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# Neuroprotective role of fibronectin in neuron-glial extrasynaptic transmission☆

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## Abstract

Most hypotheses concerning the mechanisms underlying Parkinson's disease are based on altered synaptic transmission of the nigrostriatal system. However, extrasynaptic transmission was recently found to affect dopamine neurotransmitter delivery by anisotropic diffusion in the extracellular matrix, which is modulated by various extracellular matrix components such as fibronectin. The present study reviewed the neuroprotective effect of fibronectin in extrasynaptic transmission. Fibronectin can regulate neuroactive substance diffusion and receptor activation, and exert anti-neuroinflammatory, adhesive and neuroprotective roles. Fibronectin can bind to integrin and growth factor receptors to transactivate intracellular signaling events such as the phosphatidylinositol 3-kinase/protein kinase B pathway to regulate or amplify growth factor-like neuroprotective actions. Fibronectin is assembled into a fibrillar network around cells to facilitate cell migration, molecule and ion diffusion, and even drug delivery and treatment. In addition, the present study analyzed the neuroprotective mechanism of fibronectin in the pathogenesis of Parkinson's disease, involving integrin and growth factor receptor interactions, and discussed the possible therapeutic and diagnostic significance of fibronectin in Parkinson's disease.

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## Key Words

neural regeneration; neurodegenerative diseases; Parkinson's disease; fibronectin; integrin; extrasynaptic transmission; neuroglia; neuroprotection; grants-supported paper; photographs-containing paper; neuroregeneration

## Research Highlights

(1) This study reviewed the neuroprotective effect of fibronectin, a major extracellular matrix component, in extrasynaptic transmission and its possible therapeutic and diagnostic significance for Parkinson's disease.
(2) Evidence showed that fibronectin can bind to integrins and growth factor receptors (such as insulin-like growth factor 1 receptor) to transactivate intracellular signaling events, such as the phosphatidylinositol 3-kinase/protein kinase B pathway, and regulate or amplify growth factor-like neuroprotective actions.

## INTRODUCTION

Traditionally, the major mechanism underlying Parkinson's disease was thought to be reduced dopaminergic synaptic transmission in the nigrostriatal system. However, neurons may also communicate by extrasynaptic transmission, which was recently found to affect dopamine neurotransmitter delivery through diffusion in the extracellular matrix[1]. Fibronectin, a ubiquitous extracellular matrix component,

participates in the formation and regulation of anisotropic diffusion (*i.e*., diffusion facilitated in a certain direction) of the extracellular matrix, and dynamically regulates neuronal functional activities, such as neuroactive substance diffusion and receptor activation, anti-neuroinflammation, and cell adhesion[2].

Studies over the past two decades have demonstrated that there exist two major modes of neuron-glial communication in the central nervous system: synaptic transmission (or wiring transmission) and extrasynaptic transmission[3]. In synaptic transmission, synaptically evoked astrocytes produce elevated $Ca^{2+}$ signals, which can trigger the release of gliotransmitters and play neuromodulatory and information-integration roles in neuronal activity, synaptic transmission and plasticity[3]. Extrasynaptic transmission involves secretion of a wide variety of bioactive substances by neurons and neuroglia that are released or leaked into the extracellular space. These substances mediate bidirectional communication between neurons and neuroglia through molecular diffusion, resulting in a sustained neuromodulatory action on neuronal activity[3]. This information processing is also known as “diffusion transmission”, “volume transmission” and “intercellular communication”[4], all of which reflect the specific function of extracellular space. There are four types of extrasynaptic transmission in the central nervous system (Figure 1)[5-7]: including the intercellular short distances, the cerebrospinal fluid, the long distances around nerve fibers, and long distances around blood vessels. The latter two types of extrasynaptic transmission display the properties of faster and longer signal transmission that occur among brain nuclei, cerebral areas and even cerebral hemispheres, and involve the movement of various bioactive substances, such as ions, neuropeptides, neurohormones and metabolites, as well as pathological hematologic exudates such as cell adhesion molecules, growth factors and inflammatory molecules[8-10]. Thus, extrasynaptic transmission plays important modulatory roles in neuronal functional activities. In the central nervous system, fibronectin is produced and secreted by neuroglial cells and endothelial cells and is assembled into the extracellular matrix. Thus, fibronectin is important for extrasynaptic transmission, and to some degree exerts neuroprotective effects, such as anti-neuroinflammation[2, 11]. However, the neuroprotective mechanism of fibronectin remains to be thoroughly analyzed to reveal its important clinical value and to enhance understanding of extrasynaptic transmission and the functional role of the neuron- glia network. In turn, it is hoped that this knowledge will unveil the molecular pathogenesis and new therapeutic approaches in neurodegenerative disorders such as Parkinson’s disease. Here, we summarize the molecular structures and roles of fibronectin and integrin receptors in extrasynaptic transmission, the neuroprotective roles of fibronectin and its potential significance in Parkinson’s disease.

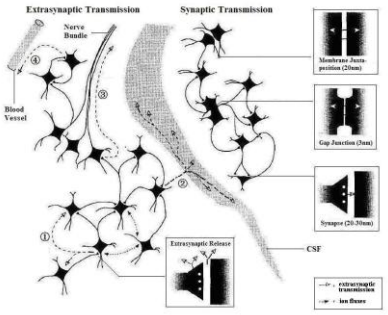


Figure 1 Schematic diagram of the principal types of cerebral extrasynaptic transmission (modified and adapted from references[5-7]).

The four types of extrasynaptic transmission in the central nervous system involve: ① short distances for simple diffusion, such as autocrine and paracrine transmission, ② cerebrospinal fluid (CSF) for endocrine diffusion, ③ long distances around nerve bundles for preferential diffusion, and ④ long distances around blood vessels for preferential diffusion.

The left section shows the functional tracks of extrasynaptic transmission or volume transmission, and the right section shows the functional tracks of synaptic transmission (neural wiring transmission) without neuroactive substance leakage into the extracellular space.

## MOLECULAR STRUCTURE AND FUNCTIONS OF FIBRONECTIN AND ITS INTEGRIN RECEPTORS

Fibronectin is a heterodimeric glycoprotein encoded by a single gene and is disulfide-bonded at its carboxyl terminal. Each monomer contains three types of repeats (type I, II or III) and constitutes multiple domains. The middle domain contains an Arg-Leu-Asp (RGD)-binding motif that can bind to integrin and non-integrin receptors. The carboxyl terminal domain containing a heparin binding site and a variable sequence has a higher expression level in the embryonic period that becomes lower in the elderly, and displays a neuroprotective effect[12]. Fibronectin has a wide variety of cell sources, such as astrocytes[13], epithelial cells, fibroblasts, and mesenchymal cells[9], and participates in cell adhesion, proliferation and differentiation, epithelial tissue repair, immune regulation, neural regeneration, and other physiological activities[14]. Integrins, the receptors for fibronectin, are a family of transmembrane glycoprotein

receptors and their molecular structure comprises one α and one β subunit bound by non-covalent bonds. They can recognize and bind to fibronectin and other extracellular matrix proteins or other receptors, and exert dual functions of cell adhesion and signal transduction. At present, it is well-established that there are nineteen α and eight β subunits that can combine to form at least 25 different integrin receptors in mammals[12]. The majority of α subunits only bind to one β subunit and sometimes to multiple β subunits, such as α4β1, α4β7, α6β1, α6β4, αvβ1, αvβ3, αvβ5, αvβ6 and αvβ8. Both α and β subunits have a large extracellular region (important for binding to the RGD sequence in various integrin ligands such as matrix molecules), a transmembrane region and a small intracellular region (no catalytic effect). Integrins are functionally divided into three main subfamilies: β1 integrins (*i.e*., very late antigen integrins), β2 integrins (*i.e*., leukocyte integrins), and αv integrins, with β3 integrins (*i.e*., cell adhesion integrins) also given more attention recently. Each integrin has its own extracellular matrix ligand and mediates bidirectional signal transduction. That is, the binding of an integrin to its ligand can activate intracellular signaling events, which in turn affect the affinity of ligand and integrin. In most cases, integrins can combine with neighboring receptors (*i.e*., counter receptors) to form integrin-receptor complexes, or receptor mosaics, on the cell surface[15] that transactivate intracellular signaling and modulate biological effects. This characteristic reveals the diversity and complexity of integrins in regulating cell function.

## NEUROPROTECTIVE ROLE OF FIBRONECTIN AND ITS MOLECULAR MECHANISM

The fibronectin gene is pleiotropic and fibronectin has extensive roles in promoting cell growth[16-17]. For example, in the cerebrovascular endothelial cells, fibronectin mediates the mitogen-activated protein kinase signaling pathway *via* α5β1 and αvβ3 receptors and promotes cell survival and proliferation[18]. fibronectin protects cells and promotes functional recovery in liver cells treated with lipipolysaccharide[14, 19]. Moreover, fibronectin plays a neurotrophic and anti-inflammatory role in the brain and promotes the growth and survival of neurons[20-22]. It has been confirmed that the fibronectin type III (fibronectin 3) modules of the neural cell adhesion molecule are involved in the direct interaction between neural cell adhesion molecule and fibroblast growth factor receptor in dopaminergic, hippocampal and cortical neurons[20], and then activate the mitogen-activated protein kinase and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signal transduction pathways and induce neuronal differentiation and proliferation *in vitro* [21]. The administration of synthetic fibronectin peptide V can increase the survival of dopaminergic neurons in neural grafts *in vivo* and ameliorate motor dysfunction in Parkinson's disease animals, suggesting the anti-apoptotic effect of fibronectin[22]. Fibronectin can also inhibit the development of mechanical allodynia by injection into the spinal dorsal column after spinal injury[2]. In microglia, fibronectin can activate the PI3K-Akt and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway, enhance the expression levels of neurotrophic factors[23], and attenuate the release of the pro-inflammatory factor interleukin 1, all of which contribute to neural repair and neuronal survival[24]. Traumatic brain injury induced significantly increased lesion volume and apoptotic cell death in fibronectin knockout mice, but intravenous injection of fibronectin before the injury reversed the neural deficits, indicating that fibronectin is neuroprotective against traumatic brain injury and a novel target for therapeutic interventions[25]. fibronectin promotes axon growth in spinal cord injury[26] and cultured oligodendrocytes[27-28]. Fibronectin can also promote survival and migration of transplanted primary neural stem cells in a mouse model of traumatic brain injury, and act as a possible therapeutic tool for traumatic brain injury[29]. Taken together, findings from the studies on the neuroprotective role of fibronectin are expected to lead to the development of new therapeutic approaches for Parkinson's disease and other neurodegenerative diseases, and indicate that fibronectin could become an important pharmacological tool for the study of specific functional aspects of extrasynaptic transmission, including neuroprotection and neuromodulation.

The three major subfamilies (β1, β2 and αv) of integrins are all able to recognize and bind to extracellular matrix proteins and counter receptors and trigger a great deal of intracellular structural and signaling changes. These changes include the assembly of multi-molecular complexes onto cytoplasmic integrin tails to engage and organize the cytoskeleton, as well as the activation of signaling pathways that modify function and gene expression[12, 30-31]. Cross-talk between integrin-mediated signaling and growth factor-mediated signaling can occur at various levels[17, 31]. Furthermore, integrin-fibronectin ligand interactions play roles in cell adhesion, and in combination with growth factor receptors, regulate functional activities of growth factors *via* receptor transactivation and intracellular signaling events[17]. In the central nervous system, β1 and αv are extensively

expressed in several cell types such as neurons, glia and epithelial cells, while β2 is only expressed in microglia. α5β1 is the only integrin receptor containing the α5 subunit and binds to only one fibronectin ligand[32], which, along with α3β1 and α4β1, promotes growth and regulates function in neural cells[33-34] and cerebrovascular endothelial cells[18]. It has been demonstrated that β1 and αv integrins can transactivate a variety of growth factor receptors and mimic the somatotrophic or neuroprotective effect of related growth factors, such as fibroblast growth factor, insulin-like growth factor (IGF)-1 and glial cell line-derived neurotrophic factor[30-31]. In the dopaminergic neurons of the substantia nigra that have a high level of constitutive IGF-1 receptor (IGF-1R) expression, β1 integrins (*e.g*., α3, α4, 5β1) can activate the IGF-1R/ phosphatidylinositol 3-kinase/protein kinase B signaling pathway by the IGF-1-independent transactivation of IGF-1R, and enhance IGF-mediated neurotrophic effects in degenerating dopaminergic neurons[35-36]. Analogous mechanisms often also exist in other cell types. For example, fibronectin is abundant in pancreatic tumors and engages IGF-IR to inhibit cell death by stimulating formation of a complex between β3 integrin and protein-tyrosine phosphatase SHP-2. Formation of this complex prevents SHP-2 from dephosphorylating IGF-IR and results in sustained phosphorylation of IGF-IR and downstream activation of Akt kinase, and the inhibition of apoptosis through up-regulation of the anti-apoptotic factor Bcl[16]. β1 integrin expression is required for IGF-IR-mediated prostate cancer cell proliferation and anchorage-independent growth[17], and can bring about the extended activation of IGF-1R and mimic and amplify the biological effects of IGF-1[37]. Therefore, fibronectin-induced neuroprotection could be fully mediated by IGF-IR without involvement of IGF-1, suggesting that fibronectin and IGF-IR could be important targets for the development of pharmaceuticals that mediate pro-survival signals[38].

## FIBRONECTIN IS A CONSTITUTIVE COMPONENT AND REGULATOR OF EXTRASYNAPTIC TRANSMISSION

Fibronectin is a non-collagen component among extracellular matrix proteins that are synthesized by many cell types, such as astrocytes, endothelial cells, fibroblasts and myoblasts. Extracellular matrix proteins are then assembled into three-dimensional fibrillar networks surrounding neural cells to form a pericellular microenvironment and to support biomolecular flow. However, this microenvironment is not homogeneous allowing for the directional facilitation of information flow down different dynamic pathways, *i.e*., intercellular channels, to regulate neuron-glial extrasynaptic transmission[8-10]. During brain development or injury, fibronectin and other matrix proteins may support and promote differentiation and migration of neuronal progenitor cells, or directional outgrowth of neurites[39]. In the adult brain, the fibrillar fibronectin guides and controls the flow of extracellular fluid and the diffusion of various substances, which are driven by energy gradients, such as concentration, temperature and pressure gradients, and have slower diffusion properties, less safety, less spatial constraint and wider diffusion ranges[40]. The diffusion capability of extrasynaptic transmission is determined by three parameters: 1) extracellular space volume fraction α (α = extracellular space volume/total tissue volume), which can be reduced due to cerebral atrophy in the elderly, especially in neurodegenerative diseases[5], 2) tortuosity λ, reflecting the condition of diffusion barriers such as altered fibrillar fibronectin architecture and other extracellular matrix macromolecules, fine neural processes, charged molecules and degrading enzymes[5], 3) nonspecific cellular uptake (k'), indicating the degree of cell swelling. These diffusion parameters differ in various brain regions, showing heterogeneous diffusion in the central nervous system, and are easily affected by physiological and pathological factors such as molecular rearrangement, glial remodeling, cell swelling and elderly extracellular space shrinkage[41-42]. Therefore, the expression level of fibronectin can directly influence the diffusion and permeability of various neuroactive substances, to some degree by directional facilitation through intercellular channels due to local changes in homeostasis. These preferential channels exert an important regulatory role on neurotransmitter diffusion, and intercellular short distance and peri-neurofiber long distance extrasynaptic transmission. Thus, they might adversely underlie disease pathology and be used as a potential target for the treatment of neurodegenerative diseases such as Parkinson's disease[43-44]. In geriatric patients, there are significant alterations in volume, tortuosity and anisotropy of brain extracellular space. These changes may seriously affect intercellular channel permeability and communication through the neuron-glia network, and bring about synapse-transmitter leakage and transmitter-receptor mismatches[41-42, 45] that give rise to abnormal accumulation and diffusion of neuroactive substances. This mechanism might contribute to the pathogenesis of Parkinson's disease or other neurodegenerative diseases, and provide a pharmacological target to ameliorate deficiencies in neurotransmission, cell migration and drug

delivery and treatment[40].

## ROLES OF FIBRONECTIN IN NEURON-GLIAL EXTRASYNAPTIC TRANSMISSION AND PATHOGENESIS

Along with other components of the extracellular matrix, such as glycosaminoglycans and proteoglycans, fibronectin accumulates in the extracellular matrix to form poriferous perineuronal nets to regulate matrix organization[46-47]. For example, fibronectin may specifically bind to growth factor receptors or be involved in clearance of degraded products and direct cell behaviors, such as receptor activation that transduces signals into cells, in addition to its supportive and adhesive roles. These effects of fibronectin could bring about the altered structural and functional properties of extracellular matrix (*e.g.*, neurotransmitter storage, metabolite clearance, and diffusion parameters), and underlie the molecular mechanism of neurodegenerative disorders such as Parkinson's disease[48]. The expression level of fibronectin determines the nature and condition of extracellular matrix, and is readily affected by multiple physiological and pathological factors (*e.g.*, ageing and neuroinflammatory response), as well as genetic and epigenetic factors (*e.g.*, transcription factors and post-translational modifications)[8-9]. Meanwhile, fibronectin, like other extracellular matrix macromolecules, contributes to diffusion barriers in the extracellular space and influences neuroglial activation, diffusion of various factors or neurotransmitters, information transmission and neurotrophic microenvironment[4, 47], in spite of neuronal and glial processes also disturbing the local extracellular matrix architecture of the central nervous system. The neuroprotective mechanism of fibronectin is mediated by both integrins and growth factor receptors[16-17, 20]. Briefly, binding of fibronectin to integrins (β1, β2, and αv) triggers intracellular structural alterations and signaling cascades, including integrin-mediated signaling which can crosstalk with growth factor-mediated signaling at various levels[49] and mimic the functions of growth factors *via* receptor transactivation and intracellular signaling events. Therefore, fibronectin could be applied to study neuroprotection in neurodegenerative diseases such as Parkinson's disease. In the Parkinson's disease brain, the transmission of dopamine in the nigrostriatal pathway is greatly abated or blocked for two reasons: 1) deficit of striatal dopamine in the Parkinson's disease brain because of decreased dopamine synthesis in degenerating nigral neurons, and 2) altered matrix content and increased diffusion barriers to extrasynaptic transmission along the nigrostriatal pathway. The latter is the main pathological change in the Parkinson's disease brain because the nigrostriatal dopamine pathway mainly operates *via* volume transmission; that is, nigral dopamine reaches target cells mostly by diffusion along the dopamine concentration gradient of the extracellular space[5, 50]. Although the downregulated expression of fibronectin in the elderly brain can compensative and reduce the diffusion barrier and partly ameliorate deficits in dopamine diffusion, the increased volume fraction is still not reversed[6, 48]. Therefore, fibronectin could be administered as a neuroprotective drug to augment the fibronectin levels in plasma and brain, which would not only enhance survival of dopaminergic neurons but would also maintain a better extracellular matrix status for unrestricted diffusion and traffic of dopamine along the nigrostriatal pathway. In particular, under circumstances in which wiring transmission is blocked, the use of extrinsic fibronectin has an important compensatory effect on the striatal dopamine deficit and protects against the development of Parkinson's disease[43-44, 48]. Moreover, it is reasonable to predict that the molecular status of plasma fibronectin could be used as an additional diagnostic biomarker for risk assessment of Parkinson's disease[51], and that the increase of fibronectin in the cerebrospinal fluid could be an important parameter used to diagnose certain neurodegenerative diseases such as amyotrophic lateral sclerosis and multiple sclerosis[51]. The proneuronal and metabolic effects of fibronectin will be helpful in formulating new therapeutic and diagnostic strategies.

## CONCLUSION

Fibronectin can bind to and activate both integrin receptors and IGF-1R, thus triggering IGF-1R/ phosphatidylinositol 3-kinase/protein kinase B signaling and enhancing survival of dopamine neurons. We refer to this cascade (summarized in Figure 2) as the "fibronectin-integrin-growth factor receptor-signal transduction-gene and protein expression cascade", through which altered extrasynaptic transmission may modulate the functional outputs of cells to compensate for deficits in synaptic transmission. Therefore, fibronectin could likely be used as an endogenous repair protein of extracellular matrix, and its clinical application ameliorate the poor brain extracellular environment and achieve some therapeutic effects in neurodegenerative diseases. The role of fibronectin in the geriatric pathogenesis of neurodegeneration reflects its

diagnostic value[25, 29, 39]. The study of the functional manipulation of fibronectin in neuron-glial extrasynaptic transmission should be expanded to broaden our understanding of the complex fibronectin- and integrin-mediated signaling networks, and to determine a new and effective approach to diagnosis and treatment of certain neurodegenerative diseases.

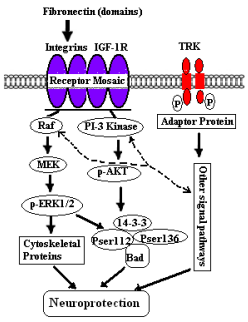


Figure 2 A proposed schematic map of the neuroprotective mechanism of fibronectin.

Fibronectin may mediate a receptor-receptor interaction between integrins and IGF-1R in the cell surface membrane. Molecular cross-talk likely occurs between the intracellular signaling cascades resulting from this interaction, to finally produce the neuroprotective effects.

TRK: Tyrosine receptor kinase; IGF-1R: insulin-like growth factor-1 receptor; MEK: mitogen-activated protein kinase kinase; ERK: extracellular signal-regulated kinase; PI-3K/Akt: phosphatidylinositol 3-kinases/protein kinase B.

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**Author contributions:** Jintang Wang collected and analyzed experimental data and wrote the manuscript. Ling Yin collected reference material on extrasynaptic transmission. Zheng Chen revised the manuscript. All authors approved the final version of the paper.

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## REFERENCES

[1] Rice ME, Patel JC, Cragg SJ. Dopamine release in the basal ganglia. Neuroscience. 2011;198:112-137.

[2] Lin CY, Lee YS, Lin VW, et al. Fibronectin inhibits chronic pain development after spinal cord injury. J Neurotrauma. 2012;29(3):589-599.

[3] Araque A. Astrocytes process synaptic information. Neuron Glia Biol. 2008;4(1):3-10.

[4] Johnstone S, Isakson B, Locke D. Biological and biophysical properties of vascular connexin channels. Int Rev Cell Mol Biol. 2009;278:69-118.

[5] Syková E, Mazel T, Simonová Z. Diffusion constraints and neuron-glia interaction during aging. Exp Gerontol. 1998; 33(7-8):837-851.

[6] Syková E. Glial diffusion barriers during aging and pathological states. Prog Brain Res. 2001;132:339-363.

[7] Agnati LF, Zoli M, Strömberg I, et al. Intercellular communication in the brain: wiring versus volume transmission. Neuroscience. 1995;69(3):711-726.

[8] Wierzbicka-Patynowski I, Mao Y, Schwarzbauer JE. Analysis of fibronectin matrix assembly. Curr Protoc Cell Biol. 2004;Chapter 10:Unit 10.12.

[9] Zhang GN, Yang YS. Biologic features and current research status of cellular fibronectin. Shiyong Yiyuan Linchuang Zazhi. 2007;4(6):104-105.

[10] Lohr C, Thyssen A, Hirnet D. Extrasynaptic neuron-glia communication: The how and why. Commun Integr Biol. 2011;4(1):109-111.

[11] Tsuda M, Toyomitsu E, Komatsu T, et al. Fibronectin/ integrin system is involved in P2X(4) receptor upregulation in the spinal cord and neuropathic pain after nerve injury. Glia. 2008; 56(5):579-585.

[12] akagi J, Strokovich K, Springer TA, et al. Structure of integrin alpha5beta1 in complex with fibronectin. EMBO J. 2003;22(18):4607-4615.

[13] Rieske P, Augelli BJ, Stawski R, et al. A population of human brain cells expressing phenotypic markers of more than one lineage can be induced in vitro to differentiate into mesenchymal cells. Exp Cell Res. 2009;315(3):462-473.

[14] Moriya K, Sakai K, Yan MH, et al. Fibronectin is essential for survival but is dispensable for proliferation of hepatocytes in acute liver injury in mice. Hepatology. 2012;56(1):311-321.

[15] Guidolin D, Fuxe K, Neri G, et al. On the role of receptor-receptor interactions and volume transmission in learning and memory. Brain Res Rev. 2007;55(1):119-133.

[16] Edderkaoui M, Hong P, Lee JK, et al. Insulin-like growth factor-I receptor mediates the prosurvival effect of fibronectin. J Biol Chem. 2007;282(37):26646-26655.

[17] Goel HL, Breen M, Zhang J, et al. beta1A integrin expression is required for type 1 insulin-like growth factor receptor mitogenic and transforming activities and localization to focal contacts. Cancer Res. 2005;65(15): 6692-6700.

[18] Wang J, Milner R. Fibronectin promotes brain capillary endothelial cell survival and proliferation through alpha5beta1 and alphavbeta3 integrins via MAP kinase signalling. J Neurochem. 2006;96(1):148-159.

[19] Kao CL, Lin HT, Chen YW, et al. Fibronectin suppresses lipopolysaccharide-induced liver damage and promotes the cytoprotection abilities of hepatocyte-like cells derived from human bone marrow mesenchymal stem cells. Transplant Proc. 2007;39(10):3444-3445.

[20] Neiiendam JL, Køhler LB, Christensen C, et al. An NCAM-derived FGF-receptor agonist, the FGL-peptide, induces neurite outgrowth and neuronal survival in primary rat neurons. J Neurochem. 2004;91(4):920-935.
[21] Hansen SM, Køhler LB, Li S, et al. NCAM-derived peptides function as agonists for the fibroblast growth factor receptor. J Neurochem. 2008;106(5):2030-2041.
[22] Duan WM, Zhao LR, Westerman M, et al. Enhancement of nigral graft survival in rat brain with the systemic administration of synthetic fibronectin peptide V. Neuroscience. 2000;100(3):521-530.
[23] Tsuda M, Toyomitsu E, Kometani M, et al. Mechanisms underlying fibronectin-induced up-regulation of P2X4R expression in microglia: distinct roles of PI3K-Akt and MEK-ERK signalling pathways. J Cell Mol Med. 2009; 13(9B):3251-3259.
[24] Summers L, Kielty C, Pinteaux E. Adhesion to fibronectin regulates interleukin-1 beta expression in microglial cells. Mol Cell Neurosci. 2009;41(2):148-155.
[25] Tate CC, García AJ, LaPlaca MC. Plasma fibronectin is neuroprotective following traumatic brain injury. Exp Neurol. 2007;207(1):13-22.
[26] King VR, Phillips JB, Hunt-Grubbe H, et al. Characterization of non-neuronal elements within fibronectin mats implanted into the damaged adult rat spinal cord. Biomaterials. 2006;27(3):485-496.
[27] Hu J, Deng L, Wang X, et al. Effects of extracellular matrix molecules on the growth properties of oligodendrocyte progenitor cells in vitro. J Neurosci Res. 2009;87(13): 2854-2862.
[28] King VR, Alovskaya A, Wei DY, et al. The use of injectable forms of fibrin and fibronectin to support axonal ingrowth after spinal cord injury. Biomaterials. 2010;31(15): 4447-4456.
[29] Tate MC, Shear DA, Hoffman SW, et al. Fibronectin promotes survival and migration of primary neural stem cells transplanted into the traumatically injured mouse brain. Cell Transplant. 2002;11(3):283-295.
[30] Cao JP, Yu JK, Li C, et al. Integrin beta1 is involved in the signaling of glial cell line-derived neurotrophic factor. J Comp Neurol. 2008;509(2):203-210.
[31] Chao CC, Ma YL, Chu KY, et al. Integrin alphav and NCAM mediate the effects of GDNF on DA neuron survival, outgrowth, DA turnover and motor activity in rats. Neurobiol Aging. 2003;24(1):105-116.
[32] King VR, McBride A, Priestley JV. Immunohistochemical expression of the alpha5 integrin subunit in the normal adult rat central nervous system. J Neurocytol. 2001; 30(3):243-252.
[33] Li JH, Mu DZ. Roles of integrins in the central nervous system. Guoji Erke Zazhi. 2008;35(1):38-40.
[34] Milner R, Crocker SJ, Hung S, et al. Fibronectin- and vitronectin-induced microglial activation and matrix metalloproteinase-9 expression is mediated by integrins alpha5beta1 and alphavbeta5. J Immunol. 2007;178(12): 8158-8167.
[35] Wang JY, Grabacka M, Marcinkiewicz C, et al. Involvement of alpha1beta1 integrin in insulin-like growth factor-1-mediated protection of PC12 neuronal processes from tumor necrosis factor-alpha-induced injury. J Neurosci Res. 2006;83(1):7-18.
[36] Clemmons DR, Maile LA. Interaction between insulin-like growth factor-I receptor and alphaVbeta3 integrin linked signaling pathways: cellular responses to changes in multiple signaling inputs. Mol Endocrinol. 2005;19(1):1-11.
[37] Legate KR, Wickström SA, Fässler R. Genetic and cell biological analysis of integrin outside-in signaling. Genes Dev. 2009;23(4):397-418.
[38] Sperlágh B, Vizi ES. The role of extracellular adenosine in chemical neurotransmission in the hippocampus and Basal Ganglia: pharmacological and clinical aspects. Curr Top Med Chem. 2011;11(8):1034-1046.
[39] Tonge DA, de Burgh HT, Docherty R, et al. Fibronectin supports neurite outgrowth and axonal regeneration of adult brain neurons in vitro. Brain Res. 2012;1453:8-16.
[40] Vargová L, Syková E. Extracellular space diffusion and extrasynaptic transmission. Physiol Res. 2008;57 Suppl 3:S89-99.
[41] Ridet I, Privat A. Volume transmission. Trends Neurosci. 2000;23:58-59.
[42] Vargova L, Homola A, Cicanic M, et al. The diffusion parameters of the extracellular space are altered in focal cortical dysplasias. Neurosci Lett. 2011;499:19-23.
[43] Nowak P, Szczerbak G, Dabrowska J, et al. Molecular mechanisms of levodopa action in animal models of Parkinson's disease. Neurol Neurochir Pol. 2006;40:517-525.
[44] Schneider JS, Rothblat DS, DiStefano L. Volume transmission of dopamine over large distances may contribute to recovery from experimental parkinsonism. Brain Res. 1994;643(1-2):86-91.
[45] Fuxe K, Rivera A, Jacobsen KX, et al. Dynamics of volume transmission in the brain. Focus on catecholamine and opioid peptide communication and the role of uncoupling protein 2. J Neural Transm. 2005;112(1): 65-76.
[46] Oláh S, Füle M, Komlósi G, et al. Regulation of cortical microcircuits by unitary GABA-mediated volume transmission. Nature. 2009;461(7268):1278-1281.
[47] Hynes RO. The extracellular matrix: not just pretty fibrils. Science. 2009;326(5957):1216-1219.
[48] Fuxe K, Manger P, Genedani S, et al. The nigrostriatal DA pathway and Parkinson's disease. J Neural Transm Suppl. 2006;(70):71-83.
[49] Meland MN, Herndon ME, Stipp CS. Expression of alpha5 integrin rescues fibronectin responsiveness in NT2N CNS neuronal cells. J Neurosci Res. 2010;88(1):222-232.
[50] Fuxe K, Dahlström AB, Jonsson G, et al. The discovery of central monoamine neurons gave volume transmission to the wired brain. Prog Neurobiol. 2010;90(2):82-100.
[51] Merino García LC, González Sarmiento E, Rubio del Val MC, et al. Fibronectin as a diagnostic marker in several determined neurological diseases. An Med Interna. 2000; 17(8):406-409.

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