerous pillars has also been followed experimentally in the rat femoral vein after perivenous administration of PGE2 and glycerol.

IPEH is a reactive process that occurs predominantly in dilated veins and that must be histologically differentiated from angiosarcoma, among other vessel tumors. Vein thrombosis is common. This process presents myriad intravascular pillars (Fig. 7A,B) and is therefore very useful for pillar study. Pillars vary in size (giant, large and small), show the structure outlined above and appear aggregated or isolated. When aggregated, the pillars form irregular groups (Fig. 7A,B) and occasionally alignments. Pillar connections can be by contact between the ECs that form their cover (Fig. 7A,B), core-to-core (Fig. 7A,B), EC extensions forming nascent pillars (Fig. 7B) or very thin pillars with scarce collagenous cores (Fig. 7E). Pillars that appear isolated in 2D sections show connections when observed in 3D images and serial sections. Depending on the pillar core, two principal types of pillars are present in this lesion. In one, the parietal type, the core corresponds to ITSs formed by vessel loops in the vein wall. In the other, the thrombotic type, the initial pillar core is formed by fibrin, followed by collagenization. In both types, the pillar cover originates from the vein intimal endothelium.

Since the morphological findings of IPEH mentioned above were observed when the lesions were well developed, we carried out an experimental model that allowed us to follow the evolution of the pillar formation process in veins (Díaz-Flores et al., 2017b). This experimental model was based on a previous study demonstrating high vein wall neovascularization from ECs of the vein wall itself after PGE2 and glycerol administration around the femoral vein (Díaz-Flores et al., 1994, 2010). In this study, the sequential pillar formation followed two overlapping phases. In the initial phase, the formation of vessel loops in the vein wall encircling ITSs was the principal mechanism, with predominance of sprouting angiogenesis. In the subsequent phase, intussusceptive angiogenesis was the predominant mechanism, with pillar formation and transport to the vein lumen.

In some lymphangiomas/lymphatic malformations (cystic/cavernous, circumscriptum and acquired progressive lymphangiomas), a similar exuberant formation of pillars as seen in IPEH is observed in dilated lymphatic spaces (Díaz-Flores 2019a) (Figs. 6D, 7D). The principal difference with IPEH is that thrombosis does not occur in lymphatic vessels, although they may occasionally contain fibrin, which could contribute to the formation of fibrinous pillar cores, followed by collagenization. The presence of intussusceptive lymphangiogenesis in these lymphatic diseases provided a basis for studying lymphatic intussusception in other conditions, such as in the sinuses of developing human fetal lymph nodes (Díaz-Flores et al., 2019b) and in the vascular transformation of lymph node sinuses (Díaz-Flores et al., 2019c). New studies are required to further

knowledge of intussusceptive lymphangiogenesis in other conditions, including tumors of different degrees of malignancy, such as papillary intralymphatic angioendothelioma (PILA) (Dabska tumor) and lymphangiosarcoma, as well as lymphedemas and lymphatic vessels in inflammation and tumors.

Influence of IA/IL in the morphogenesis of vessel tumors/pseudotumors

The morphogenic role of IA/IL in vascularization in physiologic conditions has its pathologic counterpart in the aberrant morphogenesis of some vessel diseases, including vessel tumors/pseudotumors (Díaz-Flores et al., 2020). Indeed, the prevalence of certain structures involved in pillar formation (primary structures) and resulting from pillar grouping (secondary structures) condition the morphology of the vessel lesion. Following, we outline an example of this prevalence in the morphologic pattern in four types of vessel tumors/pseudotumors, sinusoidal hemangioma, IPEH (Díaz-Flores et al., 2016a, 2018b), lymphangiomas/lymphatic malformations (Díaz-Flores et al., 2019a) and lobular capillary hemangioma (Díaz-Flores et al., 2020). Indeed, in these tumors/pseudotumors, vessel loops encircling ITSs are an important mechanism of pillar formation, while the variability of the interendothelial contacts between the opposite walls of the loops, as well as the number, arrangement and characteristics of the groups formed by pillars condition their different morphological pattern.

In sinusoidal hemangioma, groups of pillars formed from loops in the vessel walls or from other pillars acquire a linear arrangement forming incomplete intravascular septa, which adopt vessel wall characteristics between intercommunicating vascular spaces (sinusoidal pattern) (Fig. 7C). In IPEH, pillars are formed from vessel loops in the vessel walls and in thrombotic material (IPEH generally presents thrombosis, which considerably increases pillar numbers), grouping in an irregular arrangement (intravascular pillar/papillary hyperplastic pattern). Pillars are also formed in lymphangiomas/lymphatic malformations from vessel walls or other pillars, but the intravascular pillar/papillary hyperplastic pattern (IPEH-like morphology) occurs occasionally due to the absence of thrombosis. In lobular capillary hemangioma, numerous interendothelial contacts occur between the opposite walls of the loops, intravascular ITS transport and pillar formation are scarce, and intercalated open lumens between the contacts of the loops persist as capillary-sized vessels (capillary pattern).

Control, regulation and modulation of IA and IL

The mechanisms of control and regulation in IA have been explored in recent decades, whereas knowledge of these mechanisms in IL is scarce due to the recent description of this lymphangiogenic type (Díaz-Flores et al., 2019a,b,c). Hemodynamic conditions, hypoxia, and several molecules participate in IA control (Eginnton et al., 2001; Djonov et al., 2002; Rivilis et al., 2002; Kurz et al., 2003; Crivellato et al., 2004; le Noble et al., 2005; Paku et al., 2005; Milkievicz et al., 2006; Williams et al., 2006a,b; Tressel et al., 2007; Hlushchuk et al., 2008, 2011a, 2017; Turhan et al., 2008; Filipovic et al., 2009; Miele et al., 2009; Szczerba et al., 2009; Tsuda et al., 2009; Baum et al., 2010; Lee et al., 2010, Taylor et al., 2010; Gianni-Barrera et al., 2011; Lee et al., 2011; Nico et al., 2011; Paku et al., 2011; Dill et al., 2012; Ackermann et al., 2013; Dimova et al., 2013; Gianni-Barrera et al., 2013, 2014, 2016, 2018; Mentzer and Konerding, 2014; Föhst et al., 2015; Groppa et al., 2018; Vilmalraj et al., 2018; Esteban et al., 2019; Rajabi et al., 2019; Vilmalraj et al., 2019; Uccelli et al., 2019).

Hemodynamic conditions

Blood flow intensity and velocity, pressure changes and shear stress (stress resulting from blood flow) are the related hemodynamic conditions in IA. These hemodynamic conditions have a critical and rapid (minutes/hours) action on vascular adaptation and formation of intravascular pillars (Egginton et al., 2001; Djonov et al., 2002; Kurz et al., 2003; Lee et al., 2010, 2011), as well as on vessel diameter (Djonov et al., 2002; Kurz et al., 2003; le Noble et al., 2005). Likewise, hemodynamic conditions coincide with cellular rearrangements (Kochhan et al., 2013) and influence branching remodelling, depending on location, orientation, and periodicity of developing pillars (Turhan et al., 2008; Tsuda et al., 2009; Lee et al., 2010; Lee et al., 2011; Styp-Rekowska et al., 2011; Ackermann et al., 2013). In addition, shear stress acts on EC behaviour and on molecular control, according to whether the flow is laminar (parallel or tangential to EC surface) or turbulent (oscillatory) (see below, EC behaviour and molecular control of IA/IL).

In IL, lymphatic vessel dilation and lymph stasis facilitate pillar formation (Díaz-Flores et al., 2019a,b,c). This vessel dilation may occur by lymphatic obstruction and stasis due to cardiac insufficiency, venous obstruction, chronic infection, surgery and irradiation.

EC behaviour and molecular control of IA/IL

Molecular signals that participate in IA are less known than in SA. As for IL, the role of these molecular signals is in an initial phase of exploration. The factors that influence IA include VEGF (Baum et al., 2010; Gianni-Barrera et al., 2013; Uccelli et al., 2019), Ang-2, ephrinB2/EphB4 signalling (Groppa et al., 2018), endoglin (Hlushchuk et al., 2017), Notch signalling (Dill et al., 2012; Dimova et al., 2013), nitric oxide (Vimalraj et al., 2018) and endothelial cell MT1-MMP.

The hemodynamic changes outlined above modify EC behaviour and molecular control. When the shear stress is laminar, IA occurs by a) down regulation of

angiopoietin 2 (Ang-2), through the tyrosine kinase receptor 2 (Tie-2), with the inhibition of EC migration and tubule formation (Suri et al., 1996; Tressel et al., 2007) and b) induction of protease inhibitor expression in ECs through the protein C-ets-1 and preservation of vessel wall integrity (Milkievicz et al., 2006). When the shear stress is turbulent, SA occurs by a) mechanical cell stretch, b) up-regulation of MMPs and VEGF (Rivilis et al., 2002) and c) Ang-2 production by ECs (Tressel et al., 2007). In addition, shear stress may participate in the regulation of other molecules and receptors, including nitric oxide, CD31, cNos, VEGFR-2 and growth factors.

The response of VEGF is heterogeneous (Pettersson et al., 2000) and its signalling in sprouting or intussusception varies depending on process, location and experimental model. Thus, in certain conditions, high levels of VEGF induce sprouting angiogenesis, while lower levels of VEGF facilitate intussusception (Hlushchuk et al., 2008, 2011a,b). This would explain the persistence of angiogenesis (by IA) after anti-VEGF therapy in tumors. Conversely, VEGF over-expression in skeletal muscle induces angiogenesis by intussusception rather than sprouting (Gianni-Barrera et al., 2013). Indeed, the VEGF dose located in the microenvironment has an important role in intussusception. Thus, over-expression of VEGF in skeletal muscle (in the limited amount of extracellular matrix) blocks the formation of a gradient to induce IA, preventing tip cell migration in blood vessels (Gianni-Barrera et al., 2013; Uccelli et al., 2019). Other factors may regulate the action of VEGF (see below). We proposed a similar mechanism for IL during intussusceptive pillar formation in the sinuses of developing lymphatic nodes, based on the fact that the absence of VEGF-C gradient results in the non-sprouting engulfing of the LN anlage by LECs (Bovay et al., 2018). Indeed, the high expression of VEGF-C by LT0 cells (Okuda et al., 2007) and the low production of guidance NPR2 by lymphatic ECs of the lymph nodes (NPR2 promotes VEGF-C-driven lymphatic LEC sprouting - Xu et al., 2010) could explain the switching of IA to IL.

PDGF-BB, which stimulates pericyte recruitment, regulates splitting angiogenesis depending on its balance with VEGF. Thus, PDGF-BB accelerates splitting angiogenesis and limits circular enlargement of vessels, endothelial proliferation and pericyte loss induced by high VEGF, and modulates VEGF-R2, preventing VEGF induced aberrant angiogenesis (Gianni-Barrera et al., 2014, 2016, 2018).

Hypoxia is also a regulator of IA. Thus, hypoxia-inducible factors (e.g. HI-2 alpha) stimulate the expression of erythropoietin, which can enhance IA (Crivellato et al., 2004; Nico et al., 2011). In addition, ischemia, hypoxia and Notch inhibition facilitate the recruitment and extravasation of mononuclear cells

Inhibition of Notch signalling induces IA in existing vasculature (Dill et al., 2012; Dimova et al., 2013) with pericyte detachment, extravasation of mononuclear cells and transluminal pillar formation (Dimova et al., 2013), and development of angiosarcomas in the liver (Dill et al., 2012). Notch inhibition induces recruitment of mononuclear cells, which is associated with SDF-1 and CXCR4 increase. Likewise, inhibition of SDF-1/CXCR4 annulates mononuclear cell recruitment (Dimova et al., 2019).

Endoglin/CD 105 inhibition induces IA via up-regulation of ovalbumin upstream promoter transcription factor 2 (COUP-TF2) (Hlushchuk et al., 2017).

EphrinB2/EphB4 signalling modulates IA by VEGF (the outcome of VEGF gene delivery) (Groppa et al., 2018). The modulation of VEGFR2 phosphate-ERK1/2 participates in this mechanism.

Nitric oxide NOS inhibitors participate in the transition of SA to IA in the early phase of wound repair. IA can be continued by NO donors in the last phase.

Endothelial cell MMT1-MMP participates in the cleavage of thrombospondin-1 and the c-terminal fragment joins $\alpha v\beta 3$ integrin, facilitating nitric oxide production (Esteban et al., 2019).

Acknowledgements. The authors would like to thank Kim Eddy for the English revision.

References

Ackermann M., Tsuda A., Secomb T.W., Mentzer S.J. and Konerding M.A. (2013). Intussusceptive remodeling of vascular branch angles in chemically-induced murine colitis. Microvasc. Res. 87, 75-82.

Ackermann M., Houdek J.P., Gibney B.C., Ysasi A., Wagner W., Belle J., Schittny J.C., Enzmann F., Tsuda A., Mentzer S.J. and Konerding M.A. (2014). Sprouting and intussusceptive angiogenesis in postpneumonectomy lung growth: mechanisms of alveolar neovascularization. Angiogenesis 17, 541-551.

Ali Z., Mukwaya A., Biesemeier A., Ntzouni M., Ramsköld D., Giatrellis S., Mammadzada P., Cao R., Lennikov A., Marass M., Gerri C., Hildesjö C., Taylor M., Deng Q., Peebo B., Del Peso L., Kvanta A., Sandberg R., Schraermeyer U., Andre H., Steffensen J.F., Lagali N., Cao Y., Kele J. and Jensen L.D. (2019). Intussusceptive Vascular Remodeling Precedes Pathological Neovascularization. Arterioscler. Thromb. Vasc. Biol. 39, 1402-1418.

Andres A.C. and Djonov V. (2010). The mammary gland vasculature revisited. J. Mammary Gland Biol. Neoplasia 15, 319-328.

Augustin H.G. (2001). Tubes, branches, and pillars: the many ways of forming a new vasculature. Circ. Res. 89, 645-647.

Baum O., Suter F., Gerber B., Tschanz S.A., Buergy R., Blank F., Hlushchuk R. and Djonov V. (2010). VEGF-A promotes intussusceptive angiogenesis in the developing chicken chorioallantoic membrane. Microcirculation 17, 447-457.

Belle J., Ysasi A., Bennett R.D., Filipovic N., Nejad M.I., Trumper D.L., Ackermann M., Wagner W., Tsuda A., Konerding M.A. and Mentzer S.J. (2014). Stretch-induced intussusceptive and sprouting angiogenesis in the chick chorioallantoic membrane. Microvasc. Res. 95, 60-67.

Bovay E., Sabine A., Prat-Luri B., Kim S., Son K., Willrodt A.H., Olsson C., Halin C., Kiefer F., Betsholtz C., Jeon N.L., Luther S.A. and Petrova T.V. (2018). Multiple roles of lymphatic vessels in peripheral lymph node development. J. Exp. Med. 215, 2760-2777.

Bugyik E., Renyi-Vamos F., Szabo V., Dezso K., Ecker N., Rokusz A.,

Nagy P., Dome B. and Paku S. (2016). Mechanisms of vascularization in murine models of primary and metastatic tumor growth. Chin. J. Cancer 35, 19.

Burri P.H. (1990). Development and growth of the respiratory system. Arch. Int. Physiol. Biochim. 98, A109-A111.

Burri P.H. (1992). Intussusceptive microvascular growth, a new mechanism of capillary network formation. EXS 61, 32-39.

Burri P.H. and Tarek M.R. (1990). A novel mechanism of capillary growth in the rat pulmonary microcirculation. Anat. Rec. 228, 35-45.

Burri P.H. and Djonov V. (2002). Intussusceptive angiogenesis--the alternative to capillary sprouting. Mol. Aspects Med. 23, S1-27.

Burri P.H., Hlushchuk R. and Djonov V. (2004). Intussusceptive angiogenesis: its emergence, its characteristics, and its significance. Dev. Dyn. 231, 474-488.

Caduff J.H., Fischer L.C. and Burri P.H. (1986). Scanning electron microscope study of the developing microvasculature in the postnatal rat lung. Anat. Rec. 216, 154-164.

Clark E.R. (1918). Studies on the growth of blood-vessels in the tail of the frog larva. By observation and experiment on the living animal. Am. J. Anat. 23, 37-88.

Crivellato E., Nico B., Vacca A. and Ribatti D. (2003). B-cell non-Hodgkin's lymphomas express heterogeneous patterns of neovascularization. Haematologica 88, 671-678.

Crivellato E., Nico B., Vacca A., Djonov V., Presta M. and Ribatti D. (2004). Recombinant human erythropoietin induces intussusceptive microvascular growth *in vivo*. Leukemia 18, 331-336.

D'Amico G., Muñoz-Félix J.M., Pedrosa A.R. and Hodivala-Dilke K.M. (2019). "Splitting the matrix": intussusceptive angiogenesis meets MT1-MMP. EMBO Mol. Med. 20, e11663.

De Paepe M.E., V Benny M.K., Priolo L., Luks F.I. and Shapiro S. (2017). Florid Intussusceptive-like microvascular dysangiogenesis in a preterm lung. Pediatr. Dev. Pathol. 20, 432-439.

De Spiegelaere W., Cornillie P., Erkens T., Van Loo D., Casteleyn C., Van Poucke M., Burvenich C., Van Hoorebeke L., Van Ginneken C., Peelman L. and Van den Broeck W. (2010). Expression and localization of angiogenic growth factors in developing porcine mesonephric glomeruli. J. Histochem. Cytochem. 58, 1045-1056.

De Spiegelaere W., Casteleyn C., Van den Broeck W., Plendl J., Bahramsoltani M., Simoens, P. Djonov V. and Cornillie P. (2012). Intussusceptive angiogenesis: a biologically relevant form of angiogenesis. J. Vasc. Res. 49, 390-404.

Díaz-Flores L., Gutierrez R., Valladares F., Varela H., Perez M. (1994). Intense vascular sprouting from rat femoral vein induced by prostaglandins E1 and E2. Anat. Rec. 238, 68-76.

Díaz-Flores L., Gutiérrez R., Madrid J.F., Varela H., Valladares F., Acosta E., Martín-Vasallo P. and Díaz-Flores L. Jr. (2009a). Pericytes. Morphofunction, interactions and pathology in a quiescent and activated mesenchymal cell niche. Histol. Histopathol. 24, 909-969.

Díaz-Flores L. Jr., Gutierrez R., Madrid J.F., Varela H., Valladares F. and Díaz-Flores L. (2009b). Adult stem cells and repair through granulation tissue. Front. Biosci. (Landmark Ed). 14, 1433-1470.

Díaz-Flores L. Jr., Gutiérrez R., Madrid J.F., Sáez F.J., Valladares F., Villar J. and Díaz-Flores L. (2010). Peg-and-socket junctions between smooth muscle cells and endothelial cells in femoral veins are stimulated to angiogenesis by prostaglandin E_2 and glycerols. Histol. Histopathol. 26, 623-630.

Díaz-Flores L., Gutiérrez R., García M.P., Sáez F.J., Díaz-Flores L. Jr., Valladares F. and Madrid J.F. (2014). CD34+ stromal cells/fibroblasts/fibrocytes/telocytes as a tissue reserve and a principal source of mesenchymal cells. Location, morphology, function and role in pathology. Histol. Histopathol. 29, 831-870.

Díaz-Flores L., Gutiérrez R., Lizartza K., Goméz M.G., García M.P., Sáez F.J., Díaz-Flores L. Jr. and Madrid J.F. (2015a). Behavior of in situ human native adipose tissue CD34+ stromal/progenitor cells during different stages of repair. Tissue-resident CD34+ stromal cells as a source of myofibroblasts. Anat. Rec. (Hoboken) 298, 917-930.

Díaz-Flores L., Gutiérrez R., García M.P., González M., Sáez F.J., Aparicio F., Díaz-Flores L. Jr. and Madrid J.F. (2015b). Human resident CD34+ stromal cells/telocytes have progenitor capacity and are a source of αSMA+ cells during repair. Histol. Histopathol. 30, 615-627.

Díaz-Flores L., Gutiérrez R., Madrid J.F., García-Suárez M.P., González-Álvarez M.P., Díaz-Flores L. Jr. and Sáez F.J. (2016a). Intravascular Papillary Endothelial Hyperplasia (IPEH). Evidence supporting a piecemeal mode of angiogenesis from vein endothelium, with vein wall neovascularization and papillary formation. Histol. Histopathol. 31, 1271-1279.

Díaz-Flores L., Gutiérrez R., Díaz-Flores L. Jr., Goméz M.G., Sáez F.J. and Madrid J.F. (2016b). Behaviour of telocytes during physiopathological activation. Semin. Cell Dev. Biol. 55, 50-61.

Díaz-Flores L., Gutiérrez R., González-Gómez M., Díaz-Flores L. Jr., Valladares F., Rancel N., Sáez F.J. and Madrid J.F. (2016c). Telocyte Behaviour During Inflammation, Repair and Tumour Stroma Formation. Adv. Exp. Med. Biol. 913, 177-191.

Díaz-Flores L., Gutiérrez R., García M.P., González M., Díaz-Flores L. Jr. and Madrid J.F. (2016d). Telocytes as a source of progenitor cells in regeneration and repair through granulation tissue. Curr. Stem Cell Res. Ther. 11, 395-403.

Díaz-Flores L., Gutiérrez R., García-Suárez M.P., Sáez F.J., Gutiérrez E., Valladares F., Carrasco J.L., Díaz-Flores L. Jr. and Madrid J.F. (2017a). Morphofunctional basis of the different types of angiogenesis and formation of postnatal angiogenesis-related secondary structures. Histol. Histopathol. 32, 1239-1279.

Díaz-Flores L., Gutiérrez R., García M.P., Sáez F.J., Díaz-Flores L. Jr. and Madrid J.F. (2017b). Piecemeal mechanism combining sprouting and intussusceptive angiogenesis in intravenous papillary formation induced by PGE2 and glycerol. Anat. Rec. (Hoboken) 300, 1781-1792.

Díaz-Flores L., Gutiérrez R., González-Gómez M., García P., Sáez F.J., Díaz-Flores L. Jr., Carrasco J.L. and Madrid J.F. (2018a). Segmentation of Dilated Hemorrhoidal Veins in Hemorrhoidal Disease. Cells Tissues Organs 205, 120-128.

Díaz-Flores L., Gutiérrez R., García Mª.P., González-Gómez M., Sáez F.J., Díaz-Flores L. Jr., Carrasco J.L. and Madrid J.F. (2018b). Sinusoidal hemangioma and intravascular papillary endothelial hyperplasia: Interrelated processes that share a histogenetic piecemeal angiogenic mechanism. Acta Histochem. 120, 255-262.

Díaz-Flores L., Gutiérrez R., García M.P., Carrasco J.L., Sáez F.J., Díaz-Flores L. Jr., González-Gómez M. and Madrid J.F. (2019a). Intussusceptive lymphangiogenesis in lymphatic malformations/lymphangiomas. Anat. Rec. (Hoboken) 302, 2003-2013.

Díaz-Flores L., Gutiérrez R., García M.P., González-Gómez M., Díaz-Flores L. Jr. and Carrasco J.L. (2019b). Intussusceptive lymphangiogenesis in the sinuses of developing human foetal lymph nodes. Ann. Anat. 226, 73-83.

Díaz-Flores L., Gutiérrez R., García M.P., González-Gómez M., Díaz-

Flores L. Jr., Carrasco J.L. and Álvarez-Argüelles H. (2019c). Intussusceptive lymphangiogenesis in vascular transformation of lymph node sinuses. Acta Histochem. 121, 392-399.

Díaz-Flores L., Gutiérrez R., González-Gómez M., García M.P., Carrasco J.L., Díaz-Flores L. Jr., Madrid J.F. and Álvarez-Argüelles H. (2020). Participation of intussusceptive angiogenesis in the morphogenesis of lobular capillary hemangioma. Sci. Rep. 10, 4987.

Dill M.T., Rothweiler S., Djonov V., Hlushchuk R., Tornillo L., Terracciano L., Meili-Butz S., Radtke F., Heim M.H. and Semela D. (2012). Disruption of Notch1 induces vascular remodeling, intussusceptive angiogenesis, and angiosarcomas in livers of mice. Gastroenterology 142, 967-977.

Dimova I., Hlushchuk R., Makanya A., Styp-Rekowska B., Ceausu A., Flueckiger S., Lang S., Semela D., Le Noble F., Chatterjee S. and Djonov V. (2013). Inhibition of Notch signaling induces extensive intussusceptive neo-angiogenesis by recruitment of mononuclear cells. Angiogenesis 16, 921-937.

Dimova I., Karthik S., Makanya A., Hlushchuk R., Semela D., Volarevic V. and Djonov V. (2019). SDF-1/CXCR4 signalling is involved in blood vessel growth and remodelling by intussusception. J. Cell Mol. Med. 23, 3916-3926.

Djonov V. and Makanya A.N. (2005). New insights into intussusceptive angiogenesis. EXS. 94, 17-33.

Djonov V., Schmid M., Tschanz S.A. and Burri P.H. (2000a). Intussusceptive angiogenesis: its role in embryonic vascular network formation. Circ. Res. 86, 286-292.

Djonov VG, Galli AB. and Burri P.H. (2000b). Intussusceptive arborization contributes to vascular tree formation in the chick chorio-allantoic membrane. Anat. Embryol. (Berl) 202, 347-357.

Djonov V., Andres A.C. and Ziemiecki A. (2001). Vascular remodelling during the normal and malignant life cycle of the mammary gland. Microsc. Res. Tech. 52, 182-189.

Djonov V.G., Kurz H. and Burri P.H. (2002). Optimality in the developing vascular system: branching remodeling by means of intussusception as an efficient adaptation mechanism. Dev. Dyn. 224, 391-402

Djonov V., Baum O. and Burri P.H. (2003). Vascular remodeling by intussusceptive angiogenesis. Cell Tissue Res. 314, 107-117.

Egginton S. (2009). Invited review: activity-induced angiogenesis. Pflugers Arch. 457, 963-977.

Egginton S., Zhou A.L., Brown M.D. and Hudlická O. (2001). Unorthodox angiogenesis in skeletal muscle. Cardiovasc Res. 49, 634-646.

Esteban S., Clemente C., Koziol A., Gonzalo P., Rius C., Martínez F., Linares P.M., Chaparro M., Urzainqui A., Andrés V., Seiki M., Gisbert J.P. and Arroyo A.G. (2019). Endothelial MT1-MMP targeting limits intussusceptive angiogenesis and colitis via TSP1/nitric oxide axis. EMBO Mol. Med. 3, e10862.

Fidan P.A., Helvacioglu F. and Dagdeviren A. (2019). Intussusceptive growth or vascular bed in human placenta. Gazi Med. J. 30, 246-251.

Filipovic N., Tsuda A., Lee G.S., Miele L.F., Lin M., Konerding M.A. and Mentzer S.J. (2009). Computational flow dynamics in a geometric model of intussusceptive angiogenesis. Microvasc. Res. 78, 286-293.

Föhst S., Wagner W., Ackermann M., Redenbach C., Schladitz K., Wirjadi O., Ysasi A.B., Mentzer S.J. and Konerding M.A. (2015). Three-dimensional image analytical detection of intussusceptive pillars in murine lung. J. Microsc. 260, 326-337.

Frontczak-Baniewicz M. and Walski M. (2002). Non-sprouting angiogenesis in neurohypophysis after traumatic injury of the cerebral cortex. Electron-microscopic studies. Neuro. Endocrinol. Lett. 23, 396-404.

Giacomini A., Ackermann M., Belleri M., Coltrini D., Nico B., Ribatti D., Konerding M.A., Presta M. and Righi M. (2015). Brain angioarchitecture and intussusceptive microvascular growth in a murine model of Krabbe disease. Angiogenesis 18, 499-510.

Gianni-Barrera R., Trani M., Reginato S. and Banfi A. (2011). To sprout or to split? VEGF, Notch and vascular morphogenesis. Biochem. Soc. Trans. 39, 1644-1648.

Gianni-Barrera R., Trani M., Fontanellaz C., Heberer M., Djonov V., Hlushchuk R. and Banfi A. (2013). VEGF over-expression in skeletal muscle induces angiogenesis by intussusception rather than sprouting. Angiogenesis 16, 123-136.

Gianni-Barrera R., Bartolomeo M., Vollmar B., Djonov V. and Banfi A. (2014). Split for the cure: VEGF, PDGF-BB and intussusception in therapeutic angiogenesis. Biochem. Soc. Trans. 42, 1637-1642.

Gianni-Barrera R., Burger M., Wolff T., Heberer M., Schaefer D.J., Gürke L., Mujagic E. and Banfi A. (2016). Long-term safety and stability of angiogenesis induced by balanced single-vector co-expression of PDGF-BB and VEGF164 in skeletal muscle. Sci. Rep. 6, 21546.

Gianni-Barrera R., Butschkau A., Uccelli A., Certelli A., Valente P., Bartolomeo M., Groppa E., Burger M.G., Hlushchuk R., Heberer M., Schaefer D.J., Gürke L., Djonov V., Vollmar B. and Banfi A. (2018). PDGF-BB regulates splitting angiogenesis in skeletal muscle by limiting VEGF-induced endothelial proliferation. Angiogenesis 21, 883-900.

Gibney B.C., Houdek J.P., Chamoto K., Lee G.S., Ackermann M., Lin M., Collings-Simpson D., Konerding M.A., Tsuda A. and Mentzer S.J. (2012). Mechanostructural adaptations preceding postpneumonectomy lung growth. Exp. Lung Res. 38, 396-405.

Groningen van J.P., Wenink A.C. and Testers L.H. (1991). Myocardial capillaries: increase in number by splitting of existing vessels. Anat. Embryol. (Berl). 184, 65-70.

Groppa E., Brkic S., Uccelli A., Wirth G., Korpisalo-Pirinen P., Filippova M., Dasen B., Sacchi V., Muraro M.G., Trani M., Reginato S., Gianni-Barrera R., Ylä-Herttuala S. and Banfi A. (2018). EphrinB2/EphB4 signaling regulates non-sprouting angiogenesis by VEGF. EMBO Rep. 19, pii: e45054.

Hansen-Smith F.M., Hudlicka O. and Egginton S. (1996). *In vivo* angiogenesis in adult rat skeletal muscle: early changes in capillary network architecture and ultrastructure. Cell Tissue Res. 286, 123-136.

Hlushchuk R., Riesterer O., Baum O., Wood J., Gruber G., Pruschy M. and Djonov V. (2008). Tumor recovery by angiogenic switch from sprouting to intussusceptive angiogenesis after treatment with PTK787/ZK222584 or ionizing radiation. Am. J. Pathol. 173, 1173-1185.

Hlushchuk R., Ehrbar M., Reichmuth P., Heinimann N., Styp-Rekowska B., Escher R., Baum O., Lienemann P., Makanya A., Keshet E. and Djonov V. (2011a). Decrease in VEGF expression induces intussusceptive vascular pruning. Arterioscler. Thromb. Vasc. Biol. 31, 2836-2844.

Hlushchuk R., Makanya A.N. and Djonov V. (2011b). Escape mechanisms after antiangiogenic treatment, or why are the tumors growing again? Int. J. Dev. Biol. 55, 563-567.

Hlushchuk R., Styp-Rekowska B., Dzambazi J., Wnuk M., Huynh-Do U., Makanya A. and Djonov V. (2017). Endoglin inhibition leads to

intussusceptive angiogenesis via activation of factors related to COUP-TFII signaling pathway. PLoS One 12, e0182813.

Hussain A., Steimle M., Hoppeler H., Baum O. and Egginton S. (2012). The vascular-disrupting agent combretastatin impairs splitting and sprouting forms of physiological angiogenesis. Microcirculation 19, 296-305.

Ji J.W., Tsoukias N.M., Goldman D. and Popel A.S. (2006). A computational model of oxygen transport in skeletal muscle for sprouting and splitting modes of angiogenesis. J. Theor. Biol. 241, 94-108.

Karthik S., Djukic T., Kim J.D., Zuber B., Makanya A., Odriozola A., Hlushchuk R., Filipovic N., Jin S.W. and Djonov V. (2018). Synergistic interaction of sprouting and intussusceptive angiogenesis during zebrafish caudal vein plexus development. Sci. Rep. 8, 9840.

Kauffman S.L. (1975). Kinetics of pulmonary epithelial proliferation during prenatal growth of the mouse lung. Anat. Rec. 183, 393-403.

Kelly P., Denver P., Satchell S.C., Ackermann M., Konerding M.A. and Mitchell C.A. (2017). Microvascular ultrastructural changes precede cognitive impairment in the murine APPswe/PS1dE9 model of Alzheimer's disease. Angiogenesis 20, 567-580.

Kilarski W.W. and Gerwins P. (2009). A new mechanism of blood vessel growth - hope for new treatment strategies. Discov. Med. 8, 23-27.

Kochhan E., Lenard A., Ellertsdottir E., Herwig L., Affolter M, Belting H.G. and Slekmann A.F (2013). Blood Flow changes coincide with cellular rearrangements during Blood vessel pruning in Zebrafish embryos. Plos One 8, 10, e75060

Konerding M.A., Turhan A., Ravnic D.J., Lin M., Fuchs C., Secomb T.W., Tsuda A. and Mentzer S.J. (2010). Inflammation-induced intussusceptive angiogenesis in murine colitis. Anat. Rec. (Hoboken). 293, 849-857.

Konerding M.A., Gibney B.C., Houdek J.P., Chamoto K., Ackermann M., Lee G.S., Lin M., Tsuda A. and Mentzer S.J. (2012). Spatial dependence of alveolar angiogenesis in post-pneumonectomy lung growth. Angiogenesis 15, 23-32.

Kurz H., Burri P.H. and Djonov V.G. (2003). Angiogenesis and vascular remodeling by intussusception: from form to function. News Physiol. Sci. 18, 65-70.

Kurz H., Fehr J., Nitschke R. and Burkhardt H. (2008). Pericytes in the mature chorioallantoic membrane capillary plexus contain desmin and alpha-smooth muscle actin: relevance for non-sprouting angiogenesis. Histochem. Cell Biol. 130, 1027-1040.

Le Noble F., Fleury V., Pries A., Corvol P., Eichmann A. and Reneman R.S. (2005). Control of arterial branching morphogenesis in embryogenesis: go with the flow. Cardiovasc. Res. 65, 619-628.

Lee G.S., Filipovic N., Miele L.F., Lin M., Simpson D.C., Giney B., Konerding M.A., Tsuda A. and Mentzer S.J. (2010). Blood flow shapes intravascular pillar geometry in the chick chorioallantoic membrane. J. Angiogenes Res. 2, 11.

Lee G.S., Filipovic N., Lin M., Gibney B.C., Simpson D.C., Konerding M.A., Tsuda A. and Mentzer S.J. (2011). Intravascular pillars and pruning in the extraembryonic vessels of chick embryos. Dev. Dyn. 240, 1335-1343.

Logothetidou A., Vandecasteele T., Van Mulken E., Vandevelde K. and Cornillie P. (2017). Intussusceptive angiogenesis and expression of Tie receptors during porcine metanephric kidney development. Histol. Histopathol. 32, 817-824.

Logothetidou A., De Spiegelaere W., Vandecasteele T., Tschulenk W., Walter I., Van den Broeck W. and Cornillie P. (2018). Intussusceptive pillar formation in developing porcine glomeruli. J. Vasc. Res. 55, 278-286.

Macchiarelli G., Jiang J.Y., Nottola S.A. and Sato E. (2006). Morphological patterns of angiogenesis in ovarian follicle capillary networks. A scanning electron microscopy study of corrosion cast. Microsc. Res. Tech. 69, 459-468.

Makanya A.N., Stauffer D., Ribatti D., Burri P.H. and Djonov V. (2005). Microvascular growth, development, and remodeling in the embryonic avian kidney: the interplay between sprouting and intussusceptive angiogenic mechanisms. Microsc. Res. Tech. 66, 275-288.

Makanya A.N., Hlushchuk R., Baum O., Velinov N., Ochs M. and Djonov V. (2007). Microvascular endowment in the developing chicken embryo lung. Am. J. Physiol. Lung Cell Mol. Physiol. 292, L1136-1146.

Makanya A.N., Hlushchuk R. and Djonov V.G. (2009). Intussusceptive angiogenesis and its role in vascular morphogenesis, patterning, and remodeling. Angiogenesis 12, 113-123.

Mentzer S.J. and Konerding M.A. (2014). Intussusceptive angiogenesis: expansion and remodeling of microvascular networks. Angiogenesis 17, 499-509.

Miele L.F., Turhan A., Lee G.S., Lin M., Ravnic D., Tsuda A., Konerding M.A. and Mentzer S.J. (2009). Blood flow patterns spatially associated with platelet aggregates in murine colitis. Anat. Rec. (Hoboken) 292, 1143-1153.

Milkiewicz M., Kelland C., Colgan S. and Haas T.L. (2006). Nitric oxide and p38 MAP kinase mediate shear stress-dependent inhibition of MMP-2 production in microvascular endothelial cells. J. Cell Physiol. 208, 229-237.

Moll R., Sievers E., Hämmerling B., Schmidt A., Barth M., Kuhn C., Grund C., Hofmann I. and Franke W.W. (2009). Endothelial and virgultar cell formations in the mammalian lymph node sinus: endothelial differentiation morphotypes characterized by a special kind of junction (complexus adhaerens). Cell Tissue Res. 335, 109-141.

Naylor A.J., McGettrick H.M., Maynard W.D., May P., Barone F., Croft A.P., Egginton S. and Buckley CD. (2014). A differential role for CD248 (Endosialin) in PDGF-mediated skeletal muscle angiogenesis. PLoS One 9, e107146.

Nico B., Crivellato E., Guidolin D., Annese T., Longo V., Finato N., Vacca A. and Ribatti D. (2010). Intussusceptive microvascular growth in human glioma. Clin. Exp. Med. 10, 93-98.

Nico B., Annese T., Guidolin D., Finato N., Crivellato E. and Ribatti D. (2011). Epo is involved in angiogenesis in human glioma. J. Neurooncol. 102, 51-58.

Okuda N., Takeda S., Shinomiya K., Muneta T., Itoh S., Noda M. and Asou Y. (2007). ED-71, a novel vitamin D analog, promotes bone formation and angiogenesis and inhibits bone resorption after bone marrow ablation. Bone 40, 281-292.

Packham I.M., Watson S.P., Bicknell R. and Egginton S. (2014). *In vivo* evidence for platelet-induced physiological angiogenesis by a COX driven mechanism. PLoS One 9, e107503

Paku S., Kopper L. and Nagy P. (2005). Development of the vasculature in "pushing-type" liver metastases of an experimental colorectal cancer. Int. J. Cancer 115, 893-902.

Paku S., Dezso K., Bugyik E., Tóvári J., Tímár J., Nagy P., Laszlo V., Klepetko W. and Döme B. (2011). A new mechanism for pillar formation during tumor-induced intussusceptive angiogenesis: inverse sprouting. Am. J. Pathol. 179, 1573-1585.

Patan S. (1998). TIE1 and TIE2 receptor tyrosine kinases inversely regulate embryonic angiogenesis by the mechanism of intussusceptive microvascular growth. Microvasc. Res. 56, 1-21.

Patan S. (2000). Vasculogenesis and angiogenesis as mechanisms of vascular network formation, growth and remodeling. J. Neurooncol. 50, 1-15.

Patan S. (2004). Vasculogenesis and angiogenesis. Cancer Treat. Res. 117, 3-32.

Patan S. (2008). Lycat and cloche at the switch between blood vessel growth and differentiation? Circ. Res. 102, 1005-1007.

Patan S., Alvarez M.J., Schittny J.C. and Burri P.H. (1992). Intussusceptive microvascular growth: a common alternative to capillary sprouting. Arch. Histol. Cytol. 55 Suppl, 5-75.

Patan S., Haenni B. and Burri P.H. (1993). Evidence for intussusceptive capillary growth in the chicken chorioallantoic membrane (CAM). Anat. Embryol. (Berl). 187, 121-130.

Patan S., Haenni B. and Burri P.H. (1996a). Implementation of intussusceptive microvascular growth in the chicken chorioallantoic membrane (CAM): 1. pillar formation by folding of the capillary wall. Microvasc. Res. 51, 80-98.

Patan S., Munn L.L. and Jain R.K. (1996b). Intussusceptive microvascular growth in a human colon adenocarcinoma xenograft: a novel mechanism of tumor angiogenesis. Microvasc. Res. 51, 260-272.

Patan S., Haenni B. and Burri P.H. (1997). Implementation of intussusceptive microvascular growth in the chicken chorioallantoic membrane (CAM). 2 Pillar formation by capillary fusion. Microvasc. Res. 53, 33-52.

Patan S., Munn L.L., Tanda S., Roberge S., Jain R.K. and Jones R.C. (2001a). Vascular morphogenesis and remodeling in a model of tissue repair: blood vessel formation and growth in the ovarian pedicle after ovariectomy. Circ. Res. 89, 723-731.

Patan S., Tanda S., Roberge S., Jones R.C., Jain R.K. and Munn L.L. (2001b). Vascular morphogenesis and remodeling in a human tumor xenograft: blood vessel formation and growth after ovariectomy and tumor implantation. Circ. Res. 89, 732-739.

Peebo B.B., Fagerholm P., Traneus-Röckert C. and Lagali N. (2011). Cellular level characterization of capillary regression in inflammatory angiogenesis using an *in vivo* corneal model. Angiogenesis 14, 393-405.

Pettersson A., Nagy J.A., Brown L.F., Sundberg C., Morgan E., Jungles S., Carter R., Krieger J.E., Manseau E.J., Harvey V.S., Eckelhoefer I.A., Feng D., Dvorak A.M., Mulligan R.C. and Dvorak H.F. (2000). Heterogeneity of the angiogenic response induced in different normal adult tissues by vascular permeability factor/vascular endothelial growth factor. Lab. Invest. 80, 99-115.

Rajabi S., Dehghan M.H., Dastmalchi R., Jalali Mashayekhi F., Salami S. and Hedayati M. (2019). The roles and role-players in thyroid cancer angiogenesis. Endocr. J. 66, 277-293.

Ribatti D. and Djonov V. (2012). Intussusceptive microvascular growth in tumors. Cancer Lett. 316, 126-131.

Ribatti D., Nico B., Floris C., Mangieri D., Piras F., Ennas M.G., Vacca A. and Sirigu P. (2005). Microvascular density, vascular endothelial growth factor immunoreactivity in tumor cells, vessel diameter and intussusceptive microvascular growth in primary melanoma. Oncol. Rep. 14, 81-84.

Rivilis I., Milkiewicz M., Boyd P., Goldstein J., Brown M.D., Egginton S., Hansen F.M., Hudlicka O. and Haas T.L. (2002). Differential involvement of MMP-2 and VEGF during muscle stretch- versus shear stress-induced angiogenesis. Am. J. Physiol. Heart Circ. Physiol. 283, H1430-1438.

Rossi-Schneider T.R., Verli F.D., Marinho S.A., Yurgel L.S. and De Souza M.A. (2010). Study of intussusceptive angiogenesis in inflammatory regional lymph nodes by scanning electron microscopy. Microsc. Res. Tech. 73, 14-19.

Schlatter P., König M.F., Karlsson L.M. and Burri P.H. (1997). Quantitative study of intussusceptive capillary growth in the chorioallantoic membrane (CAM) of the chicken embryo. Microvasc. Res. 54, 65-73.

Short R.H. (1950). Alveolar epithelium in relation to growth of the lung. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 235, 35-86.

Styp-Rekowska B., Hlushchuk R., Pries A.R. and Djonov V. (2011). Intussusceptive angiogenesis: pillars against the blood flow. Acta Physiol. (Oxf). 202, 213-223

Suri C., Jones P.F., Patan S., Bartunkova S., Maisonpierre P.C., Davis S., Sato T.N. and Yancopoulos G.D. (1996). Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. Cell 87, 1171-1180.

Szczerba D., Kurz H. and Szekely G. (2009). A computational model of intussusceptive microvascular growth and remodeling. J. Theor. Biol. 261, 570-583.

Taylor A.C., Seltz L.M., Yates P.A. and Peirce S.M. (2010). Chronic whole-body hypoxia induces intussusceptive angiogenesis and microvascular remodeling in the mouse retina. Microvasc. Res. 79, 93-101.

Thoma R. (1893). I. Histogenese des Gefaesssystems. II. Allgemeine Histomechanik des Gefaesssystems. In: Untersuchungen ueber die Histogenese und Histomechanik des Gefaesssystems. Verlag von Ferdinand Enke, Stuttgart, pp. 1-51.

Tressel S.L., Huang R.P., Tomsen N. and Jo H. (2007). Laminar shear inhibits tubule formation and migration of endothelial cells by an angiopoietin-2 dependent mechanism. Arterioscler. Thromb. Vasc. Biol. 27, 2150-2156.

Tsuda A., Turhan A., Konerding M., Ravnic D., Hanidziar D., Lin M. and Mentzer S.J. (2009). Bimodal oscillation frequencies of blood flow in the inflammatory colon microcirculation. Anat. Rec. (Hoboken) 292, 65-72.

Turhan A., Konerding M.A., Tsuda A., Ravnic D.J., Hanidziar D., Lin M. and Mentzer S.J. (2008). Bridging mucosal vessels associated with rhythmically oscillating blood flow in murine colitis. Anat. Rec. (Hoboken) 291, 74-82.

Uccelli A., Wolff T., Valente P., Di Maggio N., Pellegrino M., Gürke L., Banfi A. and Gianni-Barrera R. (2019). Vascular endothelial growth factor biology for regenerative angiogenesis. Swiss Med. Wkly. 149, w20011.

Van Steenkiste C., Trachet B., Casteleyn C., van Loo D., Van Hoorebeke L., Segers P., Geerts A., Van Vlierberghe H. and Colle I. (2010). Vascular corrosion casting: analyzing wall shear stress in the portal vein and vascular abnormalities in portal hypertensive and cirrhotic rodents. Lab. Invest. 90, 1558-1572.

Vimalraj S., Bhuvaneswari S., Lakshmikirupa S., Jyothsna G. and Chatterjee S. (2018). Nitric oxide signaling regulates tumor-induced intussusceptive-like angiogenesis. Microvasc. Res. 119, 47-59.

Vimalraj S., Pichu S., Pankajam T., Dharanibalan K., Djonov V. and Chatterjee S. (2019). Nitric oxide regulates intussusceptive-like angiogenesis in wound repair in chicken embryo and transgenic zebrafish models. Nitric Oxide 82, 48-58

Williams J.L., Cartland D., Hussain A. and Egginton S. (2006a). A

differential role for nitric oxide in two forms of physiological angiogenesis in mouse. J. Physiol. 570, 445-454.

Williams J.L., Weichert A., Zakrzewicz A., Da Silva-Azevedo L., Pries A.R., Baum O. and Egginton S. (2006b). Differential gene and protein expression in abluminal sprouting and intraluminal splitting forms of angiogenesis. Clin. Sci. (Lond). 110, 587-595.

Winnik S., Klinkert M., Kurz H., Zoeller C., Heinke J., Wu Y., Bode C., Patterson C. and Moser M. (2009). HoxB5 induces endothelial sprouting *in vitro* and modifies intussusceptive angiogenesis *in vivo* involving angiopoietin-2. Cardiovasc. Res. 83, 558-565.

Xu Y., Yuan L., Mak J., Pardanaud L., Caunt M., Kasman I., Larrivée B., Del Toro R., Suchting S., Medvinsky A., Silva J., Yang J., Thomas J.L., Koch A.W., Alitalo K., Eichmann A. and Bagri A. (2010). Neuropilin-2 mediates VEGF-C-induced lymphatic sprouting together with VEGFR3. J. Cell Biol. 188, 115-130.

Zhan K., Lun B., Wang G., Zuo B., Xie L. and Wang X. (2018). Different angiogenesis modes and endothelial responses in implanted porous biomaterials. Integr. Biol. 10, 406-410.

Zhou A.L., Egginton S., Brown M.D. and Hudlicka O. (1998). Capillary growth in overloaded, hypertrophic adult rat skeletal muscle: an ultrastructural study. Anat. Rec. 252, 49-63.

Zuazo-Gaztelu I., Pàez-Ribes M., Carrasco P., Martín L., Soler A., Martínez-Lozano M., Pons R., Llena J., Palomero L., Graupera M. and Casanovas O. (2019). Antitumor effects of anti-semaphorin 4D antibody unravel a novel proinvasive mechanism of vascular-targeting agents. Cancer Res. 79, 5328-5341.

Accepted April 24, 2020