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A. **Nota de constatare şi confirmare a indiciilor de plagiat** prin fişa suspiciunii inclusă în decizie.

Fişa suspiciunii de plagiat / Sheet of plagiarism's suspicion	
Opera suspicionată (OS)	**Opera autentică (OA)**
Suspicious work	**Authentic work**
OS	DĂNĂILĂ Leon.The cordocyte. *Proc.Rom.Acad. Series B*. **16**(2). 2014. p.83-102.
OA	PAIS Viorel, DĂNĂILĂ, Leon and PAIS Emil.Cordocytes-stem cells cooperation in the human brain with emphasis on pivotal role of cordocytes in perivascular areas of broken and thrombosed vessels.*Ultrastructural Pathology*. **37**(6). 2013. p.425-432.
Incidenţa minimă a suspiciunii / Minimum incidence of suspicion	
p.83:04 abstract - p.83:07 abstract	p.425:01 abstract - p.425: 04 abstract
p.83:11 abstract - p.83:14 abstract	p.425:09 abstract - p.425:13 abstract
p.85:07s – p.85:09s; p.83:04 - p.83:05 abstract	p.425:01 abstract
p.93:14s - p.93:54s	p.426:35s - p.426:48s; p.426:53s - p.426:07d; p.426:10d - p.426:11d; p.426:12d - p.426:21d
p.93:01d - p.93:54d	p.426:21d - p.427:01d
p.94:00s - p.94:46s	p.427:03d - p.428:06s; p.429:02s - p.429: 08s
p.94:53s - p.94:16s	p.428:06s-p.428:10s; p.428:14s -p.428:29s
p.94:17d - p.94:43d	p.428:05d-p.429:02s; p.428:30s - p.428:33s p.431:44s - p.431:00d; p.431:26d -p.431:28d; p.431:36d - p.431:39d
p.95:04d - p.95:15d	p.425:10s-02d
p.96:Fig.10b	p.427:Fig.2
p.97:Fig.12	p.427:Fig.3
p.97:Fig.13	p.428:Fig.4
p.98:Fig.15	p.428:Fig.6
Fişa întocmită pentru includerea suspiciunii în Indexul Operelor Plagiate în România de la Sheet drawn up for including the suspicion in the Index of Plagiarized Works in Romania at www.plagiate.ro	

Notă: Prin „p.72:00" se înţelege paragraful care se termină la finele pag.72. Notaţia „p.00:00" semnifică până la ultima pagină a capitolului curent, în întregime de la punctul iniţial al preluării.

Note: By „p.72:00" one understands the text ending with the end of the page 72. By „p.00:00" one understands the taking over from the initial point till the last page of the current chapter, entirely.

B. **Fişa de argumentare a calificării** de plagiat alăturată, fişă care la rândul său este parte a deciziei.

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Fişa de argumentare a calificării

Nr. crt.	Descrierea situaţiei care este încadrată drept plagiat	Se confirmă
1.	Preluarea identică a unor pasaje (piese de creaţie de tip text) dintr-o operă autentică publicată, fără precizarea întinderii şi menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	✓
2.	Preluarea a unor pasaje (piese de creaţie de tip text) dintr-o operă autentică publicată, care sunt rezumate ale unor opere anterioare operei autentice, fără precizarea întinderii şi menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
3.	Preluarea identică a unor figuri (piese de creaţie de tip grafic) dintr-o operă autentică publicată, fără menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	✓
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6.	Republicarea unei opere anterioare publicate, prin excluderea unui autor sau a unor autori din lista iniţială de autori.	
7.	Preluarea identică de pasaje (piese de creaţie) dintr-o operă autentică publicată, fără precizarea întinderii şi menţionarea provenienţei, fără nici o intervenţie personală care să justifice exemplificarea sau critica prin aportul creator al autorului care preia şi însuşirea acestora într-o lucrare ulterioară celei autentice.	✓
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12.	Preluarea identică de pasaje (piese de creaţie de tip text) ale unui cuvânt înainte sau ale unei prefeţe care se referă la două opere, diferite, publicate în două momente diferite de timp.	

Notă:

a) Prin „provenienţă" se înţelege informaţia din care se pot identifica cel puţin numele autorului / autorilor, titlul operei, anul apariţiei.

b) Plagiatul este definit prin textul legii[1].

> *„ …plagiatul – expunerea într-o operă scrisă sau o comunicare orală, inclusiv în format electronic, a unor texte, idei, demonstraţii, date, ipoteze, teorii, rezultate ori metode ştiinţifice extrase din opere scrise, inclusiv în format electronic, ale altor autori, fără a menţiona acest lucru şi fără a face trimitere la operele originale…".*

Tehnic, plagiatul are la bază conceptul de **piesă de creaţie** care[2]:

> *„…este un element de comunicare prezentat în formă scrisă, ca text, imagine sau combinat, care posedă un subiect, o organizare sau o construcţie logică şi de argumentare care presupune nişte premise, un raţionament şi o concluzie. Piesa de creaţie presupune în mod necesar o formă de exprimare specifică unei persoane. Piesa de creaţie se poate asocia cu întreaga operă autentică sau cu o parte a acesteia…"*

cu care se poate face identificarea operei plagiate sau suspicionate de plagiat[3]:

> *„…O operă de creaţie se găseşte în poziţia de operă plagiată sau operă suspicionată de plagiat în raport cu o altă operă considerată autentică dacă:*
> *i) Cele două opere tratează acelaşi subiect sau subiecte înrudite.*
> *ii) Opera autentică a fost făcută publică anterior operei suspicionate.*
> *iii) Cele două opere conţin piese de creaţie identificabile comune care posedă, fiecare în parte, un subiect şi o formă de prezentare bine definită.*
> *iv) Pentru piesele de creaţie comune, adică prezente în opera autentică şi în opera suspicionată, nu există o menţionare explicită a provenienţei. Menţionarea provenienţei se face printr-o citare care permite identificarea piesei de creaţie preluate din opera autentică.*
> *v) Simpla menţionare a titlului unei opere autentice într-un capitol de bibliografie sau similar acestuia fără delimitarea întinderii preluării nu este de natură să evite punerea în discuţie a suspiciunii de plagiat.*
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> *vii) In opera suspicionată se identifică un fir sau mai multe fire logice de argumentare şi tratare care leagă aceleaşi premise cu aceleaşi concluzii ca în opera autentică…"*

[1] Legea nr. 206/2004 privind buna conduită în cercetarea ştiinţifică, dezvoltarea tehnologică şi inovare, publicată în Monitorul Oficial al României, Partea I, nr. 505 din 4 iunie 2004
[2] ISOC, D. *Ghid de acţiune împotriva plagiatului: bună-conduită, prevenire, combatere*. Cluj-Napoca: Ecou Transilvan, 2012.
[3] ISOC, D. *Prevenitor de plagiat*. Cluj-Napoca: Ecou Transilvan, 2014.

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ORIGINAL ARTICLE

Cordocytes-Stem Cells Cooperation in the Human Brain with Emphasis on Pivotal Role of Cordocytes in Perivascular Areas of Broken and Thrombosed Vessels

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ABSTRACT

This study is based on data analysis by light and transmission electron microscopy of the surgical cases in cerebral tumors, cerebrovascular malformations, thromboses in the carotid system, and other injuries such as perivascular hemorrhage. We examined cortical arteries and veins, perivascular areas with old hematic masses, vasculogenic foci, and broken large vessels. We identified, characterized, and compared both undifferentiated cells and well-differentiated cordocytes within periadventitial areas where these cells cooperate very well with precursor/stem cells to perform vital functions for cerebral vasculature with immediate effect on brain parenchyma. This useful cellular cooperation was observed by serial sections pointing out the main role of cordocytes during the entire process of collateral vessel formation after thrombosis and, respectively, in vascular wall repair after ruptures. This is the first cytohistopathological study which illustrates and explains some facets of cordocytes-stem cells cooperation around the vessels of human brain with emphasis on the fundamental role of cordocytes in response to vascular injuries. Our pioneering study will be completed for both basic science and modern medical care by further studies.

Keywords: Cooperation, cordocytes, human brain, stem cells, ultrastructure, vessels

In the past decade we have analyzed by light and electron microscopy over 1000 cerebral biopsies and cortical vessels in a large spectrum of surgical cases, identifying a new functional interstitial cell type, named by us "cordocyte" [1,2]. Our findings shed light on the roles of these mesenchymal cells which may facilitate the benefic processes and delay pathological processes being involved in fundamental events of the central nervous system development and adult life as well. Cordocytes (which form the pia mater with blood vessels) are involved in normal corticogenesis (being demonstrated by transmission electron microscopy in the cerebral ectocortex), postnatally in the maintenance of appropriate pericortical microenvironment, in vasomotion, in inhibition of hematic invasion to the brain parenchyma, especially in hypertensive humans, as well as in inhibition of microtumoral growth or any abberant cellular movement toward the cerebral cortex. At the same time, these special interstitial cells have close relations with cerebral vasculature, constantly being seen around the cortical arteries and veins, where they perform multiple and useful functions including vascular repair/remodeling and de novo vessels formation [3–5]. Significantly, cordocytes cooperate in many situations with stem cells located in the vascular niche and this cellular bidirectional cooperation has to be better documented. Here, we try to illustrate and explain, for the first time, some morphological and ultrastructural aspects in their spatial and temporal evolution related to vascular repair post-rupture and collateral vessel formation post-thrombosis when an impressive cooperation cordocytes-stem cells exists along the vascular surface.

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MATERIALS AND METHODS

We obtained the vascular segments by surgery from patients operated on for cerebral tumors (glioblastomas, oligoastrocytomas, meningiomas) and arteriovenous malformations in accordance with ethical guidelines. Using light microscopy we examined multiple segments of cortical arteries and veins by using serial sections and examined a cortical branch from a thrombosed middle cerebral artery by transmission electron microscopy. The samples observed under a light microscope were fixed with 2.5% buffered glutaraldehyde, postfixed with 1% buffered osmium tetroxide, dehydrated in alcohols and embedded in an epoxy resin (Epon 812). Sections with a thickness of 4–6 µm were cut using an ultramicrotome, mounted on glass slides, stained with 1% toluidine blue or hematoxylin and eosin, and examined by conventional light microscopy. Multiple ultrathin sections, 70 nm thick, were also cut with an ultramicrotome and contrasted with 2% uranyl acetate solution as well as Reynolds lead citrate solution. The specimens were then observed under a JEM 1200 EX (JEOL) transmission electron microscope. The electron micrographs were processed on a computer and converted into images.

RESULTS

Spatiotemporal Events Concerning Cordocytes-Stem Cells Cooperation in Perivascular Areas Revealed by Light Microscopy

To determine interactions of these cells within the vascular niche and to understand the cell phenomenology during cellular response to tissue injury, we observed multiple serial sections of vascular wall in a variety of clinical conditions. All cortical arteries and veins were surounded by well-differentiated cordocytes, some of them in spatial relations with rare mesenchymal stem cells. A very interesting relationship between these differentiated and undifferentiated cells appear around the blood vessels in situations with perivascular hemorrhage. In such cases, some cordocytes remain in their natural locations, i.e., close to the adventitial layer, while other cordocytes are closely seen in spatial relations with isolated undifferentiated cells, i.e., with mesenchymal stem cells as well as with cytogenic foci or even surrounding the new arterioles formed around the main artery. It is remarkable that the long cordocytic processes separate an early cytogenic focus from the hematic mass and create widened and empty spaces around the main artery, to facilitate cell-cell contacts during cell differentiation without erythrocytic interference. Any small vasculogenic focus

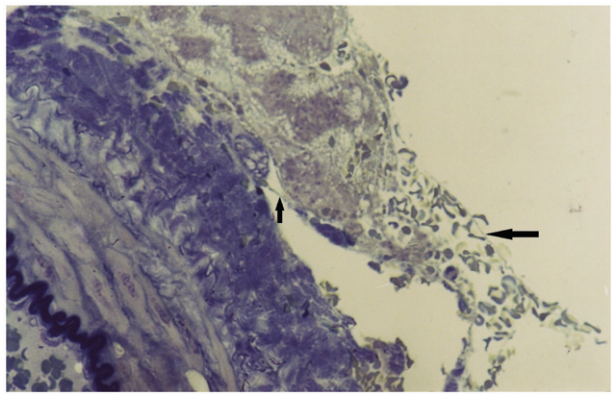

FIGURE 1. An early vasculogenic focus containing multiple centers of cell proliferation and differentiation separated by cordocytes (short arrow), while other well-differentiated cordocytes perivascularly retain segregated erythrocytes (long arrow). ×400.

contains both progenitors of vascular cell lineages and precursor cells for cordocytic lineage. In addition, any small cytogenic focus with only several precursor/stem cells is already surrounded by one or two well-differentiated cordocytes suggesting their important morphological roles in the early events of vascular morphogenesis. Thus, well-differentiated cordocytes make a clear demarcation of proliferating and differentiating cells from the hematic mass, itself a source of stem cells, gradually eliminating red blood cells from the future vasculogenic focus (Figure 1). However, in some arteriovenous malformations, multilayered cordocytes surround proliferating precursor/stem cells, whereas the hematic mass is surrounded by a monolayer of well-differentiating cells due to different cytokinetic mechanisms in multiple cell types. Normally, long and thin cordocytic processes surround the nascent vessels as well as the entire cytogenic mass suggesting a controlling role of cordocytes for all cellular events: proliferation, migration, differentiation. Cordocytes seem to gradually orchestrate all cell events in their spatiotemporal vasculogenic sequence, because they are present in direct contact with stem cells and different progenitors and surround each cytogenic focus of different age and cell composition until mature vessel formation. Cordocytes always establish contacts with mature vessels, and significantly, even with a single undifferentiated cell, suggesting their pivotal role in cell fate. All cellular divisions, migrations, and differentiations are seen in direct relation with well-differentiated cordocytes which send thin prolongations toward target cells or surround massive formations which contain many differentiating cells originating from hematopoietic stem cells or from perivascular mesenchymal stem cells. Therefore, the presence of well-differentiated cordocytes after the first divisions of stem cells appears necessary to assure normal vasculogenic events, conversely,

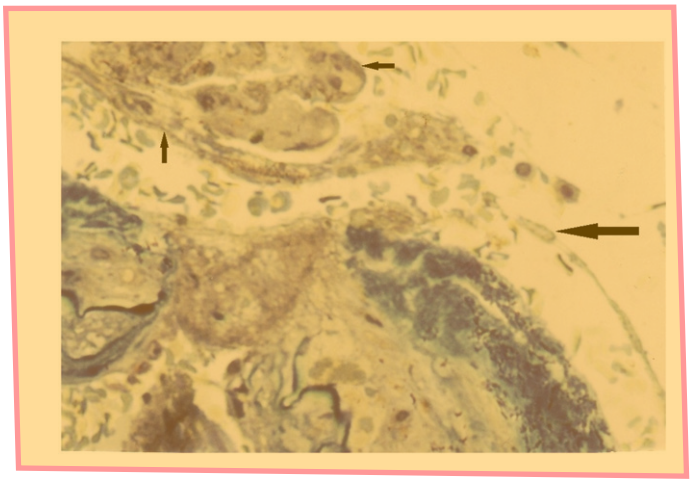

FIGURE 2. Another sectioning level of the broken artery illustrated above: one can see cytogenic foci in which well-differentiated cordocytes appear, and even precursor cells and stem cells closely distributed (short arrows). Long arrow indicates an well-differentiated cordocyte, resident in that perivascular area and migrating to the damaged place. ×200.

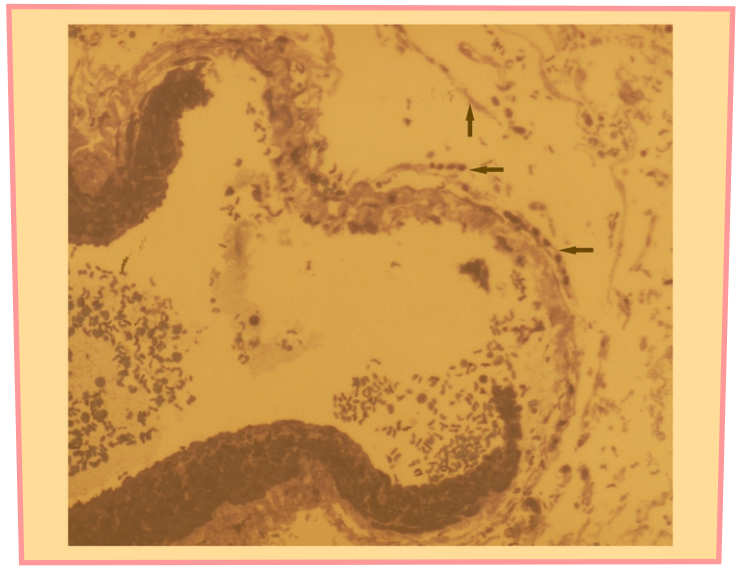

FIGURE 3. A malformed vessel of venous type in which tunica media is lacking, but instead, there is a thick band containing collagen, stem cells, and well-differentiated cordocytes. Significantly, close to this collagenous band other well-differentiated cordocytes which surround numerous stem cells are seen (arrows). ×200.

if these cells are lacking, the precursor/stem cells are spreading in the space without differentiation along the vascular lineages. In vascular segments with narrowed lumen or occlusions, it can be observed, at the vascular surface, either an accumulation of precursor/stem cells in association with cordocytes, or cytogenic foci where only cordocytes appear by directed differentiation. As a general rule, these cytogenic foci are placed in the immediate vicinity of the disrupted vascular walls, suggesting a prompt reaction of the protective cells located around the vessels. In some circumstances with transmural erythrodiapedesis, tunica adventitia itself is thickened, containing numerous precursor/stem cells but not differentiated cells to cordocytic phenotypes or vascular lineages. Serial sections from vessels with disruptions show multiple stages of vascular repair/remodeling beginning with mobilization of stem cells at the place of rupture and then proliferation and migration toward the vascular wall of the differentiating cells to cordocytic lineage, and finally, with a new cordocytic coverage at the vascular surface. Cellular dynamics and morphology are suggestive for spatial and temporal modifications which have regulated mechanisms. For such mechanisms, cordocytes themselves are responsible because they surround the stem cells and establish direct contacts with precursor/stem cells by means of their long and thin prolongations. Significantly, well-differentiated cordocytes come in direct contact with stem cells even when these isolated undifferentiated cells are distributed near those cell foci. Moreover, other well-differentiated cordocytes, resident in that zone, come to the damaged place, suggesting precise and specific signaling pathways (Figure 2). Finally, when arterial rupture is solved by cell cooperation including own smooth muscle cell activity within the tunica media, a new protective cell, i.e., a cordocyte, covers the vascular surface whereas locally cytogenic foci are dissipated in that perivascular area. A very interesting phenomenon with cordocytes playing a key role is observed in some cases with arteriovenous malformations when tunica media is lacking in some vascular segments. In such situations, well-differentiated cordocytes are capable to gather stem cells locally which become adherent to their cell membrane, exactly in the damaged area (Figure 3). In veins, by analogy with cellular cooperation from arteries, there are stem cells clustered by means of long processes and short filopodia of the local cordocytes at the damaged vascular wall (Figure 4). In addition, other well-differentiated cordocytes, running in parallel and reinforced by collagen produced by themselves, are directed toward a crossing cell column which impedes the venous wall to collapse due to the focal degeneration. In cases with different thromboses, it also exists a perivascular reaction of the cordocytic lineage, with polymorph nuclei and different sized cells being visible, in connection with well-differentiated cordocytes. In these situations even stem cells in symmetrical divisions in small cytogenic foci can be identified, as well as transitional morphological cells and well-differentiated cordocytes with their characteristic ovoid nucleus and prominent and marginal nucleolus. Respecting a general rule, these protective cells occupy a peripheral position, either at the vascular surface or around different cellular foci. However, they are found not only surrounding vessels and cytogenic foci, but in direct contact with fibroblasts and macrophages in perivascular areas with new arterioles and many foam cells. A thrombosed branch from a middle cerebral artery clearly

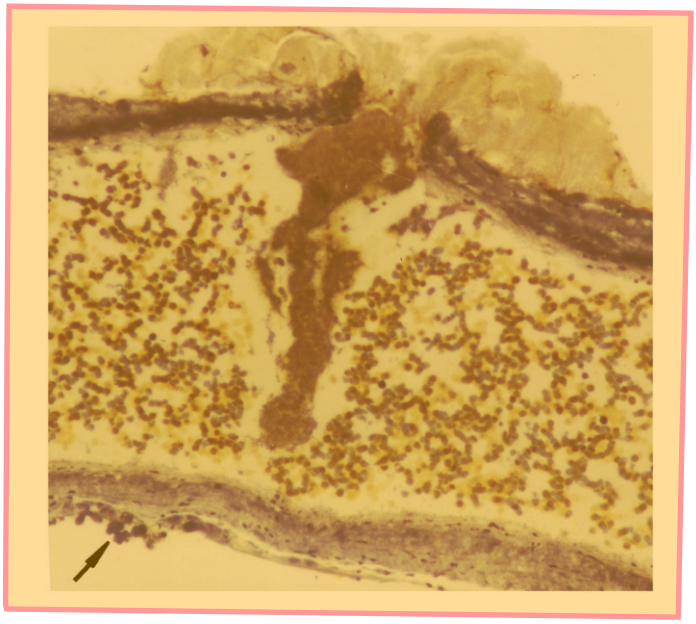

FIGURE 4. Broken cortical vein with focally degenerated wall, with a large platelet plug, and significantly, on the opposite side, one can see numerous proliferating stem cells in close contact with well-differentiated cordocytes (arrow). ×200.

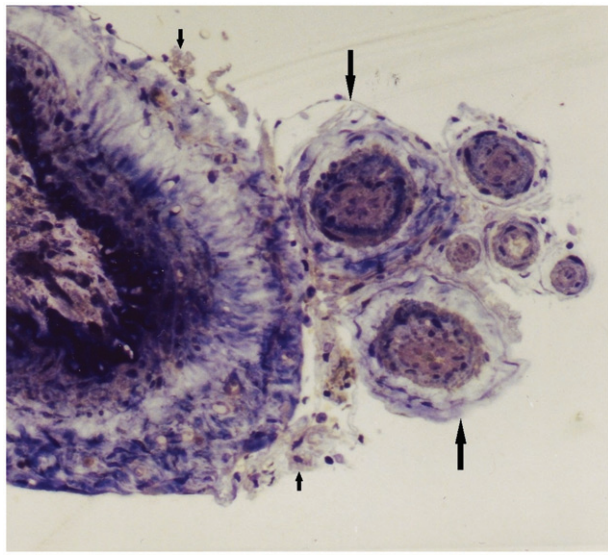

FIGURE 5. This image shows how well-differentiated cordocytes clearly delineate both incipient cytogenic foci (short arrows) and increasing vasculogenic foci (long arrows) closely to the parental vascular wall. ×100.

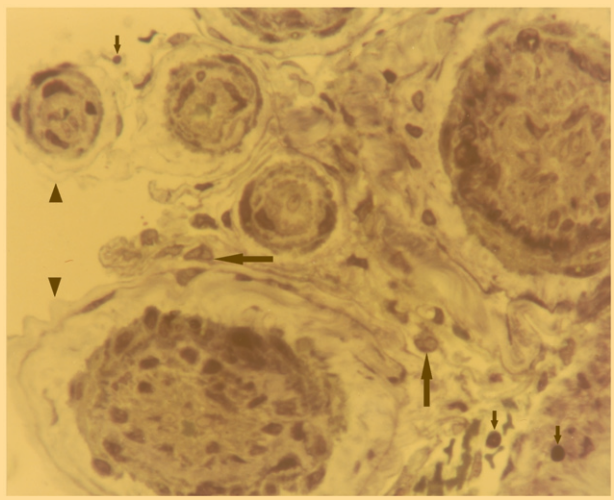

FIGURE 6. In this image, at a higher magnification, one can see stem cells in relation with cordocytes (short arrows), cells in division (long arrows), well-differentiated bilayer cordocytes disposed around the new vessels, some of them already showing a small lumen containing 1–2 red blood cells (arrowheads). ×400.

showed involvement of cordocytes, both in early vasculogenic events and maturing vessels. Well-differentiated and interconnected cordocytes surrounded main artery, totally thrombosed, as well as an incipient cytogenic focus and collateral vessels in formation. At another sectioning level it is clearly seen how a thick cell column, bordered by well-differentiated cordocytes, emerges from the outer adventitial layer including both cordocytes and a few stem cells. This cellular column will provide with well-differentiated cordocytes and fibroblasts (locally derived from precursor/stem cells by proliferation and differentiation) the outermost zone of new collateral arterioles. In the core of nascent vessels it is visible a segregation of differentiating cells, some of them becoming endothelial cells and the others smooth muscle cells. Excedentary cells, either endothelial or smooth muscle cells, may undergo apoptosis or autoschizis identified by electron microscopy. However, an heterogeneity of cell population and continuously implication of cordocytes are evident in all stages of vascular morphogenesis. When a vasculogenic focus increases in size it becomes surrounded by interconnected well-differentiated cordocytes which keep inside all cells, either undifferentiated or differentiating, i.e., stem cells and progenitors of endothelial cells, smooth muscle cells and fibroblasts, which participate in histoarhitectonics of vascular wall (Figure 5). At least it is clear that cordocytes act as guide, and then as protective cells for a cytogenic/vasculogenic focus, despite the reduced number of stem cells within the vascular niche (Figure 6).

Significant Electron Microscopic Findings Concerning Cordocytes-Precursor/Stem Cells Cooperation in Perivascular Areas of Thrombosed Middle Cerebral Arteries

Our electron microscopic observations regarding the arterial segment presented optically above demonstrate a very close rapport of perivascular cordocytes with stem cells within the vascular niche in early phases of collateral vasculogenesis when cordocytes surround from the beginning to the end all proliferating and differentiating cells to mature endothelial