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The thread-protective cell, a new cell performing multiple tasks

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Rezumat

Celula protectoare sub formă de sfoară: o nouă celulă cerebrală multifuncțională

Cercetările efectuate de noi, care ne-au dus la descoperirea noii celule cerebrale, au început în urmă cu 30 de ani. Un moment important l-a constituit anul 1986 când am evidențiat pentru prima dată celula respectivă în cadrul unui studiu efectuat pentru lămurirea unor aspecte inedite de ateroscleroză cerebrală. În anul 2006 am demarat publicarea retzultatelor cercetărilor noastre la trei congrese (Cape Town – 2006; San Diego – 2009 şi Los Angeles – 2011) şi trei atlase din 2006, 2008 şi 2010. Cu ajutorul microscopului electronic am analizat în acest scop, de la bolnavii neurochirugicali, 1176 biopsii vasculare, tumorale, corticale, de plex coroid, şi infecțioase. Celula respectivă a fost denumită cordocit-proteocit pentru a-i releva aspectul morfologic de cordon şi cel funcțional de element care protejează substanța nobilă a creierului împotriva diverselor agresiuni, în special hemoragice. Cu această ocazie am realizat că pia mater este constituită din astfel de celule protectoare şi cu rol în stoparea migrării neoblaştilor. Când chimioatacații celulelor noastre sunt insuficienți apar heterotopii celulare subcorticale la nivelul coroanei radiate (corona radiata), cortex dublu şi alte tulburări de migrare neuronală generatoare de epilepsie. În consecință, pia mater ar trebui văzută dintr-o perspectivă citodinamică. Telocitul de la nivelul organelor interne (intestine, cord etc) nu reprezintă altceva decât "interstitial cell of Cajal" (ICC) descris în urmă cu aproximativ 100 ani. Aceste ICC inițiază activitatea electrică ritmică spontană asemănătoare celulelor peacemaker-ului cardiac.

Cuvinte cheie: creier, celulă protectoare sub formă de sfoară, celula Cajal interstițială

Abstract

Our research work, which has led us to discovering the new cerebral cell, has started 30 years ago. An important moment was the year 1986, when we have highlighted it for the first time, during a study upon the clarification of some undiscovered aspects of cerebral atherosclerosis. In 2006 we have initiated the publishing of our results at three congresses (Cape Town - 2006; San Diego – 2009 and Los Angeles - 2011) as well as in three Atlases, form 2006, 2008 and 2010. By means of the electronic microscope we have analyzed to this purpose alone, a number of neurosurgery patients, with 1176 cerebral, vascular, tumoral, cortical, choroid plexus tumor and infectious biopsies. The cell in question was named cordocit-protectocit (thread-protective cell) in order to highlight its morphological aspect of a belt band and its functional one, of protective element of the noble substance of the brain, acting for its defense against various aggressions, especially hemorrhagic. On this occasion we have discovered that the pia mater is made up of such protective cells, which also play a role in preventing the neuroblasts from migrating. When the chemotactants of our cells are not numerous

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enough, subcortical cell heterotopias will occur, at the level of the corona radiata, double cortex and other neuronal migration disorders which may generate epilepsy. Therefore, the pia mater should be considered from a cytodynamic perspective. The telocyte at the internal organs level (intestine, heart etc.) is nothing else but the interstitial cell of Cajal (ICC), described by Cajal more than 100 years ago. The ICC spontaneously initiate rhythmic electrical activity, much like the peacemaker cells of the heart.

Key words: brain, the thread-protective cell, interstitial cell of Cajal

Introduction

Our research work has started from the well-known fact which states that the brain lacks lymphatic tissue and circulation. At that point, we have asked ourselves whether these functions are performed by other cellular elements of the central nervous system, which have remained unknown to us until now, but are protecting the noble substance of the brain against various aggressions. We have patiently researched, years and years on end, by means of the optical and electronic microscope, all the cerebral and medullary pathological processes (Dănăilă and all 2000 and 2002), until we have finally found, together with Doctor Biologist Viorel Păiş, this cell which performs its tasks of protecting, defending, acting as a hematoencephalic barrier, guiding the neuroblastic migration, antitumor action, support and protection for the cerebral cortex etc.

Some of the glial cells (e.g., microglia) take over certain functions of the lymphatic system, but they are not satisfying enough. At the same time, the functions of the hematoencephalic barrier are not comparable to the functions of the cell we have discovered.

Together with Viorel Păiş we have discovered a new cell in the brain. We have started the research three decades ago.

An important moment was the year 1986, when we have highlighted it for the first time, carrying out a targeted study upon cerebral atherosclerosis – we have also published two books on this issue, over one thousand pages (Dănăilă and Păiş 1988, 2004) – but back then we have not dared come up with a verdict. Afterwards, year after year – one can see from the bibliography – we have discovered and added things, so that at the moment we have no doubts that we have discovered a new morphofunctional cytologic entity.

From 2006 we have initiated the presentation of our results at three world congresses and also in an atlas.

The result of the first communicate, held in Cape Town, can be found at page 155 from "Book of Abstract" (Dănăilă and Păiş 2006).

The first Atlas which makes references to the cell we have discovered, dates in 2006 (Păiş and Dănăilă 2006).

Along with asserting new morphological and physiological features, we have asserted new communications at two other international congresses. For instance, in 2009, at the AANS/CNS congress – cerebral-vascular section in San Diego, California (Păiş and Dănăilă 2009), and in 2011, at the AANS/CNS Congress in Los Angeles, California (Păiş and Dănăilă 2011).

In 2008 and 2010 we have edited new Atlases, which contain innovative data about the anatomy and physiology of this cell (Păiş and Dănăilă 2008).

We have delayed the official announcement of our discovery due to the fact that the analyzed cell is very thin and is situated under the resolution of the optical microscope.

The California Nanosystems Institute, from the University of Los Angeles – UCLA was of a great help, supporting our research on a long term by putting at our disposal their extraordinary laboratory.

There we have succeeded during the last four years to examine the pieces by means of state of the art electronic-microscopic devices.

Material and method

At the moment, by means of the electronic microscope, we have analyzed in neurosurgery patients a number of 1176 biopsies of various types: cerebral, vascular (arteriovenous malformations, aneurisms, cavernomas, veins, arteries), hemoragic, tumoral (astrocytoma, glioblastoma, oligodendroglioma, ependymoma, choroid plexus tumors, normal choroid plexus as well, gangliocytoma, pineocytoma, pineoblastoma, germinoma, meduloblastoma, schwannoma, meningioma, hemangiopericytoma, lymphoma, craniopharyngioma, hypophyse tumors, chordoma, metastases, tuberculoma, abscesses, hydatidosis, cysticercosis and normal cerebral cortex and white cerebral substance from patients subject to surgery for unruptured cerebral aneurysms etc). All surgeries have been performed by Prof. Dănăilă from the neurological department of the National Institute for Neurology and Neurovascular Diseases in Bucharest (Dănăilă and all 2000, 2002).

Mean patient age was between 4 and 90 years.

The features of the cell we have discovered

Morphologically, our cell has been identified by optical and electronic transmission microscopy and scanning. It is a very long cell, thread shaped (thread cell), which is almost omnipresent around cortical vessels and sometimes at the surface of the cerebral cortex *(Fig. 1-9)*.

It has an ovoid nucleus with a distinct geometry of the chromatin, a small, dense nucleoli, dense electron cytoplasm, filled with filaments, numerous, large mitochondria, plus slender cellular prolongations, which are sinuous and extremely long, sometimes split into a variable number of filopodia *(Fig. 10)*, or with a discontinuous membrane.

Morphofunctionally, the cell has been identified by the functional ultrastructural features which impose taking into consideration altogether the structural features with their capacities of migration and establishing intercellular contacts,

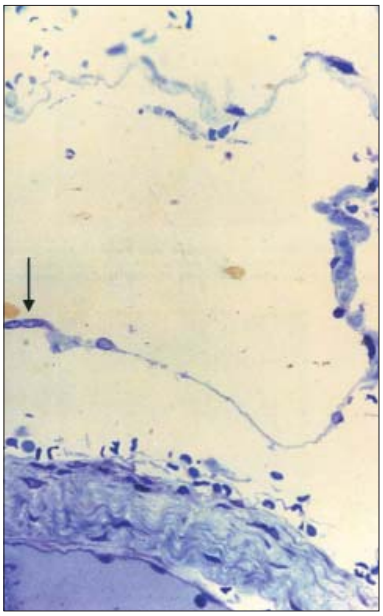

Figure 1. *The tread-protective cells in direct contact each other and an thread-protective cell in division (arrow)*

Figure 2. *A long, thin and sinuous cell process on the vessel surface (arrow) and close opposition of thread-protective cell (arrow heads)*

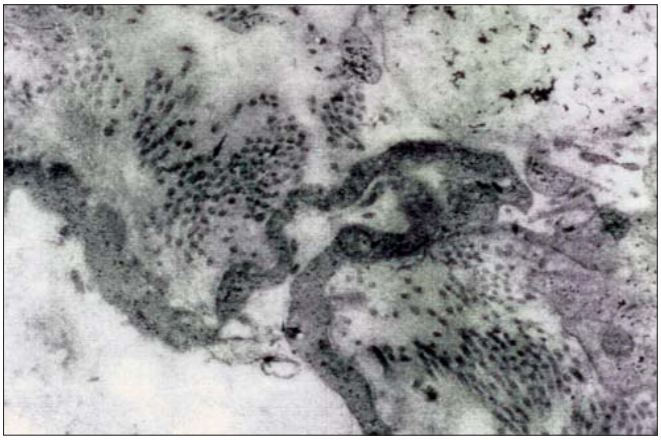

Figure 3. *Contact between two thread-protective cells which are folder inwards*

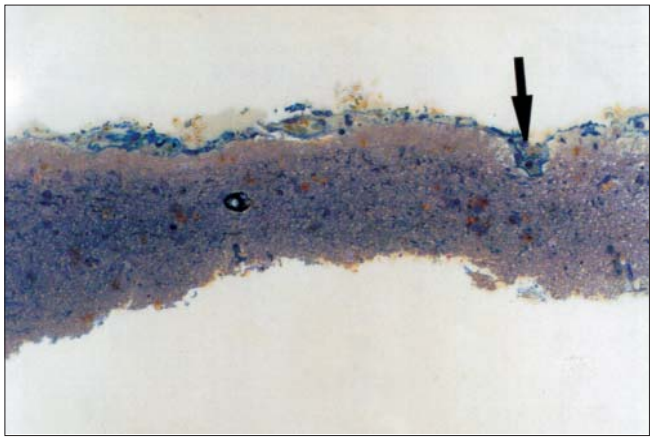

Figure 4. *The thread-protective cells on the cortical surface surrounding another cells (arrow)*

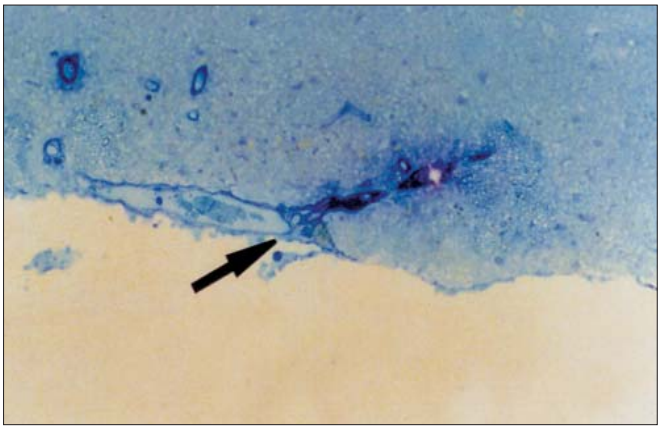

Figure 5. *Long thread cell processes surrounding small vessels in the marginal zone of the cerebral cortex, in a woman-aged 90 (arrow)*

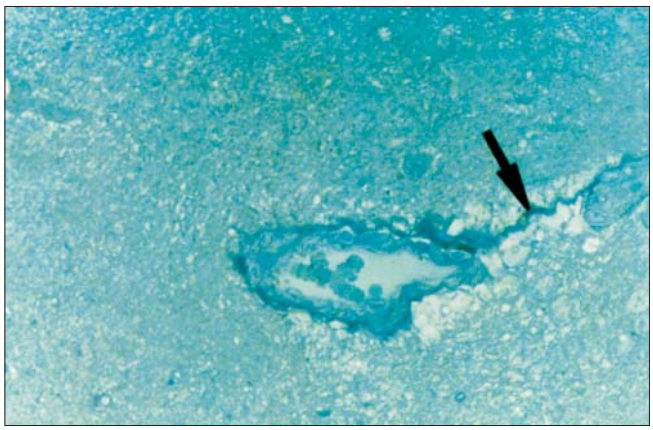

Figure 6. *The thread-protective cells surrounding two intra-parenchymatous vessels in the cerebral cortex (arow)*

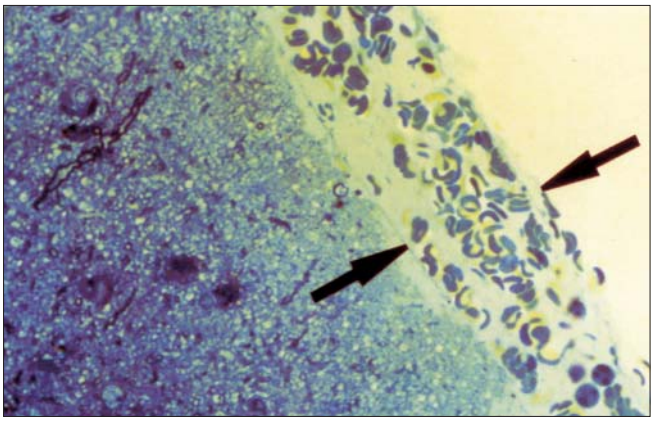

Figure 7. *Cerebral cortex with thread-protective cells isolating red blood cells on the cortical surface (arrows)*

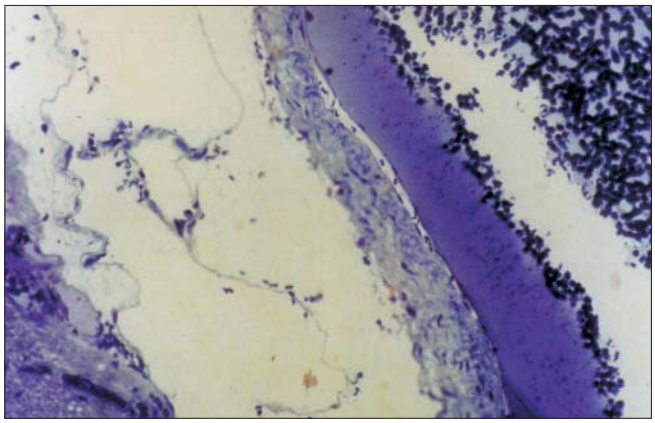

Figure 8. *Multipolar and long thread-cells with red blood cells adherent to the branches on the cortical surface and located within the subarachnoid space*

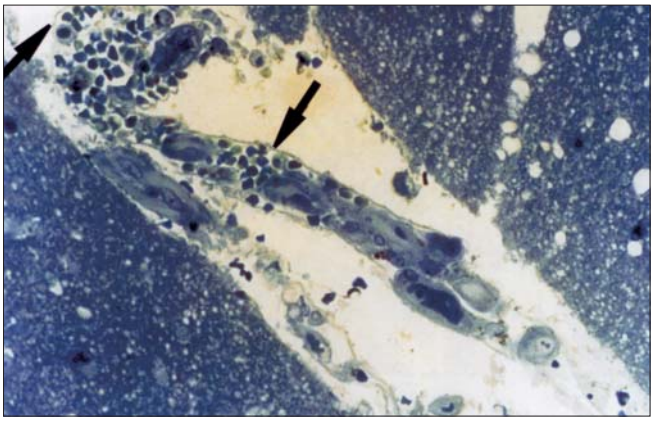

Figure 9. *Cerebellar cortex with long thread-protective cells processes surrounding small vessels and numerous red blood cells*

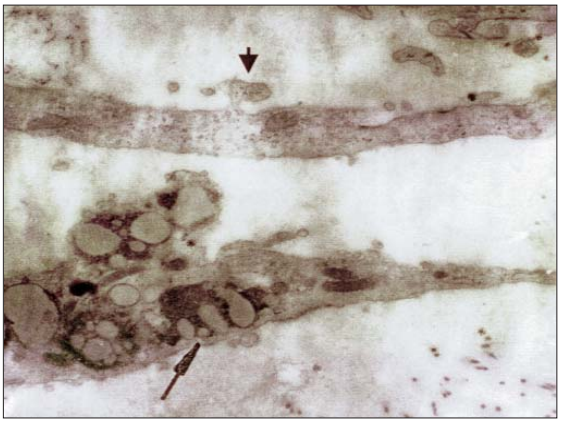

Figure 10. *Characteristic short filopodia (arrow head) and large lysosomal complex within an thread-protective cell (arrow)*

with their membrane modifications, with their cytological aspects which have a partnership relevance or, on the contrary, a spatial positioning etc. All these features may unfold subclinically, throughout the entire life, having an important physiological and afterwards, physiopathological importance.

These cells wrap tightly around the adventitia of the cerebral vessel, being difficult to exfoliate. Possibly extravasating erythrocytes are caught by these thread cells situated around the vessels, not allowing them to enter the cerebral substance which they are so carefully protecting. Their task is extraordinary, considering they act as an active and efficient warden. The receptors on their surface are really large-sized and very well built. They are real professional hunters for their prey, the erythrocytes.

Concluding, around the cerebral vessel there is a real permanent net of thread cells. Therefore, in case one of them is damaged or enters programmed cellular death, all the other cells will replace it; furthermore, in the same area there are also stem cells which may develop, by specific factors, into new cells perfectly able to replace their comrades, when they are loaded with erythrocytes *(Fig. 11)*. It is due to this feature that we have appointed to the cells a double name, which comprises both the morphological and the physiological aspects. We have called them "thread cells", because they look like a thread or a belt band (cordon) and protective cell because they play an important role in cerebral protection.

These cells do not represent a simple physical barrier, but also actively take part in various processes: from antihemorrhagic – case when they prevent the erythrocytes from invading the cerebral tissue – to their action of preventing, enclosing, limiting a possible abnormal multiplication of the cells (antitumor action). They may also be compared to a chain which encloses inflammatory, hemorrhagic *(Fig. 12)*, tumoral *(Fig. 13, 14)* degenerative processes *(Fig. 15)* and malformative vessels *(Fig. 16)*.

According to present data, the pia mater is made up of a leptomeningeal stratum of cells, which made up a transparent, delicate epithelial-like membrane, which wraps tightly around the surface of the brain, precisely following its outline. We are certain that also the pia mater is made up of the cells we have

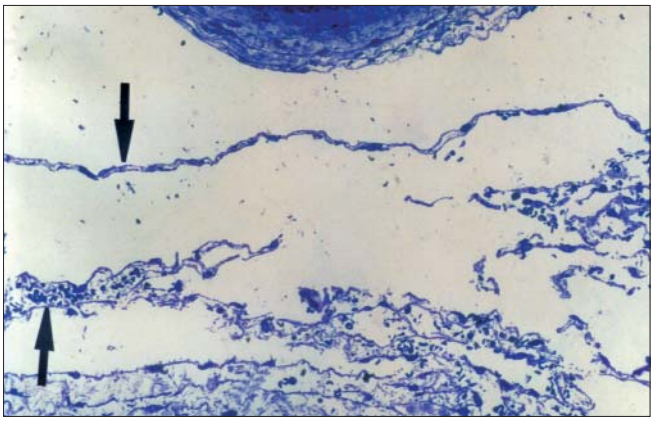

Figure 11. *Vascular wall with environmental thread-protective cells, some of them retaining red blood cells (arrows)*

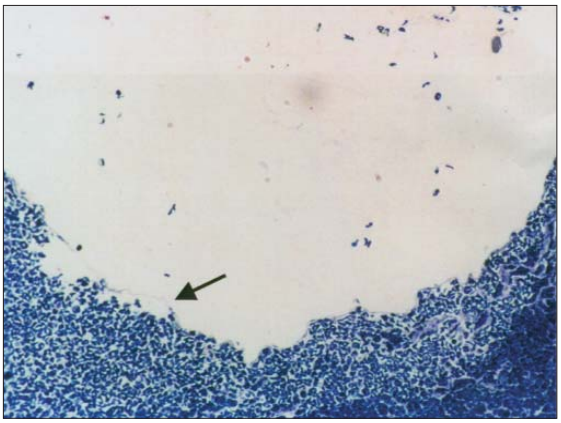

Figure 12. *Hard hematic accumulation surrounding by thread-protective cells as a border with a barrier role (arrow). One may observe only a few vasular cells outside the hematic mass, beyond of thread-protective cells*

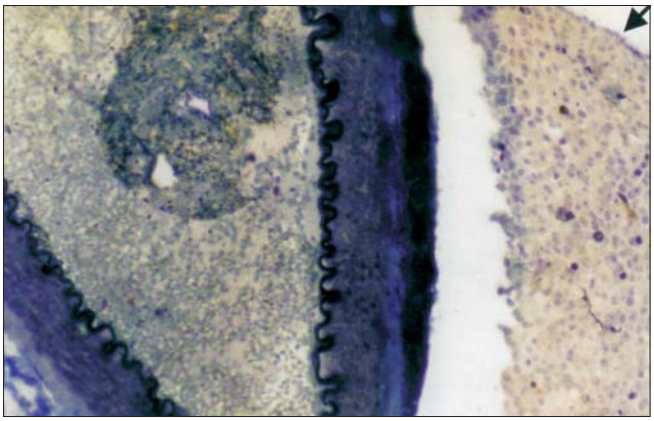

Figure 13. *An enormous cellular mass around the vascular wall which do not pass beyond the thread-protective cells line (arrow), in a case of oligoastrocytoma*

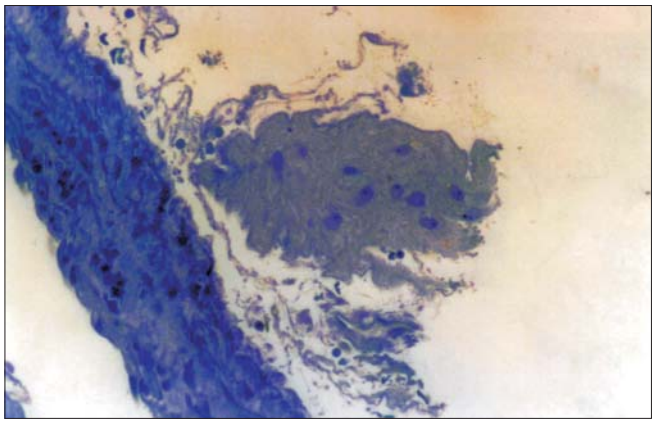

Figure 14. *Close opposition of thread-protective cells with abnormal proliferated neural tissue near the malformed vessel. Note positioning of thread-protective cells between vacular wall and abnormal cell group by multiple overlapping long cell processes.*

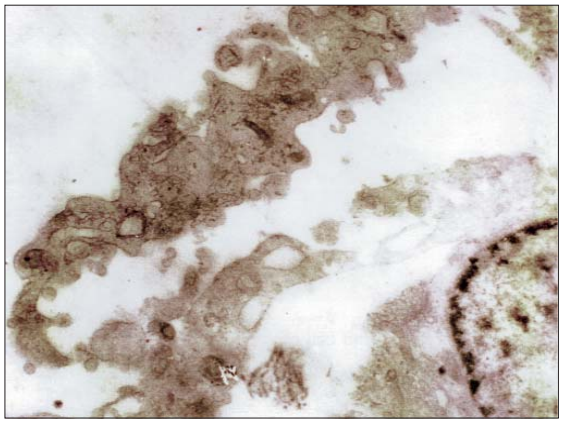

Figure 15. *Tinned cell end and, denser cell process of thread-protective cell around the degenerate cell*

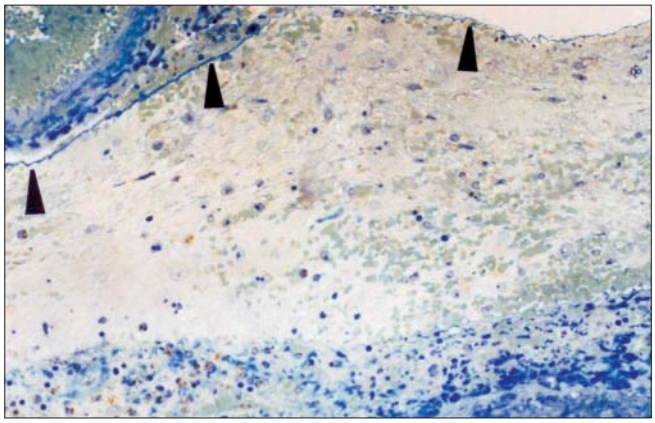

Figure 16. *Very long thread-protective cell processes surrounding neural tissue among the malformative vessels (arrowheads)*

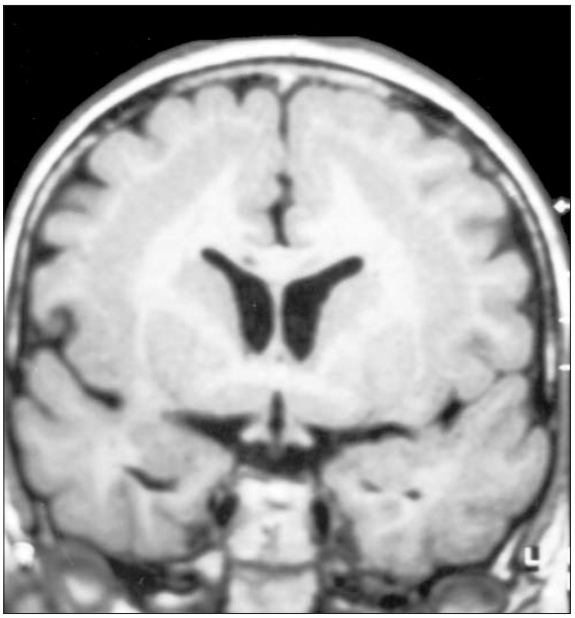

Figure 17. *Double cortex*

discovered. From the ectocortex to the deepest arachnoid exist a network of thread-protective cells who regulates numerous neuroprotective and vasculoprotective functions.

In this situation they limit cortical cell migration by the action of the chemoatactants they possess, they ensure support and protection for the cerebral cortex and prevent erythrocytes in subarachnoid hemorrhages from entering the nervous system.

When the chemoatactants of our cells are not numerous enough, subcortical cell heterotopias will occur, at the level of the corona radiate, which may generate epilepsy, double cortex *(Fig. 17)* and other neuronal migration disorders.

Nervous cells cannot accomplish their function if they find themselves in a place which is not appropriate for their physiological activity.

Therefore, the pia mater should be seen from a cyto-dynamic perspective.

In 2010 we have discovered that our cell migrates to the cortex.

On the other hand, cerebral neuroprotection is multiple, due to our intelligent and efficient defender.

Lately, we have researched whether our cells, like so many other cells in the nervous system, can or cannot develop tumors. Consequently, we have detected a few abnormal proliferations, described by famous histopathologists as unclassifiable or unseen before.

Consequently, step by step we have tried to fill in the description of the thread-protective cells from the histological, cytological, physiological, physiopathological, subclinical and clinical aspects. We have already brought some arguments upon the real role these cells play in vasculogenesis, preventing hemorrhages, inhibiting microtumor growth and limiting their expansion.

In the future, in order to outline the functions we have suggested, as well as others, it is necessary to approach the molecular mechanisms, biomarkers, proteins and the receptors of these thread cells. It is necessary to bring to light the engagement of these cells into activities of neuroprotection, neuroplasticity and neurorepair, as well as into fundamental processes of development of the central nervous system, such as corticogenesis and postnatal maintenance of pericortical ambient, the thread cell being as we speak the main cell responsible with controlling the neuronal migration.

Our warden-type cell may be especially stimulated in individuals with various cerebral lesions or degenerative diseases, in order to guide the neuroblasts from the periventricular and dentate gyrus areas towards the areas which need repair.

Although researchers have tried to investigate for years the precise role of the macrophage or of the macrophages subset in neurodegenerative diseases, we believe that our thread-protective cell is responsible for reducing the harmful, toxic deposits in the brain, which cause the Alzheimer and other degenerative diseases.

Under normal circumstances, the macrophages and their subset do not cross the hematoencephalic barrier. This action of self-defense can only be managed by the immune cells of the brain, not by the microglia, which is affected by pathological processes and neither by extracerebral macrophages. We believe that the cerebral immune system represented by the thread-protective cell plays a main role in enclosing and destroying damaged or old cells, by means of the signaling proteins and the chemokines which mediate this process.

In the future, the deposits which generate the Alzheimer disease could be reduced by stimulating the thread-protective cells.

It is highly moving to see how a thread-protective cell catches an erythrocyte extravasating from a vessel and keeping it symmetrically in the same place *(Fig. 18)*. Although it is blocked by collagen – the most resistive protein in our body – and by the thread cell pins, the erythrocyte still manages develop prolongations, trying to escape, fortunately in vain, due to the inhibiting pseudopodes of the thread cell, which can develop amazingly fast and position themselves in front of the erythrocyte.

The protective cell is neither a nervous nor a interstitial cell. Most likely it is a mesenchymal cell which belongs to the immune system. This fact is still to be clarified.

Discussions

The name of the cell discovered by Dănăilă and Păiş has varied along the years, function of the data we obtained, regarding its morphology and physiology. Consequently, with the 2006 Atlas, as well as at the Cape Town Congress (2006), this cell was disguised under the name of "interstitial cell of Cajal-like cells". In 2009, at the congress in San Diego, as well as with the 2008 atlas, it was named cerebral „interstitial cell". In 2011, at the congress in Los Angeles, it was communicated under the name of "interstitial Cajal-Like Cell".

On the interview of July 1st, 2011, given to the Romanian

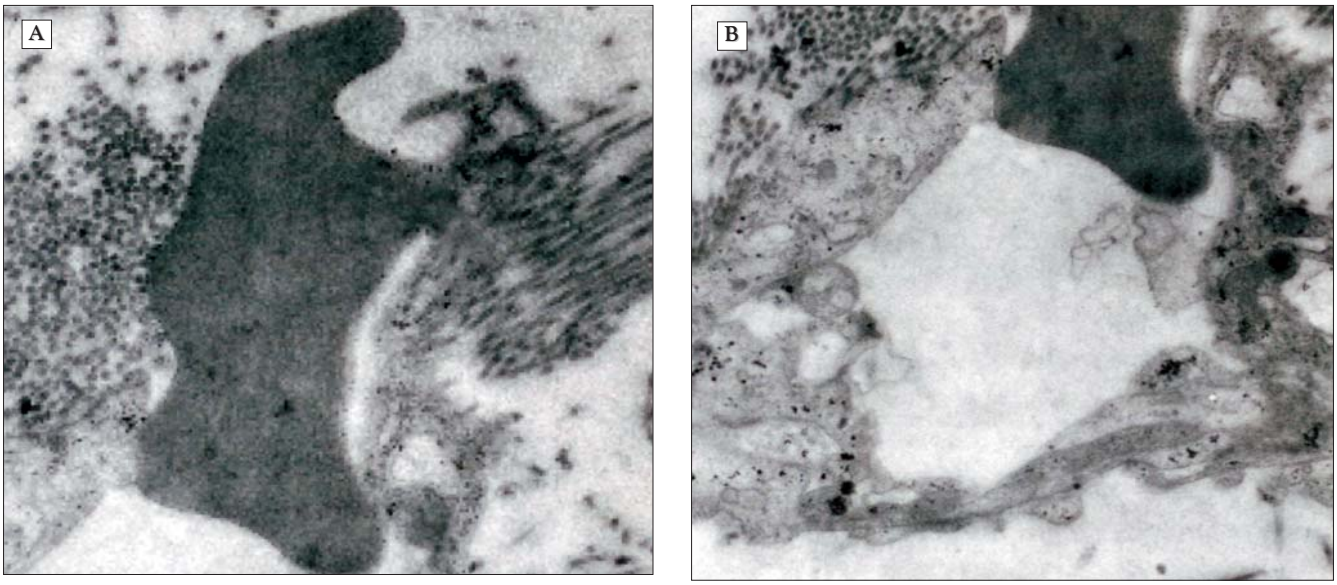

Figure 18. *These images (a and b) show thread-protective cell processes surrounding and isolated a red blood cell. The red blood cell tries to escape according to the cellular shape while predatory cell is able to develop a new thin process which cames in front of the victim cell. It is remarkable this attraction of the thread-protective cells for the red blood cells but remain to be decifred at molecular level, the mechanism involved*

newspaper "Medical Life", after closer analysis of the physiology and morphology of the cell in question, Dănăilă and Păiş have decided that was a new cytological entity, which we have called a "protectocit" – considering its functional features – and "cordocit" considering its morphological aspects. Taking into consideration both morphology as well as their main role – of protecting – we have given this cell its final name: "thread-protective cell" or "cordocit-protectocit cell".

The telocyte at the internal organs level (intestine, heart etc) is nothing else but the interstitial cell of Cajal (ICC), described by Cajal more than 100 year ago. These ICC spontaneously initiate rhythmic electrical activity, much like the pacemaker cells of the heart.

Thus, ICC has been described in digestive and extradigestive organs, and the name has been changed to telocytes, and their typical thin and long prolongations have been named telopodes.

Conclusions

The thread-protective cell was discovered by us in 1986, but the first publication was made in 2006. This cell can be found mostly around the vessels, in the pia mater and choroid plexus.

These cells are involved in certain morphogenetic events during the developmental of cortical plate.

In addition, we believe that exist a spatial and functional interrelationship between cortical vessels and cerebrum and cerebellum, rigorously regulated by means of the thread-protective cells.

Thread-protective cells are polifunctional cells that act for neuroprotection and vasoprotection through specific cellular mechanisms in a large variety of intracranial events such as immune surveillance, antimicrohemorrhage especially in hypertensive patients, anti-tumor growth, postnatal vasculogenesis, vasomotion, cell differentiation, and cell movements, etc.

Their role in guiding the neuroblast migration towards the cortex and in brain lesional processes is highly important.

In the future, by stimulating the multiplication of the thread-protective cells, the repairing, neuroprotective and anticancer features of the brain could be enhanced.

Regardless of who is being mentioned as lead author, our contribution in discovering the thread-protective cell (cordocit-proteocit) is as equal.

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