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Review Article

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The Sub-microscopic Pathology of Brain Extracellular Space in Some Neuropathological Conditions. A Review

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Abstract

The enlargement and content of perivascular and extracellular spaces in experimental and human material have been reviewed. The human edematous cerebral cortex associated to vascular anomaly, congenital hydrocephalus, brain trauma, and brain tumors were examined by transmission electron microscopy, using cortical biopsies of frontal, parietal, and temporal cortex. In congenital hydrocephalus, the pre-existing extracellular space that features immature cerebral cortex appears notably enlarged and occupied by electron transparent, non-proteinaceous interstitial edema fluid, due to the abnormal accumulation of non-circulating cerebrospinal fluid. In severe human brain trauma associated to subdural or estradural hematomas and brain tumors, the distended extracellular space contains either electron lucid non-proteinaceous edema fluid, and electron dense proteinaceous edema fluid, fibrinoid material, exosomes or extracellular vesicles, extracellular mitochondria, hemorrhagic foci, and non-nervous invading cells, such as phagocytic astrocytes, macrophages, microglia, and monocytes. In brain tumors, the widened extracellular space shows mainly electron dense proteinaceous edema fluid, and bundles of fibrinoid material and extracellular vesicles.

Keywords: Extracellular Space, Brain Pathology, Brain Edema, Electron Microscopy

Introduction

The submicroscopic pathology of brain extracellular space was earlier studied by Kvitnitskii-Ryzhov, Bondareff et al. and Arseni et al. [1-3]. Castejón reported the enlarged extracellular space in the edematous human cerebral cortex associated to vascular malformation, congenital hydrocephalus, brain trauma, and brain tumors [4-7]. The historical aspects of normal and abnormal brain fluids were earlier reviewed by Torack [8-10]. Subsequently, Hurter described the infiltration of serum proteins in peritumoralgray and white matter, and postulated a cellular uptake of extravasated proteins as a mechasnism of edema resolution. Kuroiwa et al. examined the correlation between the development of vasogenic brain edema and the extravasation of proteins into extracellular space in rabbit brain [11]. Oyanagy et al. studied the repairing process in destructive lesions in the pre-existing extracellular space during neurogenesis of developing rat brain, and found the presence of phagocytes eliminating degenerated cells present in the vast extracellular space [12]. The spread of vasogenic brain edema in hypertensive rat brain injury was examined by Kalimo et al. [13].

An immunocytochemical study of edema protein clearance by Ohata et al. was carried out in rat caudate nucleus infused with albumin for establishing the edema fluid and protein migration to the ventricular surface and the subarachnoid spaces [14]. The presence of electron dense material and active phagocytosis in the distended extracellular space was reported by Hata et al. in induced brain edema in cats [15]. Hattory et al. using horseradish peroxidase made a morphological estimation of brain extracellular fluid dynamics in cold-induced edema in rat parietal cortex, and postulated a retrogade transport by vessels as an important phenomenon for edema resolution [16]. A similar study for edemaresolution carried out by Naruse et al., using the infusion model, reported the rapid flow of extracellular fluid via the perivascular space in cat brain, and its important role in edema resolution [17]. Pierpaoli et al. made anhistopathological correlates of abnormal water diffusion in rat cerebral ischemia using diffusion weight magnetic resonance and electron microscopy [18]. Castejón reported by transmission electron microscopy the enlargement of extracellular space in hydrocephalic cerebral cortex in congenital hydrocephalus, Arnold-Chiari malformation, and postmeningitis hydrocephalus [5].

Cervós-Navarro et al. considered that the morphological evaluation of brain edema should be revised taking into account the van Harrevel´s studies to estimate the extension of extracellular space [19]. The spreading of brain edema in delayed time after rat brain irradiation was studied by Lafuente et al. using endogenous tracers [20]. The scavenging role of perivascular cells in the extracellular space was emphasized by Kida et al. in rat brain astrocytic tumors [21]. The rapid spreading of extravasated serum proteins in mature and immature rat brain was reported by Susuki et al. by means of endogenous tracers and immunohistochemistry [22]. Nielsen et al. studied the flow of water between glial cells and the cavities filled with cerebrospinal fluid (CFS), and the intravascular space of rat brain using immunocytochemistry and high resolution immunogold electron microscopy [23]. Perez-Pinzon et al. reported

the relation among calcium molecules from the extracellular space, mitochondrial hyperoxidation, and electrical recovery after anoxia in rat brain hyppocampal slices [24].

More recently, the immunohistochemical characteristic of perivascular space in advance edema was described by Nishi et al. in rat brain [25]. Hrabetova et al. found that the dead space microdomains hinder extracellular diffusion in rat neocortex during ischemia [26]. Saeki et al. (2004) studied the histological characteristics of perivascular spaces in peritumoraledema by tumors of pituitary region [27]. Abbott reviewed the evidences for the bulk flow of brain interstitial fluid, and the significance for physiology and pathology [28]. Papadopouslos et al. reported slow diffusion in brain extracelular space in cytotoxic edema due to anoxia, and enhanced diffusion in mouse models of vasogenic brain edema [29]. Castejón et al. described the inflammatory reaction, and organized proteinaceousedema fluid in the enlarged extracellular space of traumatic edematous cerebral cortex [30, 31]. Lately, aquaporin channels have been involved in water accumulation in brain edema [32, 33].

Emerging evidence indicates that extracellular vesicles (EVs) including endosome-derived exosomes and fragments of the cellular plasma membrane play a key role in intercellular communication by transporting messenger RNA, microRNA (miRNA) and proteins. In neurodegenerative diseases, secreted vesicles not only remove misfolded proteins, but also transfer aggregated proteins and prions and are thus thought to perpetuate diseases by 'infecting' neighboring cells with these pathogenic proteins. These extracellular vesicles could be used as carriers to specifically target the CNS to deliver immune modulatory drugs, neuroprotective agents and anti-cancer drugs [34].

The discovery that most cells produce extracellular vesicles (EVs) and release them in the extracellular milieu has spurred the idea that these membranous cargoes spread pathogenic mechanisms. In the brain, EVs may have multifold and important physiological functions, from deregulating synaptic activity to promoting demyelination to changes in microglial activity. The finding that small EVs (exosomes) contain α-synuclein and β-amyloid, among other pathogenic proteins, is an example of this notion, underscoring their potential role in the brains of patients with Parkinson's and Alzheimer's diseases [35].

Balusu et al. have identified the release of extracellular vesicles (EVs) by the choroid plexus epithelium (CPE) as a new mechanism of blood-brain communication [36]. These choroid plexus-derived EVs can enter the brain parenchyma and are taken up by astrocytes and microglia, inducing miRNA target repression and inflammatory gene up-regulation.

Matsumoto et al. postulate that extracellular vesicles (EVs) may play a vital role in the transport of toxic α-syn between brain regions in Parkinson disease (PD) [37]. Moreover, increasing evidence has highlighted the participation of peripheral molecules, particularly inflammatory species, which may influence or exacerbate the development of PD-related changes to the central nervous system. This transport likely occurs via adsorptive-mediated transcytosis, with EVs that transit the BBB co-localizing with brain microglia. Examination of microglial reactivity upon exposure to α-syn-containing erythrocyte EVs in vitro and in vivo revealed that uptake provoked an increase in microglial inflammatory responses.

Fibrillar inclusions of intraneuronalα-synuclein observed in Parkinson disease have been detected both within and on the outside of exosomes and other extracellular vesicles (EVs), suggesting that such structures may mediate toxic α-synuclein propagation between neurons. Vesicular transfer of α-synuclein may thereby contribute to the hierarchical spreading of pathology seen in the PD brain [38]. EVs are released by almost all cell types and carry a cargo of protein and nucleic acid that varies according to the cell of origin. EV output changes with cell status and reflects intracellular events, so surface marker expression can be used to identify the cell type from which EVs originate. EVs could, therefore, provide an enriched pool of information about core neuropathogenic, cell-specific processes [39].

A dysfunctional endosomal pathway and abnormally enlarged early endosomes in neurons are an early characteristic of Down syndrome (DS) and Alzheimer's disease (AD). Gauthier et al. have hypothesized that endosomal material can be released by endosomalmultivesicular bodies (MVBs) into the extracellular space via exosomes to relieve neurons of accumulated endosomal contents when endosomal pathway function is compromised [40]. Guix et al. demonstrate the presence of minute amounts of free-floating and exosome-contained full length tau (FL) in human biofluids.

Mitochondria and mitochondrial debris are found in the brain's extracellular space, and extracellular mitochondrial components can act as damage associated molecular pattern (DAMP) molecules. Brain extracellular mitochondria and its components can induce neuroinflammation, Extracellular mtDNA or mtDNA-associated proteins can contribute to this effect [41].

Gray matter astrocytes tightly enwrap synapses, contact blood vessels and, naturally, are also in contact with the extracellular space, where convection of fluid takes place. Thus astrocytes receive signals from several distinct extracellular domains and can get excited by numerous mechanisms, which regulate cytosolic concentration of second messengers, such as Ca^{2+} and cAMP. Excited astrocytes often secrete diverse substances (generally referred to as gliosignalling molecules) that include classical neurotransmitters such as glutamate and ATP or neuromodulators such as D-serine or neuropeptides. Astrocytic secretion occurs through several mechanisms: by diffusion through membrane channels, by translocation via plasmalemmal transporters or by vesicular exocytosis [42].

The role of extracellular matrix compositionin central nervous system pathology

Johnson et al. hypothesized that the components of the extracellular matrix (ECM), which are known to vary during development and in response to disease, determine astrocytic responses to injury and inflammation [43]. According to Miyata and Kitagawa, the extracellular matrix (ECM) of the brain is rich in glycosaminoglycans, such as chondroitin sulfate (CS) and hyaluronan [44]. These glycosaminoglycans are organized into either diffuse or condensed ECM. Diffuse ECM is distributed throughout the brain and fills perisynaptic spaces, whereas condensed ECM selectively surrounds parvalbumin-expressing inhibitory neurons (PV cells) in mesh-like structures called perineuronal nets (PNNs). The brain ECM acts as a non-specific physical barrier that modulates neural plasticity and axon regeneration. These Authors point out that the brain ECM not only forms physical barriers that modulate neural plasticity and axon

regeneration, but also forms molecular brakes that actively controls maturation of PV cells and synapse plasticity in which sulfation patterns of CS chains play a key role. Structural remodeling of the brain ECM modulates neural function during development and pathogenesis.

Reinhard et al. point out that extracellular matrix (ECM) molecules and their complementary receptors influence the behavior of neural stem cells and cancer stem cells as well as brain tumor progression [45]. These Authors focus on the expression profile and functional importance of the ECM glycoprotein tenascin-C, the chondroitin sulfate proteoglycan DSD-1-PG/phosphacan, but also on other important glycoprotein/proteoglycan constituents.

De Luca and Papa consider thatneural extracellular matrix (nECM), is paramount for the maintenance of a healthy network [46]. The loosening or the damage of the scaffold disrupts synaptic transmission with the consequent imbalance of the neurotransmitters, reactive cells invasion, astrocytosis, new matrix deposition, digestion of the previous structure and ultimately, maladaptive plasticity with the loss of neuronal viability Arba et al. recently show that in patients with ischemic cerebral events, enlarged perivascular spaces are cross-sectionally associated with age, hypertension, and white matter hyperintensities, and suggest that enlarged perivascular spaces in the basal ganglia are associated with cognitive impairment after one year [47].

The present review describes by means of conventional transmission electron microscopy the ultrastructural features, extension and content of human brain cortex perivascular and extracellular spaces in patients with vascular anomalies, congenital hydrocephalus, brain trauma, and brain tumors of patients systematically studied by more than four decades in our laboratories.

The extracellular space in an apparently normal neuropil observed in apatient with a vascular anomaly

The following findings are observed in these patients [4,6,7,30,31]. In samples of vascular anomalies, in which a moderate edema is found, the structural components of cerebral cortex neuropil show the closely applied axonal, dendritic, and glial cell processes, being separated by the membrane to membrane extracellular space, of about 20 nm in width, resembling the extracellular space classically observed by transmission electron microscopy in normal experimental animals (Figure 1).

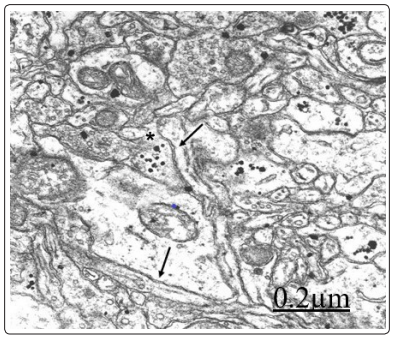

Figure 1: Anomaly of anterior cerebral artery. Right parietal cortex showing a moderate cerebral edema. Neuropil showing the apparently "normal" extracellular space formed by the membrane to membrane space of about 20 nm in width (arrows). The asterisk labels the scareextension of the extracellular space at the meeting point of several nerve cell processes

The extracellular space in congenital hydrocephalus

Cortical biopsies taken frominfant patients with congenital hydrocephalus,1 to 7 months old, corresponding to the postnatal cerebral cortex development, in which the preexisting dilated extracellular space appear further enlarged due to the presence of hydrocephalic or interstitial edema induced by the non-circulating cerebrospinal fluid (Figure 2) [5].

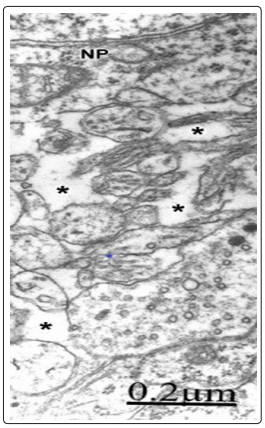

Figure 2: Arnold Chiari malformation and hydrocephalus. Left parietal cortex. Hydrocephalic interstitial edema. Swollen neuropil of right parietal cortex in the vicinity of an edematous non-pyramidal neuron (NP) exhibiting distended extracellular space (asterisks) separating the neighboring nerve cell processes. This extracellular space contains the non-circulating and electron transparent cerebrospinal fluid.

The hydrocephalic edema is mainly non-proteinaceous, and correspond to circulating or accumulated cerebrospinal fluid. Susuki et al. reported a rapid spreading and clearance of extravasated serum proteins in the immature brain [22]. There is evidence shown by Abbott of bulk flow of brain interstitial fluid along preferential pathways, specially perivascular space and axon tracts [28].

The extracellular space in traumatic brain injuries

In areas of moderate and severe traumatic brainedema,the perivascular space appear occupied by either proteinaceous or non-proteinaceousedema fluid (Figure 3).

Figure 3: Brain Trauma. Left parietal cortex. Perivascular hemorrhage. Three erithrocytes (E) are observed surrounding the capillary wall and immersed in proteinaceousedema fluid (EF)

occupying the large perivascular space. The peripheral endothelial cell (PE) show invaginations of the luminal membrane (arrows) and pinocytotic vesicles (arroheads). Note the swollen basement membrane (BM).

The perivascular region of severe and complicated brain injuries show enlarged extracellular spaces separating fragmented astrocytic perivascular end-feet attached or dissociated from the capillary basement membrane, degenerated myelinated axons, and dendritic processes (Figure 4).

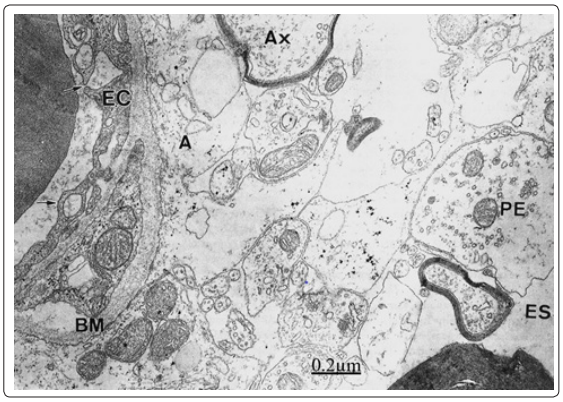

Figure 4: Brain trauma. Subdural hematoma.Electron micrograph of right parietal cortex showing the transcytosis process originating the vasogenicedema and the formation of large perivascular spaces (ES). The endothelial cell (EC) shows vacuolar transport (arrows). The basement membrane appears swollen and enclosing the edematouspericyte.The notably swollen perivascularastrocytic end foot (A) shows vacuolization.The pervascularneuropileexhibits swollen and degenerated presynaptic ending (PE), and degenerated myelinated axons.

In human brain trauma associated withsubdural hematoma the extracellular space appears occupied by proteinaceousedema fluid, extra mitochondrial profiles, exosomes,and invasive macrophages, monocytes and microglial cells, that feature the inflammatory reactions (Figure 5).

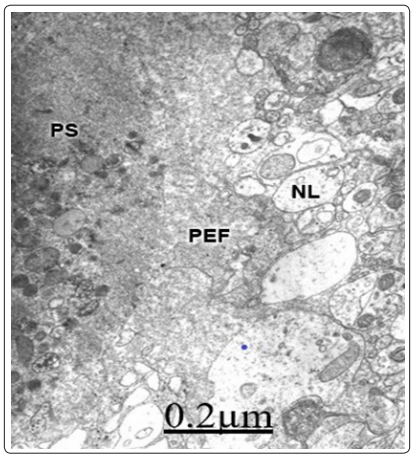

Figure 5: Brain trauma and right epidural hematoma. Severe edema. Perivascular space (PS) of right temporal cortex showing hematogenous and electron dense edema fluid (PEF) containing extravasated serum proteins, separated profiles of swollen astrocytes, exosomes or extracellular vesicles at the disrupted neighboringneuropil (NL).

Monocytes, microglial cells and phagocytic astrocytes are observed engulfing the proteinaceousedema fluid and the fibrinous dense material deposited in the enlarged extracellular space (Figure 6) [30].

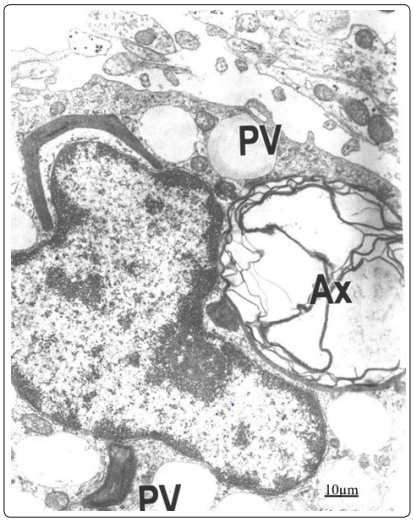

Figure 6: Brain trauma. Extradural hematoma. Right parietal cortex. Invasive monocyte located in the extracellular space of a disrupted neuropilecontaining an engulfed myelinated axon (AX) and several phagocytic vacuoles (PV).

Oyanagy et al. early reported the presence of phagocytes eliminating degenerated cells present in the vast extracellular space [12]. Hata et al. and Castejon also reported active phagocytosis of dense material in the macrophages in cat experimentally induced edema [15,30]. According to Hata el al. the water clearance of vasogenic brain edema does not commence until proteinaceous macromolecules are degraded and removed from the extracellular space [15].

In severe traumatic edematous areas, the edematousnon-proteinaceousedema fluid dissects the nerve cell processes disrupting the neuropil, separating the perisynaptic glial ensheathment, and inducing synaptic disassembly (Figure 7).

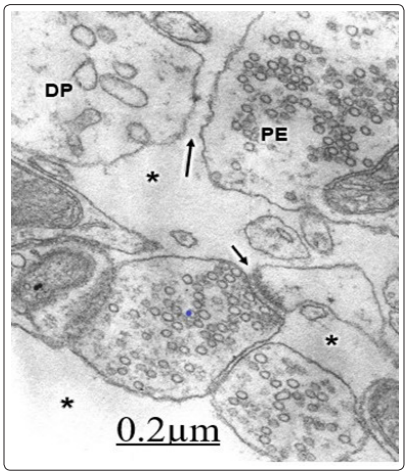

Figure 7: Brain trauma and subdural hematoma. Right temporal cortex. Severe edema. Neuropil showing the notably enlarged and electron lucent extracellular space (asterisks) containing non-proteinaceousedema fluid. The long arrow indicates the synaptic disassembly induced by the severe edema. The short arrow labels an axodendritic contact devoid of perisynaptic glial ensheathment.

Cervós-Navarro et al. studying the morphology of non-vascular intracerebral fluid spaces, compared the data obtained from cryofixed normal rat brain with irradiation edema reporting greater variance in the extension of extracellular space [19]. Lafuente et al. also studied the spreading of brain edema in a delayed time after edematous lesion induced by ultraviolet irradiation Specialized membrane domains for water transport in glial cells equipped with aquaporin water channels mediate the flow of water between glial cells and the cavities filled with cerebrospinal fluid and the intravascular space [20, 23, 48-51]. Immunohistochemical study of perivascular space by Nishi et al. identified a large variety of plasma proteins, such as amyloid P component, Ig G, albumin, apolipopoteina E, lactotransferrin, and also cellular proteins, such as ubiquitin, Tau protein, glial fibrillary acidic protein, myelin basic protein, and heparansulfate proteoglycan [25].

Organized fibrinous material embedded into the proteinaceousedema fluid is observed in human severe brain trauma with associated subdural hematoma (Figure 8).

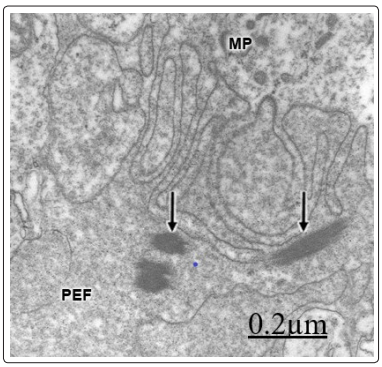

Figure 8: Brain trauma and right epidural hematoma. Neuropil of right parietal cortex showing a large lake of proteinaceousedema fluid (PEF) separating degenerated nerve cell processes, and containing deposits of fibrinoid material (arrows). The peripheral cytoplasm of a macrophage (MP) is observed phagocyting the proteinaceousedema fluid.

The extracellular space in brain tumors

The extracellular space surrounding malignant tumors, ascystic craniopharingioma and glioblastomamultiforme, containts frequently an accumulation of bundles of fibrinoid material (Figure 9).

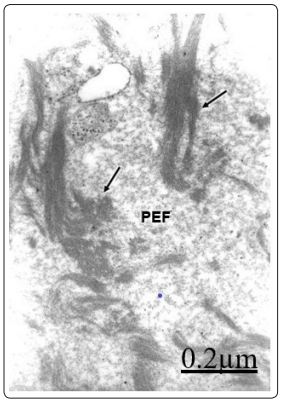

Figure 9: Cystic craniopharingioma . Right temporal cortex. Severe edema. Peritumoral edema showing abundant fibrinoid material (arrows) organized in the proteinaceous edema fluid (PEF). An extracellular vesicle also is seen.

The accumulation of a fibrin-like substance in the extravascular space, and the infiltration of inflammatory cells were described by Shibata et al. in human brain following delayed cerebral radonecrosis [52]. Similar findings were earlier reported by Susuki et al. in experimental brain tumors using exogenous tracers, and immunohystochemical localization of endogenous serum proteins [22]. Kida et al. emphasized the significance of perivascular spaces in astrocytictumors as the anatomical route for edema fluid drainage, and the scavenging role of invading perivascular cells [21]. Lately, Saeki et al. elegantly studied the peritumoraledema in tumors of pituitary region [27].

According to André-Grégoire and Gavard every cell can release EVs, glioblastoma and cancer cells co-opted this feature and efficiently unleashed them both in the tumor microenvironment and toward healthy tissues [53]. This might contribute to tumor aggressiveness and spreading. Cancer-derived EVs that contain DNA, mRNA, miRNA, and packed and transmembrane proteins can operate locally or at distance [54-58].

Conclusion

The enlargement and content of perivascular and extracellular spaces in experimental and human material have been reviewed. The human edematous cerebral cortex associated to vascular anomaly, congenital hydrocephalus, brain trauma, and brain tumors were examined by transmission electron microscopy, using cortical biopsies of frontal, parietal, and temporal cortex. In congenital hydrocephalus, the pre-existing extracellular space that features immature cerebral cortex appears notably enlarged and occupied by electron transparent, non-proteinaceous interstitial edema fluid, due to the abnormal accumulation of non-circulating cerebrospinal fluid. In severe human brain trauma associated to subdural or estradural hematomas and brain tumors, the distended extracellular space contains either electron lucid non-proteinaceous edema fluid, and electron dense proteinaceous edema fluid, fibrinoid material,exosomes or extracellular vesicles,extracellular mitochondria, hemorrhagic foci, and non-nervous invading cells, such as phagocytic astrocytes, macrophages, microglia, and monocytes. In brain tumors, the widened extracellular space shows mainly electron dense proteinaceous edema fluid, and bundles of fibrinoid material and extracellular vesicles.

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