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Fas Role in Ischemic Stroke: Not Only in Apoptosis

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Abstract

The receptors, whose ligand interaction activation was previously considered to be associated with initiation of apoptosis only, can have a range of biological effects: apoptosis, inflammation, proliferation, and differentiation. Therefore, interaction between death receptor and its ligand does not always mean the initiation of programmed cell death and blocking of this ligand-receptor interaction can affect the initiation of recovery and neuroplasticity mechanisms. Fas is one of these death receptors. The following review represents data on the conditions of Fas-dependent signal pathways induction in ischemic stroke. There is a possibility for the development of new target neuroprotective drugs with selective effects on different separated signal pathways, activated by ligand-receptor interactions in Fas-FasL (Fas ligand) system.

Keywords: Stroke; Fas; Apoptosis; Inflammation; Regeneration

Introduction

It is widely known that FasL induces apoptosis of cells that express Fas receptor. However the interaction between death receptor and its ligand does not always mean the initiation of programmed cell death and blocking of this ligand-receptor interaction can effect on activation of the recovery and neuroplasticity mechanisms (Figure 1).

Focal ischemic brain damage is accompanied by changes in the cell-cell communication and depends on the following processes: deficiency of energy, ion imbalance, acidosis, excitotoxicity, lipid peroxidation, accumulation of arachidonic acid products, cytokine-mediated cytotoxicity, complement activation, disruption of blood-brain barrier permeability, glial cell activation, and leukocyte infiltration. All these processes depend on each other and, as a result, lead to cell death or metabolic changes. The main type of cell death in the area of the most significant decrease of brain tissue perfusion (< 10–15 ml/100 g/min) is necrosis because other types of cell death require some energy reserve [1]. Necrosis area is surrounded by a functionally silent due to blood supply decrease and energy deficit, but metabolically active tissue. During the initial stages of ischemia, this border region – known as the "ischemic penumbra" – may comprise up to a half of the total lesion volume. It was shown, that neurons in the ischemic penumbra might undergo apoptosis after several hours, days and even months after the onset of a stroke. At the same time, apoptosis involves not only a periinfarct zone, but also some other regions of the ipsi- and contralateral hemisphere. The extrinsic mechanisms of apoptosis, involved in ischemic stroke pathogenesis, include cell death receptors of TNF (tumor necrosis factor) superfamily and their ligands [2]. Role of Fas/FasL system in the stroke pathogenesis was discussed in recent literature. It was shown, that increase of Fas and FasL occurs in brain regions compromised by different neurological disorders and stroke as well [3]. Studies have shown the increase of brain Fas and FasL expression in animal stroke models [4] and patients with ischemic stroke [5]. Under cerebral ischemia conditions, pharmacological elimination of FasL effects or suppression of Fas/FasL system functioning on genetic level exert a neuroprotective action [6-8]. All these data suggest an important role of Fas/FasL system in the pathogenesis of stroke and its long-term effects.

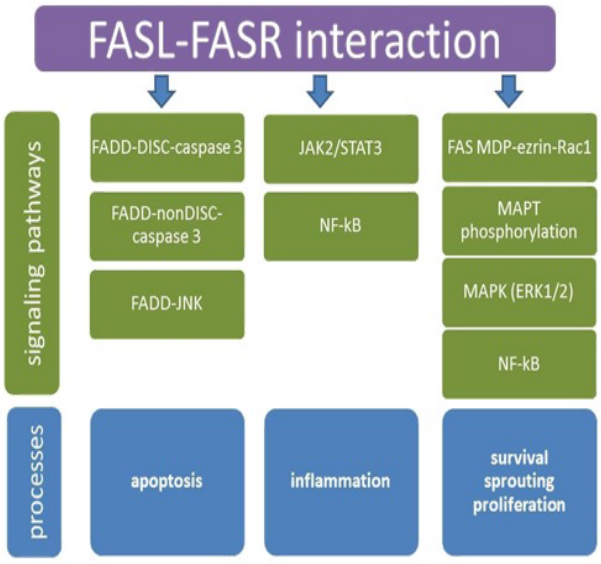

Figure 1: Activation of apoptotic, inflammation and regeneration signalling pathways by FasL-FasR interaction in the ischemic brain.

Fas receptor structure

Fas receptor (Fas, APO-1, CD95) is encoded by Fas gene, located on 10q24.1 chromosome. Gene expression occurs in almost all cell types of human body. Fas receptor consists of extracellular domains, formed by the N-terminal region, and cytoplasmic intracellular domains, formed by the C-terminal region refolding (Figure 2). There are

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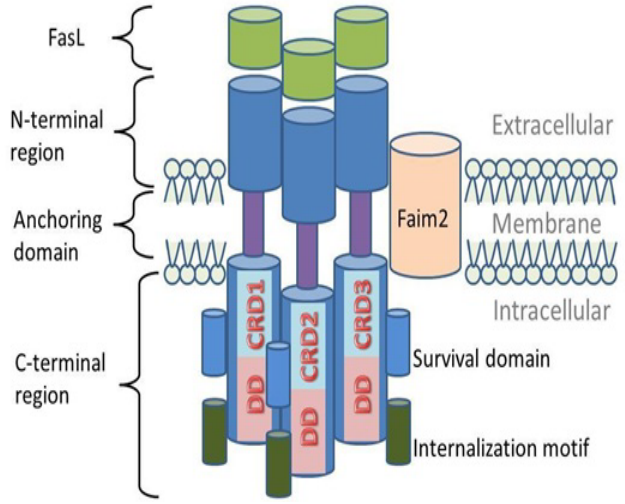

Figure 2: The Fas receptor schematic structure.

three intracellular cysteine-rich domains – CRD1, CRD2 and CRD3. Charge of CRD2 domain and upper portion of CRD3 sustains robust binding of Fas receptor with its ligand. CRD1 domain, also known as PLAD (pre-ligand assembly domain), is connected to another two CRD1 subunits that promote the homotrimeric structure of receptor. Additionally, receptor structure includes domain, anchoring it to the cell membrane, and death domain (DD) for apoptosis initiation [9]. Adjacent to Fas DD internalization motif enables actin- and clathrin-mediated internalization of the receptor. Binding of "survival domain" (CD95) at the cytoplasmic end of protein to Fas-associated phosphatase 1 (FAP1) inhibits cytotoxic properties of Fas receptor [10].

Fas ligand structure

Fas ligand (FasL, CD178) is encoded by gene fasl, located on 1q23 chromosome. This trimeric protein penetrates cell membrane. Transmembrane region of FasL includes conservative domain homologous to TNF family (aa 81–102) and differs much from intracellular region (aa 1–81), which consists of sequence of 80 amino acids. Its N-end is significantly larger as compared to the ligands of TNF (35 aa), LT b (18 aa) and TRAIL (17 aa). Only FasL contains unique conservative proline-rich domain (PRD) (aa 45–71, 22 proline and 5 leucine residues), which enables interaction with cytosolic protein, carrying domains SH3 or WW. Furthermore, only FasL exhibits casein kinase substrate motif and tyrosine kinase phosphorylation sites. Extracellular domain could be split off by membrane-type matrix metalloproteinase-3 and -7 with its subsequent secretion in the form of soluble trimer. Nevertheless, the soluble form is unstable and relatively biologically inactive, whereas membrane-bound form of FasL is a potent inducer of apoptosis. Expression level of FasL on cell surface correlates with the sensitivity of these cells to FasL-mediated external stimulatory signals [11].

Fas ligand-induced apoptosis

Fas ligand (FasL) is a well-known death system that can induce apoptotic cell death in a variety of cells expressing Fas receptor by the activation of downstream caspases via intrinsic (mitochondrial) or extrinsic (death receptor) pathways [12]. While Fas receptor is expressed in a wide variety of cells, FasL expression is tightly restricted to activated T cells [13], natural killer cells [14,15], photoreceptors [16] and liver cells [17]. Furthermore, the expression of FasL on the surface of platelets after activation during tissue damage induces apoptosis in primary murine neuronal cells, human neuroblastoma cells, and mouse embryonic fibroblasts [18]. Recent studies showed that Fas death receptor pathway contributes to apoptosis in neurons [19,20]. FasL induces the apoptosis of cells, expressing Fas receptor. Recent studies showed that Fas induces apoptosis in neurons [19,21-25]. Several proteins, such as calreticulin, can bind to FasL and inhibit Fas/FasL-mediated neuronal cell apoptosis during the early stage of ischemic stroke [26,27].

FasL exists in two forms: A 37-kDa membrane-bound FasL (mFasL) and a 30-kDa soluble FasL (sFasL). sFasL is a cleaved and soluble form of FasL released from activated cells and is traditionally considered as a cytokine that can induce apoptosis in susceptible cells [26,28,29]. mFasL apoptotic signal is initiated by the binding of membrane FasL form to Fas receptor on the membrane of another cell. In these circumstances, DD domain of Fas receptor connects with cytoplasmic protein FADD (Fas-associated protein with death domain). FADD through the death effector domain (DED) is linked to caspase-8. The binding of Fas, FADD and caspase-8 results in the formation of death-inducing signaling complex (DISC). At this level, intracellular signaling pathway bifurcates depending on the cell type and environment. The first scenario involves interaction of Fas and FasL with DISC formation and subsequent receptor internalization with all bound factors [30,31]. Thereafter DISC complex promotes procaspase-8 degradation with the activation of caspase-8. Active caspase-8 can then directly cleave procaspase-3 and activate caspase-3. Active caspase-3 is involved in the degradation of protein molecules, such as DNA reparation enzymes, cytoplasmic and nuclear structural proteins, spindle proteins, and endonucleases. In addition, caspase-3 promotes activation of procaspases -6 and -7, which are able to anticipate apoptosis [32]. Under the second scenario, DISC complex formation and subsequent procaspase-8 activation are constrained by regulatory molecules FAP1, c-FLIP and PED-PEA15. This leads to an insufficient concentration of caspase-8 for apoptosis initiation through the above-mentioned way. Also, caspase-8 mediates cleavage of Bid to truncated Bid (tBid fragment), which translocates to mitochondria and stimulates Bax incorporation into mitochondrial membrane. Bax removes Bcl-2 protection of mitochondria from cytochrome C leakage [33]. Thereafter, the cytosolic interaction of Apaf-1 (apoptosis protease-activating factor 1), procaspase-9 and cytochrome C forms a protein complex called the apoptosome followed by the caspase-9 release.

SMAC (second mitochondria-derived activator of caspases) is released from mitochondria together with cytochrome C. SMAC release blocks another proapoptotic factor XIAP (Xlinked inhibitor of apoptosis protein). Subsequently, caspase-9 activates caspase-3 by the cleavage of procaspase-3 [34]. Recent studies of cerebral ischemia in rodents reveal that inhibition or lack of the Bcl-2 family proteins can provoke ischemic excitotoxic, metabolic and oxidative neuronal injury [35,36]. Bcl-2 and Fas neuronal apoptosis-related function after cerebral ischemia and reperfusion is associated with expression STAT3 in ischemic zone, including ischemic penumbra and ischemic core zone [37].

In addition, DD domain was revealed in the structure of receptor interacting protein 1 (RIP1), so it could be considered as an inducer of Fas-mediated apoptosis with the involvement of procaspase-2 [38]. Initially formed 51-kDa C-terminal fragment containing the death domain (PIDD-C) mediates the activation of NF-κB via the recruitment of RIP1 and NEMO, subsequent formation of 37-kDa fragment (PIDD-CC) causes caspase-2 activation and, thus, cell death. In this way, auto-

proteolysis of PIDD might participate in the orchestration of the DNA damage-induced life and death signaling pathways [39].

Furthermore, the interaction of Fas and FasL could activate c-Jun N-terminal kinase (JNK). In such a case, activated JNK antagonizes NFκB-dependent expression of anti-apoptotic proteins [40]. Furthermore, JNK promotes a proteasomal degradation of c-FLIP protein, blocks caspase-8 production [41-43].

Fas ligand in inflammatory response

Inflammation is an important component of nervous tissue damage progression under the conditions of cerebral ischemia [44-48]. The development and maintenance of neurogenic inflammation are associated with astrocyte and microglia activation, leukocyte attraction andincrease of inflammatory mediators concentration, including IL-1b, TNF-a, monocyte-derived chemokines MIP-1a and MCP-1, etc. [49-52]. Furthermore, the degree of inflammatory reaction correlates with brain damage severity and long-term outcome of ischemic stroke [53-58]. FasL is able to activate pathways of signal transduction, inducing inflammatory response [59-61]. Studies results suggest that FasL-mediated induction of proinflammatory cytokines and chemokines (e.g. IL-6, MCP-1 and IL-8) expression occurs in different cell types [62-67]. Activated microglia and astrocytes are the main source of cytokines in CNS [68]. Ischemic neurons release sFasL, which contributes to M1-microglial polarization. The underlying mechanisms may involve the activation of JAK2/STAT3 and NF-κB signaling pathways [69].

Inactivation of FasL in FasL-mutant (gld) mice by point mutation results in the decrease of cerebral and systemic inflammatory response, protecting brain from a damage in the model of ischemic stroke or in the test with the lipopolysaccharide administration-induced inflammatory response. At the same time, this mutation has no influence on the intensity of apoptotic neuronal response. Inflammatory effect of FasL is mediated by the activation of CNS resident immunocompetent cells with the subsequent involvement of circulating leukocytes. The maximal infiltration of ischemized area with neutrophils and T-cells occurs in 24 hours after cerebrovascular accident [70,71]. In the animal model of ischemic stroke, Fas ligand was able to modulate T-cell response and degree of neutrophil infiltration. It has been shown, that the mutation of FasL in gld mice abolishes activation of the above mentioned glial elements and cytokine release with subsequent attraction of peripheral blood leukocytes related to ischemic stroke. Additional changes included a shift in immune response from type Th1 to Th2 [56,72,73]. Th1-cells predominantly secrete proinflammatory cytokines, e.g. IL-1b, TNF-a, and IFN-c. Th1-cells are considered to play a negative role in the stroke development, whereas Th2-cells are able to secrete anti-inflammatory cytokines, such as IL-4 and IL-10, that impact on the neuroprotective effect [56]. It is demonstrated that the interaction between inflammation and neurogenesis takes place after the stroke [74-77]. Furthermore, acute inflammation initiates a regenerative response in the adult brain [78]. But the effect of the post-ischemic neuroinflammatory immune response on neurogenesis is not well understood [79]. The understanding of poststroke inflammation mechanisms could reveal new targets for treatment and rehabilitation.

Regenerative role of Fas in the nervous system

Poststroke recovery depends on many clinical and biological factors [80,81]. There are several types of functional recovery after the ischemic stroke. The recovery of functions to the initial level is possible only in the absence of neuronal death, when the lesion predominantly consists of cells, inactivated by swelling, hypoxia and diaschisis. Another variant of recovery includes a functional reorganization with the involvement of new, earlier inactive structures. The most unfavorable outcome is readaptation with the arrangement to the existing defect [82]. Recovery at any level during the post-stroke period is mediated by neuroplasticity. Neuroplasticity presumes an ability of nervous tissue to change its structural and functional organization amid external and internal factors, while maintaining the adaptation and functional state of organism [83-88]. The anatomical basis of the plasticity is a cortical reorganization with the increase of functional effectiveness of preserved structures and an active involvement of alternative descending tracts. At the cellular level, these processes include synaptic remodeling, neosynaptogenesis, extrasynaptic neurotransmission, changes in dendritic structure, and axonal sprouting [89]. Metabolic changes affect neurons, glial elements and neuronal-glial interactions [90]. Data on the favorable effect of synaptic transmission via Fas receptors on neurogenesis induction [91,92] and neuritogenesis [93] suggest the neuroplastic potential of Fas. For example, in the neuronal culture Fas activation by monoclonal antibodies resulted in the enhancement of neuronal branching through the development of new axons. Experiments have shown that Fas initiates this process via binding with DD domain. In addition, Fas regulates neuronal branching by the phosphorylation of certain cytoskeletal components, e.g. microtubule-associated protein tau (MAPT), whose binding with microtubules depends on phosphorylation. This interaction contributes towards microtubules stability. The addition of FasL to neuronal culture was associated with higher levels of dephosphorylated Tau (Ser 199/202) [94]. *In vitro* experiments on cell lines and primary mouse embryonic cortical neuronal cultures have shown that Fas directly regulates the morphological structure of neurons without apoptosis activation. New cytoplasmic membrane proximal domain (MPD), which is essential for Fas-induced process, growth was described in the structure of all TNFR superfamily members. The Fas MPD recruits ezrin, a molecule that links transmembrane proteins to the cytoskeleton and activates the small GTPase Rac1. Deletion of the MPD, but not the DD domain, abolished Rac1 activation and the process of neurogenesis. Furthermore, an ezrin-derived inhibitory peptide prevented Fas-induced neurite growth in primary neurons [95].

Studies have shown the presence of anti-apoptotic signaling pathway, induced by the Fas-FasL system. In the absence of receptor internalization, the formation of DISC complex is very slow, so activating signal spreads on MAPK (mitogen activated protein kinase) and NFκB pathways. The activation of these effector pathways promotes cell survival. Nonetheless, Fas stimulation increases MAPK and NFκB activation even in case of receptor internalization [33]. The MAPK family consists of three main members: ERK1/2 (extracellular signal–regulated kinase), JNK (c-Jun N-terminal kinases, phosphorylating c-Jun transcription factor), and p38 protein. By responding to extracellular stimulus, MAPK kinases initiate a broad spectrum of cellular processes, including cellular metabolic level, motility, mitosis, differentiation, inflammation, death, and survival. ERK1/2 activation is predominantly associated with neuronal proliferation, differentiation and sprouting [96]. In ischemic stroke model, the amount of phosphorylated ERK was increased in different brain regions, with higher levels of this kinase expression in penumbra, but not in the ischemic core. Observations in the models of global ischemia demonstrated the most prominent expression of ERK in resistant to hypoxia brain regions [97]. Binding of Fas with its ligand in spinal ganglion cells leads to the DD-independent activation of ERK that finally results in axon elongation without any apoptotic effects [66]. Specific protein Faim2 (Fas apoptotic inhibitory molecule 2) has been shown to be an evolutionary conserved, neuron-specific inhibitor of Fas/CD95-mediated apoptosis. In the oxygen-glucose deprivation model, the lack of Faim2 caused an increase in

the caspase-associated death of primary neurons [98,99]. It is reported that Faim2 acts as a neuroprotectant during Fas-mediated apoptosis of photoreceptors. The expression of Faim2 is regulated by the ERK signaling pathway. The modulation of ERK signaling that increases Faim2 expression may be a potential therapeutic option to prevent photoreceptor death [100].

NFκB (Nuclear Factor Kappa-light-chain enhancer of activated B cells) is a transcription factor, formed by two subunits of the Rel family, represented by seven members: p65 (Rel A), p50 (NFκB1), C-Rel, Rel B, p100, p105, and p52. The activation of NFκB factor demands phosphorylation of inhibitory protein, associated with NFκB complex. This leads to the dissociation of complex with subsequent NFκB dimerization, translocation of the dimers to the nucleus and binding them to DNA elements, accompanied by the activation of target genes transcription. The above mentioned family of transcription factors is responsible for the regulation of genes, involved in inflammatory and other immune reactions, cellular proliferation and apoptosis. NFκB is involved in responses to stimuli such as different types of stress, effects of cytokines, growth factors, bacterial and viral antigens [101]. NFκB activation in brain tissue occurs normally, but is also associated with adaptation processes under extreme conditions. In such cases, this transcription factor is involved in the processes of neuronal survival, synaptic plasticity and memory [102,103]. Recent evidence has shown, that 72 hours after the excitotoxic kainic acid administration, the level of the p-FADD dependent transcription factor NF-κB in the hippocampus was also increased (+61%) [104]. It was demonstrated, that FADD is a multifunctional protein, and its phosphorylated form (p-Ser191/194) mediates antiapoptotic actions *in vitro* and neuroadaptations *in vivo* [105]. Therefore, the ratio of p-FADD to FADD in brain tissue has been proposed as the index of neuroplasticity [106].

In addition, it has been demonstrated, that lower dosages of soluble FasL (sFasL) enhanced proliferation and migration of the brain endothelial bEnd.3 cells. Effects of sFasL included increase in the endothelial secretion of vascular endothelial growth factor (VEGF) and up-regulation of expression of FADD, FLIP, TRAF, and NF-kB. Additionally, SiRNA inhibition of endothelial Fas expression completely abolished the proliferative effect of FasL, increase in VEGF secretion, and up-regulation of FADD–FLIP–TRAF–NF-kB pathway. Therefore, it could be concluded that the proliferation and migration of the brain endothelial cells could be directly regulated by Fas/FasL complex [107].

TCF4 (T-cell factor 4) was found to be an important transcription factor of the Wnt signaling system. The regulation of target genes depends on cytoplasmic accumulation of β-catenin (the upstream protein of TCF4) and its subsequent translocation to the nucleus with concomitant activation of the β-catenin/Tcell factor/lymphoid enhancer factor (TCF/LEF) transcriptional machinery. Studies have shown that TCF4 is involved in a cell proliferation and apoptosis [108]. *In vivo* and *in vitro* tests show that cell death and/or cell activation are triggered by complexes, formed by TCF4 binding elements (TBEs) of FasL and the TCF4 and β-catenin transcription factors. FasL is expected to be the target gene of the β-catenin/T-cell factor pathway as far as the co-transfection of LEF-1 and β-catenin transcription factors results in the significant increase of FasL promoter activities [109]. Traumatic brain injury (TBI) model in adult rats shows, that TCF4 might promote neuronal apoptosis and microglial proliferation after TBI [110].

Conclusion

The activation of Fas receptor-Fas ligand system could result in a broad spectrum of biological effects, including apoptosis, inflammation, proliferation and differentiation. Fas has no intrinsic enzymatic activity, but is associated with adaptor proteins, which initiate a wide range of signal pathways, such as MAPK, NFκB, JNK, ERK, phosphorylation of cytoskeletal proteins, and caspase-dependent apoptosis. In the nervous system of human and animal adults, the level of Fas expression is very low. Nonetheless, Fas receptor expression increases significantly in response to damage, associated with oxidative stress, trauma, ischemic stroke, excitotoxicity, pharmacological toxicity, neurodegenerative processes, etc. FasL is capable of activating signal transduction pathway, involved in the induction of inflammatory response. However, during ischemic stroke Fas is responsible not only for cell death and inflammation, but also for the realization of recovery processes as well, where neuronal plasticity plays a crucial role. This fact is of a great clinical importance for the future development, testing and clinical assessment of neuroprotective drugs.

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