AINO JOURNAL, Vol. 15, 2016, pp. 81-87

Review

The characteristics and functions of NTAK/Neuregulin-2

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Abstract

Neuregulin-2 (NRG2), also known as NTAK (neural- and thymus-derived activator for ErbB kinases), is a member of the epidermal growth factor (EGF) family. The EGF family is involved in cell survival, proliferation, and development, and the ErbB family comprises receptor tyrosine kinases for the EGF family. NTAK/NRG2 is structurally homologous to NRG1, which is a member of the EGF family. NTAK/NRG2 as well as NRG1 binds directly to ErbB3 and ErbB4, and transactivates ErbB1 and ErbB2 *via* heterodimerization with ErbB3 or ErbB4. NTAK/NRG2 is only expressed in the brain of rat E11.5 embryos, and in the brain and thymus of adult rats *in vivo*, whereas NRG1 is expressed in the brain, heart, liver, kidneys, spinal cord, ovaries, and skin. NTAK/NRG2 has more than 10 alternatively spliced isoforms. NTAKα and NTAKβ preferentially induce ErbB3 and ErbB4 phosphorylation, respectively, and stimulate the growth of human breast cancer cells. It has been revealed that NTAK/NRG2 functions to control vascular endothelial cells and neurons. NTAKγ and δ inhibit vascular endothelial cell growth and display anti-angiogenic activity in the chick embryo chorioallantoic membrane *in vivo*, whereas NTAKα and β have no activity to angiogenesis. NTAKδ prevents hyper-phosphorylation of the retinoblastoma tumor suppressor protein and causes G_1 arrest in vascular endothelial cells. In the nervous system, NTAK/NRG2 is expressed in cultured hippocampal neurons and astrocytes, and NTAK/NRG2 secreted from astrocytes binds to ErbB3 on neurons, and promotes neuronal survival and neurite extension.

Key words: NTAK/neuregulin-2, EGF family, ErbB, neuron

Introduction

Growth factors are soluble polypeptides, involved in cell survival, proliferation, and development. Epidermal growth factor (EGF), its specific receptor (EGFR), and their relatives play important roles under physiological and pathological conditions, including tumor development and schizophrenia.

Neuregulin-2 (NRG2), also known as NTAK (neural- and thymus-derived activator for ErbB kinases), was purified and cloned two decades ago (Higashiyama et al., 1997; Chang et al., 1997; Carraway et al., 1997; Busfield et al., 1997). NTAK/NRG2 is similar to NRG1 in its structure and receptor characteristics. However, the biological functions of NTAK/NRG2 have not been sufficiently investigated.

In this review, we briefly summarize the knowledge of the EGF and ErbB families, and focus on the biological functions of NTAK/NRG2.

EGF Family

EGF is a soluble polypeptide that stimulates the proliferation, differentiation, and survival of various kinds of cells. EGF was first purified from the mouse salivary gland, together with nerve growth factor (NGF), as a molecule involved in opening the eyelids and tooth eruption in the newborn mouse (Cohen, 1962). Subsequent studies identified and characterized several novel members of the EGF family, and, to date, the EGF family consists of 13 members: EGF, transforming growth factor-α (TGF-α), amphiregulin, heparin-binding EGF-like growth factor (HB-EGF), betacellulin, epiregulin, epigen, NRG-1, NRG-2, NRG-3, NRG-4, NRG-5, and NRG-6

(Derynck et al., 1984 ; Shoyab et al., 1989 ; Higashiyama et al., 1991 ; Shing et al., 1993 ; Toyoda et al., 1995 ; Strachan et al., 2001 ; Wen et al., 1992 ; Chang et al., 1997 ; Carraway et al., 1997 ; Zhang et al., 1999 ; Harari et al., 1999 ; Uchida et al., 1999 ; Kinugasa et al., 2004).

All members of the EGF family are type I transmembrane proteins and contain the EGF-like domain, which has three disulfide bonds and an evolutionary conserved core structure. The members of the EGF family are synthesized on cell surfaces as transmembrane precursors, and the precursors can be cleaved by cell surface proteases, such as metalloproteases ADAMs family, to be released as soluble ligands that contain the EGF-like domain. This cleavage, termed ectodomain shedding, is a crucial step in the control of ligand availability and receptor activation. The production of soluble EGF family ligands by ectodomain shedding occurs in response to various physiological and pharmacological agonists, including 12-*O*-tetradecanoylphorbol 13-acetate, calcium ionophores, angiotensin II, interleukin-1, and growth factors (Goishi et al., 1995 ; Higashiyama et al., 2008).

ErbB Family

EGFR is a type I transmembrane protein first identified as the receptor for EGF. The gene of EGFR is homologous to the erythroblastic leukemia viral oncogene, *erbB*. The ErbB family comprises receptor tyrosine kinases, and consists of four members : EGFR (ErbB1), ErbB2 (HER2/Neu), ErbB3 (HER3), and ErbB4 (HER4) (Ullrich et al., 1984 ; Coussens et al., 1985 ; Plowman et al., 1990 ; Plowman et al., 1993). ErbB3 lacks kinase activity.

The ErbB bound by an EGF ligand induces dimer formation of the ErbB receptor and then transphosphorylates the partner ErbB. Each member of the EGF family has a specific binding preference for a member of ErbB. EGF has high affinity for ErbB1, HB-EGF binds to ErbB1 and ErbB4, and NRG1 and NRG2 bind to both ErbB3 and ErbB4 (Fig. 1). The transphosphorylation of ErbB leads to the activation of intracellular signaling transduction pathways in a specific way, and induces cellular responses including proliferation, migration, differentiation, and survival or apoptosis. Regardless of the ErbB member bound by the ligand, their signals will be transmitted from both the partner ErbB and receptor ErbB (Schlessinger, 2000 ; Gullick, 2001 ; Iwakura et al., 2013).

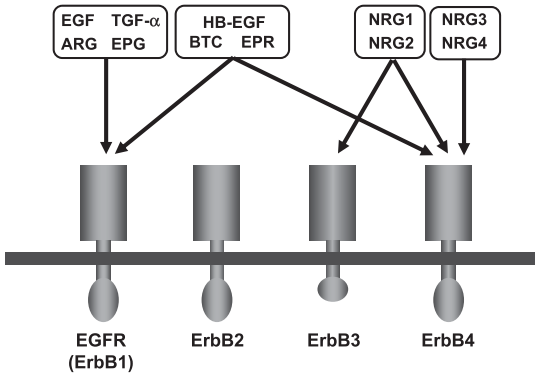

Fig. 1 The EGF-ErbB relationship. All members of the EGF family bind to the ErbB receptor. Each member of the EGF family has a specific binding preference with an ErbB subtype ; for example, EGF has a high affinity for ErbB1, HB-EGF interacts with ErbB1 and ErbB4, and NRG1 and NRG2 bind to ErbB3 and ErbB4.

Knockout studies have shown that ErbBs are crucial for the development of the central nervous systems and cardiac muscle. Cardiac abnormalities include aborted development of the endocardial cushion, which is dependent on mesenchymal cell growth and development of the endocardial endothelium (Burden et al., 1997). Insufficient ErbB signaling in humans is associated with the development of neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis (Bubil et al., 2007). On the other hand, overexpression of ErbBs or constitutive stimulation is associated with several types of human malignancies, including tumors of the breast, ovary, prostate, pancreas, lung, and brain (Citri et al., 2006). Therefore, ErbBs are attractive candidates for targeted therapy, and anti-EGFR and anti-ErbB2 therapeutics using humanized neutralizing antibodies have been developed, and some of them are in clinical use (Hynes et al., 2005 ; Bubil et al., 2007).

Neuregulins

Among the EGF family, NRGs comprise a large family that has different properties and functions from other members of the EGF family. Heregulin (HRG), neu differentiation factors (NDF), acetylcholine receptor synthesis stimulator (ARIA), glial growth factor (GGF), and sensory and motor neuron-derived factor (SMDF) were discovered to be the products of the same gene, and they were named neuregulin (NRG1) (Wen et al., 1992 ; Holmes et al., 1992 ; Falls et al., 1993 ; Marchionni et al., 1993 ; Schroering et al., 1998). NRG1 has several biological functions, including interaction with ErbB3 and ErbB4, the

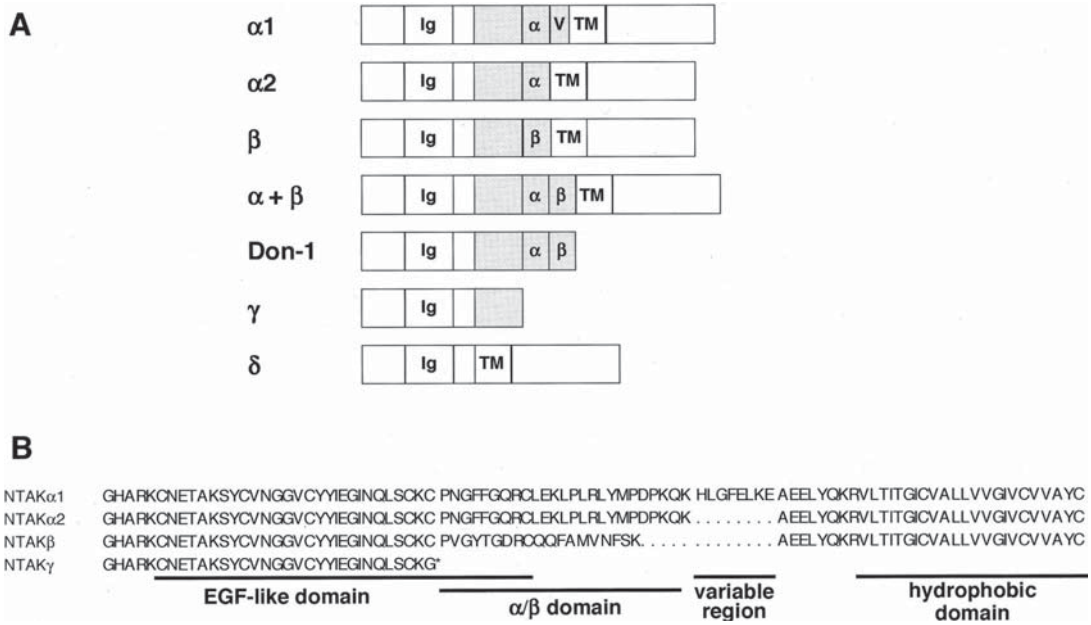

Fig. 2 Isoforms of NTAK. (A) The isoforms of NTAK and NRG2/Don-1 are schematically illustrated. *Gray boxes* indicate the EGF-like domain. *Ig*, immunoglobulin-like domain; *TM*, transmembrane domain; *V*, variable region. (B) The *α*, *β*, and *γ* isoforms of NTAK are aligned. *Asterisk*, COOH terminus. Gaps are inserted in the sequence for optimal alignment.

stimulation of Schwann cell growth, and induction of acetylcholine receptor expression (Meyer et al., 1995; Falls, 2003). To date, five additional members of NRGs (NRG2–6) have been identified (Higashiyama et al., 1997; Carraway et al., 1997; Chang et al., 1997; Zhang et al., 1999 Harari et al., 1999; Uchida et al., 1999; Kinugasa et al., 2004). Whereas NRG1 and NRG2 stimulate both ErbB3 and ErbB4, NRG3–5 bind to ErbB4, and NRG6 binds to ErbB3. NRGs, especially NRG1–3, have several alternatively splicing isoforms. NRG1 and NRG2 are denoted as either *α* or *β* isoforms depending on the sequence of the EGF-like domain (Fig. 2). These isoforms differ in their tissue-specific expression patterns, specific binding preference, and biological activities, thereby contributing to the marked diversity of the *in vivo* functions of NRGs (Mei et al., 2008; Kao et al., 2010).

NRGs are involved in cell-cell communication during development and disease. Especially, NRG1 functions have been extensively studied. NRG1 is expressed in the brain, heart, liver, kidneys, spinal cord, ovaries, and skin. NRG1 plays important roles during the development of the nervous system, heart, and mammary glands. For example, NRG1 has essential functions in the development of neural crest cells, Schwann cells, and sympathetic neurons. NRG1 also controls the trabeculation of the myocardial musculature, and ductal differentiation of the mammary epithelium (Burden et al., 1997). Moreover, NRG1 is involved in human diseases, including cancer and schizophrenia. On the other hand, the biological functions of NRG2–6 are comparatively poorly understood.

NTAK/NRG2

NTAK is derived from the same gene as NRG2 and divergent of neuregulin-1 (Don-1) (Higashiyama et al., 1997; Chang et al., 1997; Carraway et al., 1997; Busfield et al., 1997). NTAK/NRG2 is structurally homologous to NRG1 in terms of its immunoglobulin (Ig)-like, EGF-like, and hydrophobic domains. In the same way as NRG1, NTAK/NRG2 binds directly to ErbB3 and ErbB4 and transactivates ErbB1 and ErbB2 *via* heterodimerization with ErbB3 or ErbB4. NTAK/NRG2 is only expressed in the brain of rat E11.5 embryos, and in the brain and thymus of adult rats *in vivo* (Higashiyama et al., 1997).

NTAK/NRG2 has more than 10 alternatively spliced isoforms. The human *NTAK* gene comprises 12 exons spanning in excess of 55 kilobases. Among the products of alternative splicing, the *α* isoform of the *NTAK* gene is expressed in all tissues including the brain, and the *β* isoform is restricted to the brain. The *γ* isoform is expressed in a rat pheochromocytoma cell line, PC-12 cells. NTAK*δ* is an isoform missing the EGF-like domain, and it is expressed in a human neuroblastoma cell line, SK-N-SH cells (Fig. 2, Yamada

et al., 2000). NTAKα and NTAKβ preferentially induce ErbB3 and ErbB4 phosphorylation, respectively, and then both NTAK isoforms induce transactivation of the tyrosine phosphorylation of ErbB2, and stimulate the growth of human breast cancer cells (Nakano et al., 2000).

NTAK/NRG2 knockout mice showed no obvious histological differences in the major organs (Britto et al., 2004), while NRG1 is crucial for the development of the central nervous system and cardiac muscle (Burden et al., 1997). The differences in the biological roles and functions between NRG1 and NTAK/NRG2, including NRG3–6, still remain unknown, because there have been few reports on NTAK/NRG2 and NRG3–6.

Function of NTAK/NRG2 in Angiogenesis

Angiogenesis is the process of new vascular formation from pre-existing blood vessels, and it is tightly regulated by the balance of angiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2), and angiogenic inhibitors, such as angiostatin, endostatin, and NK4. Under normal conditions, vascular endothelial cells are quiescent due to the dominance of angiogenic inhibitory factors (Hanahan et al., 1996). Angiogenesis occurs during pathological events such as solid tumor growth and metastasis, diabetic retinopathy, atherosclerosis, and rheumatoid arthritis. Angiogenic inhibitors are capable of preventing tumor growth and metastasis, and, in fact, a number of angiogenic inhibitors are in clinical use for cancer and angiogenic diseases (Bergers et al., 2003).

ErbB signaling has also been implicated in angiogenesis. Neutralizing antibodies against ErbB1 and ErbB2 downregulate VEGF and inhibit tumor growth and angiogenesis *in vivo*. NRG1 has been reported to activate ErbBs in endothelial cells and induce angiogenesis. NRG1 binds to heparan sulfate proteoglycan (HSPG) *via* the Ig-like domain, and NRG1-HSPG interaction potentiates ErbB phosphorylation by the EGF-like domain of NRG1. Targeted deletion of the Ig-like domain of NRG1 in mice leads to the embryonic lethality associated with a deficiency of ventricular myocardial trabeculation and impairment of cranial ganglion development. NTAK/NRG2 is also concerned with aniogenesis. NTAKγ and δ, including the Ig-like domain but not the EGF-like domain, inhibit vascular endothelial cell growth and display anti-angiogenic activity in the chick embryo chorioallantoic membrane *in vivo*, whereas NTAKα and β had no activity to angiogenesis (Fig. 3). NTAKδ prevented hyper-phosphorylation of the retinoblastoma tumor suppressor protein and caused G_1 arrest in vascular endothelial cells (Nakano et al., 2004).

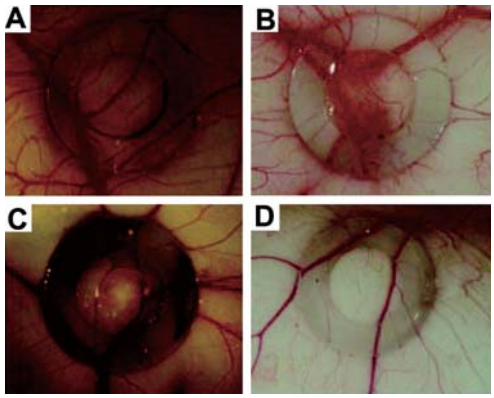

Fig. 3 Effect of NTAK on angiogenesis in CAMs. Fertilized white Leghorn chicken eggs were incubated at 37℃ for 5 days, and a methyl cellulose disk containing bovine serum albumin (A), NTAKα (B), NTAKγ (C), or NTAKδ (D) was placed within a 5-mm-round sterilized silicon ring on the CAMs. The eggs were incubated at 37℃ for 48 h. A white fat emulsion was injected into the chorioallantois and the vascular networks in the CAMs, and photographs were taken using a digital camera.

Function of NTAK/NRG2 in Nervous System

In the nervous system, the EGF family plays an important role. EGF in blood can penetrate into the immature brain and influence neural stem cell proliferation and neuron and glia differentiation and maturation (Xian et al., 2004 ; Nawa et al., 2006 ; Galvez-Contreras et al., 2013). In addition, NRG1 is expressed in the CNS, such as the brain and spinal cord, and is especially essential for the development and maintenance of neurons and glia in the nervous system, including Schwann cell and oligodendrocyte differentiation, axon myelination, neurotransmission, and synaptic plasticity. However, NRG1-ErbB4 signaling only has a weak effect on neuronal survival and neurite outgrowth (Mei et al., 2014). The EGF and ErbB families are associated with neuropsychiatric diseases, such as schizophrenia, bipolar disorder, and major depression, and neurodegenerative diseases, such as Alzheimer's disease and multiple sclerosis (Hahn et al., 2006 ; Bubil et al., 2007 ; Mei et al., 2008 ; Mei et al., 2014).

NTAK/NRG2 is expressed in the brain of rat E11.5 embryos and adult rats *in vivo* (Higashiyama et al., 1997), and in hippocampal neurons and astrocytes *in vitro* (Fig. 4). NTAK/NRG2 is also expressed in both neurons and

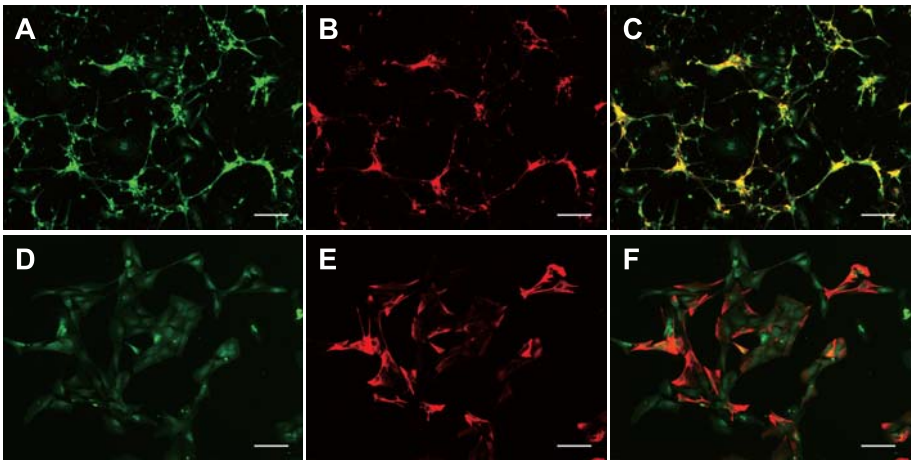

Fig. 4 Expression of NTAK/NRG2 in neurons and astrocytes. Hippocampal neurons (A-C) and astrocytes (D-F) were seeded on PLL-coated chamber slides in NB/B27 medium. After a 2-day incubation, cells were fixed and stained with NTAK/NRG2 (green, A & D), β-tubulin (red, B), or GFAP (red, E). (C) Beta-tubulin-positive neurons were positive for NTAK/NRG2 expression (yellow). (F) GFAP-positive astrocytes were also positive for NTAK/NRG2 expression. Although cells do not appear yellow, staining for NTAK/NRG2 and GFAP overlapped. Scale : 100 μm.

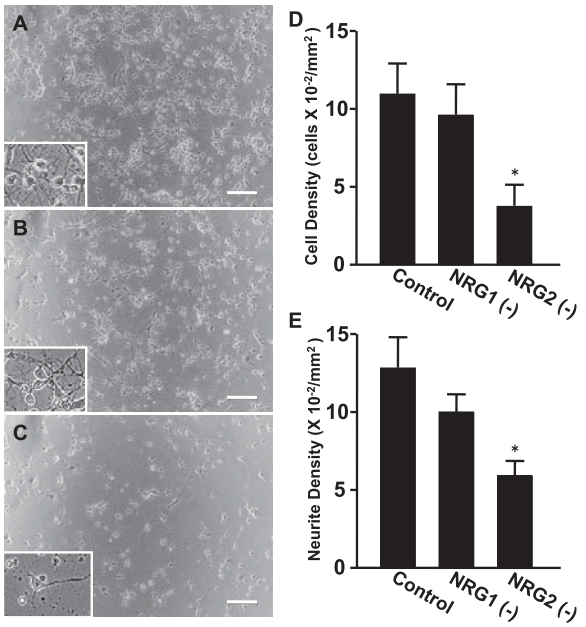

Fig. 5 Effects of the CM of astrocytes transfected with siRNA of NTAK/NRG2 on neurons. Astrocytes transfected with siRNA of NRG1 or NTAK/NRG2 were incubated for 24 h, and then were re-fed with serum-free D-MEM. Following another 24-h incubation, the CMs were collected. Neurons were re-fed with the CM of astrocytes transfected with siRNA of NRG1 (B), NTAK/NRG2 (C), or a control sequence (A). Cells were incubated for 24 h, and then the densities of neurons (E) and neurites (F) were quantified. The results are presented as the mean±SD. $^{*}p < 0.05$ versus control. Scale : 100 μm.

astrocytes. The conditioned medium (CM) from astrocytes stimulated the phosphorylation of ErbB3 in neurons, and promoted the survival and neurite outgrowth of neurons. Rates of survival and neurite outgrowth of neurons were lower in the CM of NTAK/NRG2-knockdown astrocytes than in that of control astrocytes, whereas the CM of NRG1-knockdown astrocytes had little effect on survival and neurite outgrowth (Fig. 5). Therefore, NTAK/NRG2 secreted from astrocytes bound to ErbB3 on neurons, and promoted neuronal survival and neurite extension *in vitro* (Nakano et al., 2016). There is a possibility that NTAK/NRG2-ErbB3 signaling occurs in some neuronal diseases. Further studies are necessary to reveal the biological function of NTAK/NRG2-ErbB3 signaling and promote comparisons between NTAK/NRG2 and NRG1/3–6.

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