УДК 616-092

A.A. Akanova[1], V.B. Khabizhanova[2], S.T. Zhumabekova[2], M.M. Saparbayeva[2], A.K. Yeshmanova[2], K.K. Akanova[2]
[1]Kazakh Medical University of Continuing Education
[2]Asfendiyarov Kazakh National Medical University
The department of general medicine №1 with gerontology module

THE ROLE OF MICROGLIA AND TRANSFORMING GROWTH FACTOR-B1 IN ALZHEIMER'S DISEASE (REVIEW)

Recent advances in cell imaging have provided novel insight into microglial physiology in the brain. Microglia plays important roles in the healthy brain such as it is involved in synaptic stripping during the development or experience-dependent sensory modulation, on the other hand, it is the first to respond to acute brain injury or chronic neurodegenerative diseases so it can be neuroprotective and neurotoxic depending on the context, thus, microglia represents a double-edged sword. Interestingly, an increasing amount of data suggests that neuroinflammation and microglia may represent very important participants in the development of Alzheimer's disease. Therefore, this review will describe microglial-neuronal complicated relationships under physiological and pathological conditions; furthermore, participation of microglia directly in synaptic stripping under pathological conditions, neuronal loss and synaptic stripping in the animal model of AD and finally it will be discussed that microglial derived immune cytokine such as$Tgf-\beta1$ and it main signaling cascade SMAD2/3 being not only novel players in AD pathology but also they may represent future therapeutic target for AD treatment.
Keywords: *Alzheimer's Disease, microglia, neuroinflammation, $Tgf-\beta1$, SMAD2/3 cascade*

Introduction. Alzheimer's disease is an age-associated neurodegenerative disease that is defined by extracellular amyloid deposits composed of αβ peptide and intracellular tangles composed of hyper-phosphorylated tau protein. Recent studies show that inflammation plays important role in the AD development. Microglia is myeloid-derived resident in the central nervous system that comprises 10-20 % of the non-neuronal cell population. By morphological heterogeneity,microglia is classified into quiescent/surveying, reactive/activated and amoeboid/phagocytic [26]. Microglia servethe first to respond to acute brain injury or slowly progressing neurodegenerative diseases such as AD [2]. Under pathologic conditions microglia undergoes transformation from resting to phagocytic and becomes activated in a process known as microglial priming [5]. The priming is strictly regulated and triggered by the presence of stimuli such as accumulation ofcellular debris or/and of aberrant proteins. Activated microglia produces various soluble pro- and anti-inflammatory cytokines, free radicals, proteases which has effects such as preventing infection/inflammation spread, rapid clearance of apoptotic debris at the lesion site or aberrant protein accumulations and creation of permissive environment for repair but on the other hand this may promotes neurotoxicity [16].

Microglia may represent a part of "quad"-partite synapse by modulating LTP [25] as well as GABA-ergic synaptic transmission [26]and participating of restructuring of neuronal circuits and synaptic tuning, process known as synaptic stripping, in a sensory experience dependent manner [30]. Many in-vitro studies show that microglia express a variety of variety of receptors for neurotransmitters, neuropeptides,chemokines, cytokines which in turn allows it easily acquire the priming state. Many studies show that constantly primed pro-inflammatory microglia is neurotoxic and have detrimental effects on the nervous system homeostasis and proper functioning, thus, microglia represents a double-edged sword whose activity is much context-dependent.

Recent studies show that resting microglia monitors the CNS homeostasis by making brief physical contacts and it can rapidly change its phenotype from ramified/activated/phagocytic [8]. Furthermore, two-photon in-vivo imaging and immuno-EM of double transgenic mice IBA1-EGFP-THY-1 GFP where both microglia and neurons were visualized simultaneously showed that resting microglia contacts neurons by direct physical contact in a neuronal activity dependent manner not only in healthy brain but also under ischemic conditions, so that prolonged microglia/neuronal contactswere shown to be associated with a reductions of number of spines by synaptic phagocytosis [33] (Wake et al., 2009), however, it should be noted that there was no direct evidence that the prolonged contacts triggered phagocytosis despite that the authors used relatively non-invasive laser-induced ischemia it cannot be excluded that microglia, being very reactive cells, was not already primed by anesthesia, cranial thinning as well as laser-induced phototoxicity. The other limitation is that it was the double –transgenic animal which in turn must affect others cells, so that the imaging might involve other cells such as astrocytes regardless that specific promoters to the microglia and thalamic/cortical neurons were used. Nevertheless, it was shown in-vivo under appropriate resolution and that microglia promotes synaptic stripping very rapidly under pathological conditions thereby providing promising directions in the study of microglia-neuron relationships so that understanding what cellular mechanism triggers/promotes such fast stripping may help to develop pharmacological drugs that would alleviate synaptic stripping under pathological conditions thereby partially solving cognitive problems resulting from neuronal disconnection.

Inflammation and Alzheimer's disease.

Alzheimer Disease (AD) is an age-associated neurodegenerative disease characterized by progressive loss of neurons leading to cognitive disturbances in patients. Pathophysiologically, the disease is defined by cerebral amyloid deposits composed of 40-42 amino-acid peptide (aβ) and intracellular neurofibrillary tangles (NFT) comprised of hyperphosphorylated tau protein. It is believed that aberrant Amyloid Precursor Protein (APP) cleavage may lead to toxic aβ accumulation thereby leading to aβ oligomerization and plaques generation. A few retrospective epidemiological studies indicated than non-steroidal anti-inflammatory drugs application reduced the risk of AD suggesting that inflammation plays a role in AD [17]. Furthermore, starting from 1990's it has been proposed that it is the immune response to aberrant protein accumulation leads to AD development [4]. For example, it was shown that detectable microglial activation in tau overexpressing mice takes place long before NFT manifestation and synapse loss; moreover, immune suppression not only increased lifespan but also attenuated tau pathology [35]. Many in-vitro and in-vivo studies show that C-terminal of APP/ tau overexpression induce inflammation and immune response [3], but it should be noted that most of the studies explore primed microglial activity under pro-

inflammatory systemic conditions induced by pathogens such as LPS injections, so whether aβ or tau can prime resting microglia directly warrants further investigation. On the other hand, Wallerian degeneration, may prime microglia and provoke a classical pro-inflammatory profile [24] thus it may be said aβ and tau trigger microglia activation indirectly participating in neuronal degeneration and indeed increase in inflammation-associated cytokines proteins is an invariant feature of AD compared with normal brain. This essay will particularly focus ontransforming growth factor-β($Tgf-\beta1$) a multifunctional and a very contradictory cytokine strikingly increased in AD patients, for instance, immunofluorescent, in-vitro and MRI studies showed that $TGF-\beta1$ levels are increased in the frontal cortex, cerebrospinal fluid as well as along blood vessels, plaques, astrocytes, neurons and microglia of AD patients compared to age-matched healthy controls [31] so the exact role of $TGF-\beta1$ warrants further investigation. Interestingly, in contradiction to $Tgf-\beta1$ anti-inflammatory roles, some studies reported that $TGF-\beta1$ overexpression promote cerebral angiopathy very similar to AD at the very early stage of life [29]. Moreover, enzyme-like immunosorbent assay showed that incubation with TGF-B1 promoted expression of pro-inflammatory cytokines by brain endothelial cells [1, 32] as well as pharmacological $Tgf-\beta1$/SMAD2-3 blocking mitigated $\alpha\beta$ depositions and improved $\alpha\beta$ phagocytosis in APP overexpressing mouse [18,29,34] though $TGF-\beta1$ promotes APP upregulation via SMAD-3 binding to APP promoter [31](rev. in Ueberham et al., 2006), moreover, it seems that $Tgf-\beta1$ and $\alpha\beta$ interact with each other and may even have synergistic effects in AD pathology. So, for instance, $Tgf-\beta1$ overexpressing mice developed almost double amount of $\alpha\beta$ deposits compared to control animals [15, 25]. Moreover, as $Tgf-\beta1$ upregulates extracellular matrix proteins, it may impair $\alpha\beta$ proteolytic degradation thereby promoting $\alpha\beta$ accumulation [12]. Although recent data suggest that AD hallmarks such as $\alpha\beta$ and NFT interfere with $Tgf-\beta1$ signaling, so for example, immunofluorescent studies showed that aberrant pSMAD2-3 cellular localization such as cytoplasmic pSMAD2-3 bound to NFT [7] or nuclear overaccumulation of pSMAD2-3 [31]. Chronic overexpression of $Tgf-\beta1$ promotes NFT accumulation and leads to microvascular degeneration in mice through ectopic pSMAD2-3 accumulations [18]. On the other hand, in-vitro transwell assays, pharmacological, RT-PCR and biochemical studies show that $Tgf-\beta1$/SMADs not only promote immediate $\alpha\beta$ uptake by microglia (Huang et al., 2010) but also promote upregulation of scavenger receptors on its surface as well as reduce production of microglial cytotoxic NO^{-}[28]; furthermore, $Tgf-\beta1$/SMAD2-3 being critical for $\alpha\beta$ induced microglial transformation from quiescent to phagocytic state [1] where blocking $Tgf-\beta1$ signaling in rat hippocampal slices amplifies significantly $\alpha\beta$ induced neurotoxicity [6,34] whereas pre-treatment by $Tgf-\beta1$ increases neuronal resistance to $\alpha\beta$-mediated cytotoxicity [18].

AD, microglia and microglial-derived $Tgf-\beta1$.

Recent paper by Fuhrmann and colleagues provided direct evidence that microglia is involved in neuronal loss and synaptic stripping in mice overexpressing both APP and tau [17], by means of two photon in-vivo imaging microscopy individual microglial cells and neurons were visualized simultaneously and were monitored for 28 days in the living animal. It was shown that microglia directly contacts neurons; moreover, based on microglial density and velocity of movement around neurons it was suggested that microglia participates directly in synaptic stripping and neuronal death at least in the animal modelof AD [17]. However, it should be noted that it is not clear whether microglia induced neuronal death or was clearing cellular debris of dying/dead neurons due to aberrant overexpression of tau/APP, although KO of microglial receptor CX3CR1 (key receptor for microglial chemotaxis towards injured neurons) rescued neurons suggesting activated and cytotoxic microglia drives neuronal death directly. One of the limitations is that it should be noted that it is a 5xTg mice which in turn must have alternated the cellular phenotype so neurons might already be dying and microglia overactivated due to expression of proteins not only far from physiological levels but also in their aberrant form; laser photoxicityand cranial thinning. Furthermore, it should be noted that as the GFP/YFP could also be expressed in other cells such as astrocytes though the authors used cells specific promoter. Furthermore, although CX3CR1 KO rescued neurons there were no direct evidence that microglia induce neuronal death it might be that dying neurons due to many pathologic process promote immune cytotoxic response. Nevertheless, this paper provided in-vivo evidence under good resolution that microglia is involved in neuronal and synaptic loss as well as it provided evidence that CX3CR1 signaling cascade plays an important in the animal model of AD.

$TGF-\beta1$is a pleiotropic cytokine, primarily produced by microglial at the very early stages of inflammation, that is involved in cell proliferation/ differentiation and apoptosis [20]. $TGF-\beta$ KO mice die at 3-4 weeks postnatally from severe neuroinflammation; moreover, in-vitro cultured primary neurons deprived of $TGF-\beta$ signaling had reduced survival; some studies show that $TGF-\beta$ overexpression protects from neurons fromacute and chronic cytotoxicity. For instance,in-vitro microarray, pharmacological and immunocytochemical studies showed $Tgf-\beta1$ inhibited primed microglial reactivity by inhibiting microglial proliferation [3,19] bydownregulating of pro-inflammatorycytokines [10], free radicals and upregulating of not only anti-inflammatory molecules [14, 22, 23]regulating microglial quiescence [4, 27] but also those involved in chemotaxis and even LTP [25]. In contrast, some studies report contradictory data, so for example, $TGF-\beta$overexpression was reported to be pro-inflammatory and exacerbatingexcitotoxicity in newborn mice [21]; moreover, mice overexpressing $TGF-\beta$ were often hydrocephalic [34]; in-vitro studies show that $TGF-\beta$ treatment promotes neuronal cell death and induce and microgliosis[3].

TGF **$-\beta1$- SMAD2-3 signaling cascade.**

The biological effects of TGF-Bs are exerted through $TGF-\beta$ type I and type II receptors that belong to the family of serine-threonine kinases. Upon ligand binding, type II phosphorylates type I followedby phosphorylation of SMAD proteins [20]. Phosphorylated SMAD (pSMAD) form oligomers composed of SMAD2 and SMAD3/SMAD4 and translocate to the nucleus where they directly bind to promoter sequence via specific SMAD binding element with following gene expression [20] such as cell migratory genes , for example, CX3-CR1 [1,23].Recent in-vitro RT-PCR, immunocytochemical, genetic interference a ndstudy of brain microglial and primary microglial cell cultures by De- Simone and colleagues showed that $Tgf-\beta1$ promotes microglial chemotaxis through purinergic receptors such as P2Y1 and P2y12 as well as upregulates proteins such as Arg-1 that promote microglial quiescent and thus neuroprotective state. This study showed that $Tgf-\beta1$ is a negative regulator of microglial activation but it promotes chemotaxis and increase migratory response of resting microglia[9].However, it should be noted that ADP concentrations used in-vitro were far from physiological range but several two-photon in-vivo imaging studies proved that ADP/PY12 represent microglial chemotactic signaling pathway under resting conditions [8,13]. Furthermore, primary cultures should be considered in caution as there might be another cell types such as

astrocytes which may also control microglial physiology that were also affected on by ADP as well as microglia present there might possess different morphological states; moreover, under experimental conditions microglia may have altered phenotype. Nevertheless, this study showed that $Tgf-\beta1$ directly involved in microglial chemotaxis towards injured neurons, promotion of its own expression and microglial motility genes upregulation.

Conclusion.

Therefore, as the data above suggest loss of $Tgf-\beta1$-SMAD signaling cascade might represent important stage in ADdevelopment by overactivation of resting microglia. Nevertheless, it is not clear whether aberrant SMAD localization emanates from AD-associated abnormal protein aggregation or$Tgf-\beta1$ –SMAD promoting "permissive environment" for AD development by promoting microglial chemotaxis and toxicity in the inflamed brain. It is clear that activated microglia represent immune response to overcome aberrant protein accumulations however it is not clear whether microglial response drives cellular death or there are agents/factors, such as age, pathological conditions that oversensitize microgliathereby leading to neurodegeneration. To summarize, this review described microglial function in adult healthy and AD brains; moreover, it described one of the central chemokines such as$Tgf-\beta1$ that clearly plays a role in AD by modulating microglial state, furthermore, this essay discussed papers by Wake and colleague that showed that microglia directly involved in synaptic stripping in healthy and ischemic conditions in-vivo [33]; by Furhmann and colleagues that showed that microglia involved in neuronal and synaptic loss in the animal model of AD and KO of microglial receptors resulted in neuronal rescue in vivo [11] and paper by De-Simone and colleagues that showed that $Tgf-\beta1$ promotes microglial chemotaxis towards injured in neurons [9]. Altogether, they provide some consistent evidence that microglia and $Tgf-\beta1$ /SMAD signaling may represent a potential target in AD treatment, so for example, modulation of immune response in AD might help alleviate the problem of cognitive disturbance by modulating the process of neuronal death and synaptic stripping and thus preserving neuronal connectivity.

REFERENCES

1 Abitbul S, Shapiro J, Szaingurten-Solodkin I, Levy N, Carmy Y, Baron R, Jung S and Monsonego A. TGF-β Signaling Through SMAD2/3 Induces the Quiescent Microglial Phenotype Within the CNS Environment // GLIA. – 2012. - Vol. 60. - P.1160-1171.

2 Blank T and Prinz M. Microglia as Modulaotrs of Cognition and Neuropsychiatric Disorders // GLIA. - 2013. - Vol. 61. - P. 62-70.

3 Boche D, Cunningham C, Docagne F, Scott and Perry VH . TGFβ1 regulates the inflammatory response during chronic neurodegeneration // Neurobiol Dis. -2006. - Vol. 22. - P.638-650.

4 Brionne TC, Tesseur I, Masliah E and Wyss-Coray T. Loss of TGF-β1 Leads to Increased Neuronal Cell Death and Microgliosis in Mouse Brain // Neuron. - 2003. - Vol. 40. - P.1133-1145.

5 Cunningham C. Microglia and Neurodegeneration: The Role of Systemic Inflammation // GLIA. – 2013. - Vol.61. - P.71-90.

6 Caraci F, Battaglia G, Busceti C, Biagioni F, Mastroiacovo F, Bosco P, Drago F, Nicoletti F, Sortino MA and Copani A. TGF-β1 protects against Aβ neurotoxicity via the phosphatidylinositol-3-kinase pathway // Neurobiol Dis. – 2008. - Vol. 30. -P. 234-242.

7 Chalmers KA and Love S.Phosphorylated Smad2/3 Colocalizes With Phospho-tau Inclusions in Pick Diseases, Progressive Supranuclear Palsy, and Corticobasal Degeneration but Not With α-Synuclein Inclusions in Multiple System Atrophy or Dementia With Lewy Bodies // J NeuropatholExp Neurol. – 2007. - Vol. 66., №11. - P.1019-1026.

8 Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB ATP mediates rapid microglial response to local brain injury in vivo // Nat Neurosci.-2005. - Vol. 8., №6. - P.752-758.

9 De Simone R, Niturad CE, De Nuccio C, Ajmone-Cat MA, VisentinS and Minghetti L . TGF-β and LPS modulate ADP-induced migration of microglial cells through P2Y1 and P2Y12 receptor expression // J Neurochem. – 2007. - Vol. 115. - P. 450-459.

10 Echeverry S, Shi XQ, Haw A, Liu H, Zhang Z and Zhang J. Transforming growth factor-β1 impairs neuropathic pain through pleiotropic effects // Mol Pain. – 2009. - Vol. 5., №16. - P.1-18.

11 Fuhrmann M, Bittnerr T, Jung CKE, Burgold S, Page RM, Mitteregger G, Haass C, LaFerla FM, Kretzschmar and Herms J. Microglial Cx3cr1 knockout prevents neuron loss in a mouse model of Alzheimer's disease //Nat Neurosci. – 2010. - Vol.13, №4. - P.411-413.

12 Harris-White ME, Chu T, Balverde Z, Sigel JJ, Flanders KC and Frautschy SA.Effects of Transforming Growth Factor-β (Isoforms 1-3) on Amyloid-β Deposition, Inflammation and Cell Targeting in Organotypic Hippocampal Slice Cultures // J Neurosci. – 1998. - Vol.18, №24. - P. 10366-10374.

13 Haynes SE, Hollopeter G, Yang G, Kurpius D, Dailey ME, Gan WB and Julius D. The P2Y12 receptor regulates microglial activation by extracellular nucleotides // Nat Neurosci. – 2006. - Vol. 9, №12. - P.1512-1519.

14 Herrera-Molina R and von Bernhardi R. Transforming growth factor-β1 produced by hippocampal cells modulates microglial reactivity in culture // Neurobiol Dis. – 2005. - Vol.19. - P.229-236.

15 Huang WC, Yen FC, Shie FS, Pan CM, Shiao YJ, Yang CN, Huang FL, Sung YJ and TsayHJ . TGF-β1 blockade of microglial chemotaxis toward Aβ aggregates involves SMAD signaling and down-regulation of CCL5 // J Neuroinflam. – 2010. - Vol. 7, №28. - P. 1-11.

16 Kettenmann H, Kirchhoff F and Verkhratsky. Microglia: New Roles for the Synaptic Stripper // Neuron. – 2013. - Vol.77. - P.10-18.

17 Krstic D and Kruesel I. Deciphering the mechanism underlying late-onset Alzheimer disease // Nat Rev Neurol. – 2013. - Vol. 9. - P. 25-34.

18 Lee Hg, Ueda M, Zhu X, Perry G and Smith MA. Ectopic Expression of Phospho-Smad2 in Alzheimer's Disease :Uncoupling of the Transforming Growth Factor-β Pathway? // J Neurosci Res.-2006. - Vol. 84. - P.1856-1861.

19 Makwana M, Jones LI, Cuthill D, Bohatschek M, Hristova M, Friedrichsen S, Ormsby I, Bueringer D, Koppius A, Bauer K, Doeschman T and Raivich G. Endogenous Transforming Growth Factor β1 Supresses Inflammation and Promotes Survival in Adult CNS // J Neurosci. -2007. - Vol. 27, №42. - P.11201-11213.

20 Massagué J. TGFβ signaling in context //Nat Rev Mol Cell Biol. – 2012. - Vol. 13. - P.616-630.

21 Mesplès B, Fontaine RH, Lelièvre, Launay JM and Gressens P. Neuronal TGF-β1 mediates IL-9/mast cell interaction and exacerbates excitotoxicity in newborn mice // Neurobiol Dis.-2005. - Vol.18. - P.193-205.
22 Napoli I and Neumann H. Protective effects of microglia in multiple sclerosis // Exp Neurol. – 2010. - Vol. 225. - P. 24-28.
23 Paglinawan R, Malipiero U, Schlapbach R, Frei K, Reith W and Fontana A. TGFβ Directs Gene Expression of Activated Microglia to an Anti-Inflammatory Phenotype Strongly Focusing on Chemokine Genes and Cell Migratory Genes // GLIA. - 2003. - Vol. 44. -P.219-231.
24 Palin K, Cunningham C, Forse P, Perry VH and Platt N. Systemic inflammation switches the inflammatory cytokine profile in CNS Walleriandegeneration //Neurobiol Dis. – 2008. - Vol. 30. - P.19-29.
25 Rogers JT, Morganti JM, Bachstetter AD, Hudsin CE, Peters MM, Grimmig BA, Weeber EJ, Bickford PC and Gemma C. CX3CR1 Deficiency Leads to Impairment of Hippocampal Cognitive Function and Syanptic Plasticity //J Neurosci. – 2011. - Vol.31, №45. - P.16241-16250.
26 Schafer DP,Lehrman EK and Stevens B. The "Quad-Partite" Synapse: Microglial-Synapse Interactions in the Developing and Mature CNS // GLIA. – 2013. - Vol. 61. -P.24-36.
27 Spittau B, Wullkopf L, Zhou Z, Rilka J, Pfeifer D and Krieglstein K. Endogenous Transforming Growth Factor-Beta Promotes Quiescence of Primary Microglia In Vitro // GLIA. -2013. - Vol. 61. - P.287-300.
28 Tichauer JE and von Bernhardi R. Transforming Growth Factor-β Stimulates β Amyloid Uptake byy Microglia Trough Smad3-Dependent Mechanisms // J Neurosci Res. – 2012. - Vol. 90. - P.1970-1980.
29 Town T, Laouar Y, Pittenger C, Mori T, Szekely AC, Tan J, Duman RS and Flavell RA. Blocking TGF-β-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology // Nat Med. – 2008. - Vol. 14, №6. - P. 681-687.
30 Tremblay ME, Zettel ML, Ison JR, Allen PD and Majewska AK. Effects of Aging and Sensory Loss on Glial Cells in Mouse Visual and Auditory Cortices // GLIA. – 2012. - Vol. 60. - P.541-558.
31 Ueberham U, Ueberham E, Gruschka H and Arendt T. Altered subcellular location of phosphorylated Smads in Alzheimer's disease //Eur J Neurosci. – 2006. - Vol. 24. - P.2327-2334.
32 von Bernhardi R, Ramirez G, Toro R and Eugenin J .Pro-inflammatory conditions promote neuronal damage mediated by Amyloid PrecurosrProtien and decrease in phagocytosis and degradation by microglial cells in culture // Neurobiol Dis.- 2007. - Vol. 26. - P.153-164.
33 Wake H, Moorhouse AJ, Jinno S, Kohsaka S and Nabekura A. Resting Microglia Directly Monitor the Functional State of Synapses In Vivo and Determine the Fate of Ischemic Terminal // J Neurosci. – 2009. - Vol. 29, №13. - P.3974-3980.
34 Wirths O, Breyhan H, Marcello A, Cotel MC, Brück W, and Bayer TA. Inflammatory changes are tightly associated with neurodegeneration in the brain and spinal cord of the APP/PS1K1 mouse model of Alzheimer's disease // Neuorobiol Aging. – 2010. - Vol. 31. - P.747-757.
35 Yoshiyama Y, Higuchi M, Zhang B, Huang SM, Iwata N, Saido TC, Maeda J, Suhara T, Trojanowski JQ and Lee VMY. Synapse Loss and Microglial Activation Precede Tangles in a P301S Tauopathy Mouse Model // Neuron. – 2007. - Vol.53. - P. 337-351.

А.А.Аканова[1], В.Б.Хабижанова[2], С.Т.Жумабекова[2], М.М.Сапарбаева[2], А.К.Ешманова[2], К.К.Аканова[2]
[1]Қазақ медициналық үздіксіз білім беру университеті
[2]С.Ж.Асфендияроватд.Қазақ Ұлттық медицина университеті
№1 геронтология курсымен жалпы практика кафедрасының дәрігері

АЛЬЦГЕЙМЕР АУРУЫ КЕЗІНДЕГІ МИКРОГЛИЯ РОЛІ ЖӘНЕ В1 ӨСУІНІҢ ТҮРЛЕНДІРМЕЛІ ФАКТОРЫ (ӘДЕБИЕТ ШОЛУ)

Түйін: Нейровизуализация әдісін пайдалана отырып, заманауи зерттеу жүргізу мидағы микроглия физиологиясын түсінудің жаңа аспектілерін ашуға көмектесті. Микроглия көптеген үдерістерге қатысады, мысалы, пренаталды кезеңде түйіспелік десорбцияға немесе сенсорлық еске сақтау модуляциясы кезінде қатысады, екінші жақтан, микроглия жіті бас-ми жарақатын немесе созылмалы нейродегенеративті ауруларды бірініші сезінеді, сондықтан микроглия ролі физиологиялық контексіне байланысты нейропротекторлық та, нейроуытты да болуы мүмкін. Деректер санының өсуі Альцгеймер ауруының (АА) дамуында нейроинфламмация және микроглия триггерлік роль атқаратыны қызықты. Осы шолудың мақсаты физиологиялық және патологиялық жағдайлардағы микроглиалды-нейронды байланыстарды сипаттау болып табылады; сонымен қатар, микроглия Альгеймер ауруының жануар моделіндегі үлгісінде нейродегенерацияға апаратын патологиялық жағдайлар кезінде синаптикалық десорбцияға, сонымен қатар микроглиалды иммунды цитокин, Tgf-β1 ролі, және оның негізгі дабылды каскадына SMAD2 / 3 тікелей қатысады. Аталған патологиялық механизмдер үлкен қызығушылық туғызып отыр, себебі олар тек АА дамуында тікелей роль атқармайды, сондай-ақ АА терапиялық тұрғыдан емдеу мүмкіндігімен қызығушылық туғызып отыр.
Түйінді сөздер: Альцгеймер ауруы, микроглия, нейроинфламмация, Tgf-β1, дабылды каскады SMAD2 / 3

А.А.Аканова[1], В.Б.Хабижанова[2], С.Т.Жумабекова[2], М.М.Сапарбаева[2], А.К.Ешманова[2], К.К.Аканова[2]
[1]Казахский Медицинский Университет Непрерывного Образования
[2]Казахский Национальный Медицинский Университет имени С.Д.Асфендиярова
Кафедра врача общей практики №1 с курсом геронтологии

РОЛЬ МИКРОГЛИИ И ТРАНСФОРМАЦИОННОГО ФАКТОРА РОСТА-В1 ПРИ БОЛЕЗНИ АЛЬЦГЕЙМЕРА (ЛИТЕРАТУРНЫЙ ОБЗОР)

Резюме: Современные исследования с использованием методов нейровизуализации помогли открыть новые аспекты в понимании физиологии микроглии в головном мозге. Микроглия участвует во многих процессах, например, участвует в синаптической десорбции во время пренатального периода или при модуляции сенсорного запоминания, с другой стороны, микроглия первой реагирует на острую черепно-мозговую травму или хронические нейродегенеративные заболевания, поэтому роль микроглии может быть как нейропротекторной так и и нейротоксической в зависимости от физиологического контекста. Интересно, что растущее количество данных свидетельствует о том, что нейроинфламмация и микроглия могут играть триггерную роль при развитии болезни Альцгеймера. Целью данного обзора является описание микроглиально-нейронных связей в физиологических и патологических условиях; а также участие микроглии непосредственно в синаптической десорбции при патологических условиях, ведущих к нейродегенерации на примере животной модели болезни Альгеймера, а также роль микроглиального иммунного цитокина,Tgf-β1, и его основной сигнальный каскады SMAD2 / 3. Данные патологические механизмы представляют большой интерес, так как они не только могут играть непосредственную роль в развитии БА, но и представлять собой интерес с терапевтической точки возможного лечения БА.
Ключевые слова: болезнь Альцгеймера, микроглия, нейроинфламмация, Tgf-β1, сигнальные каскады SMAD2 / 3