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Neuregulin-1 (Nrg1): An Emerging Regulator of Prolactin (PRL) Secretion

Weijiang Zhao

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1. Introduction

1.1. Definition and structure of Neuregulin-1 (Nrg1)

Hypothalamus-derived dopamine and thyrotrophin-releasing hormone (TRH) have long been considered the main sources of prolactin (PRL) regulators in the anterior pituitary, whereas other substances also modulate PRL expression and secretion (Borrelli et al., 1992; Cai et al., 1999; Spuch et al., 2006). Recently, Vlotides for the first time observed that recombinant Nrg1 can control PRL secretion from rat RPL and growth hormone (GH) secreting lactosomatotroph GH3 cells, suggesting the emerging role of Nrg1 as a PRL regulator (Vlotides et al., 2009).

Neuregulins are homologous to epidermal growth factor (EGF) and are mainly encoded by four alternatively spliced genes: NRG-1 to -4 (Orr-Urtreger et al., 1993). Diverse splicing of the NRG-1 gene gives rise to at least six main types of Nrg1 (types I–VI) with ectodomain variation, whereas type I to III Nrg1. are the most intensively investigated. All types of Nrg1 contain an EGF-like domain, which can be classified as either α or β (Jacobsen et al., 1996; Rosnack et al., 1994). Distinct from soluble Nrg1, a membrane-tethered Nrg1 precursor has been identified that contains a transmembrane (TM) domain and an intracellular domain (ICD). The ICD can be further characterized as ICD a, b and c. The structure that links the ectodomain and the transmembrane (TM) domain is called a stalk (S), which can be further classified as S1, S2 and S4. Proteolysis of the Nrg1 precursor, a tightly regulated process, releases the soluble domains and leads to formation of autocrine/paracrine loops. However, recruitment of S3, which contains the stop codon, terminates the extension of the ectodomain into the cytoplasm and thus leads to the formation of non-membrane anchored Nrg1α/β **(See Fig 1)**.
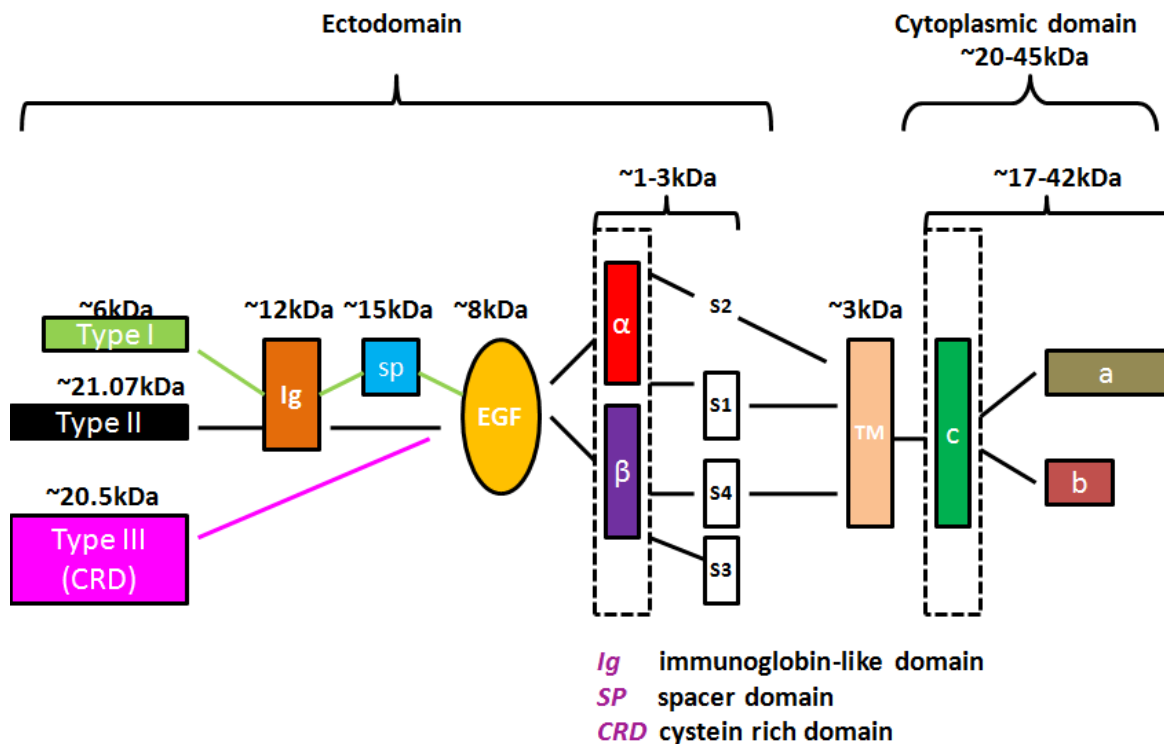
Figure 1. **Schematic of type I- III Nrg1** Diverse splicing of NRG-1 gene gives rise to Type I-III Nrg1s, whose structures were schematically diagrammed. α, EGF-like domain α; β, EGF-like domain β; Ig, Ig-like domain; s, stalk domain; sp, spacer domain.

1.2. Interaction of Nrg1 with its cognate receptors and related biological functions

The bioactivity of Nrg1 is mainly mediated by homodimers comprised of their cognate receptors ErbB4 (Hahn et al., 2006) or ErbB3/ErbB2 and ErbB4/ErbB2 heterodimeric complexes (Liu et al., 2002) (See Fig 2). Nrg1 was found to specifically activate the tyrosine kinase receptor ErbB2 as a growth factor extracted from the conditioned medium of a human breast tumor cell line (Holmes et al., 1992). It exerts mitogenic activity on cultured Schwann cells as type II Nrg1 (Glial growth factor, GGF) purified from the brain and bovine pituitary anterior lobe (Lemake et al., 1984). The acetylcholine receptor-inducing activity protein (ARIA), another Nrg1 type, was shown to promote acetylcholine receptor synthesis in cultured skeletal muscle and myotubes (Jessell et al., 1979; Usdin et al., 1986). The ligand-receptor interaction initiates a complex intracellular signaling cascade in which extracellular signal-regulated kinase (ERK), serine/threonine protein kinase (AKT), mitogen-activated protein kinase (MAPK), phosphatidyl-inositol 3-kinase γ (PIK3γ), protein kinase C (PKC), and Janus kinase-signal transducers and activators of transcription (Jak-STAT) are activated. Activation of this signaling pathway leads to, among other events, tumorigenic development, cell cycle arrest, cell proliferation, differentiation, and anti-apoptotic processes (Peles et al., 1993; Liu and Kern et al., 2002; Puricelli et al., 2002). Recently, Nrgβ1 has been reported to signal mitogenesis of cortical astrocytes through ErbB1⁄ErbB3 heterodimeric complex (Sharif et al., 2009).
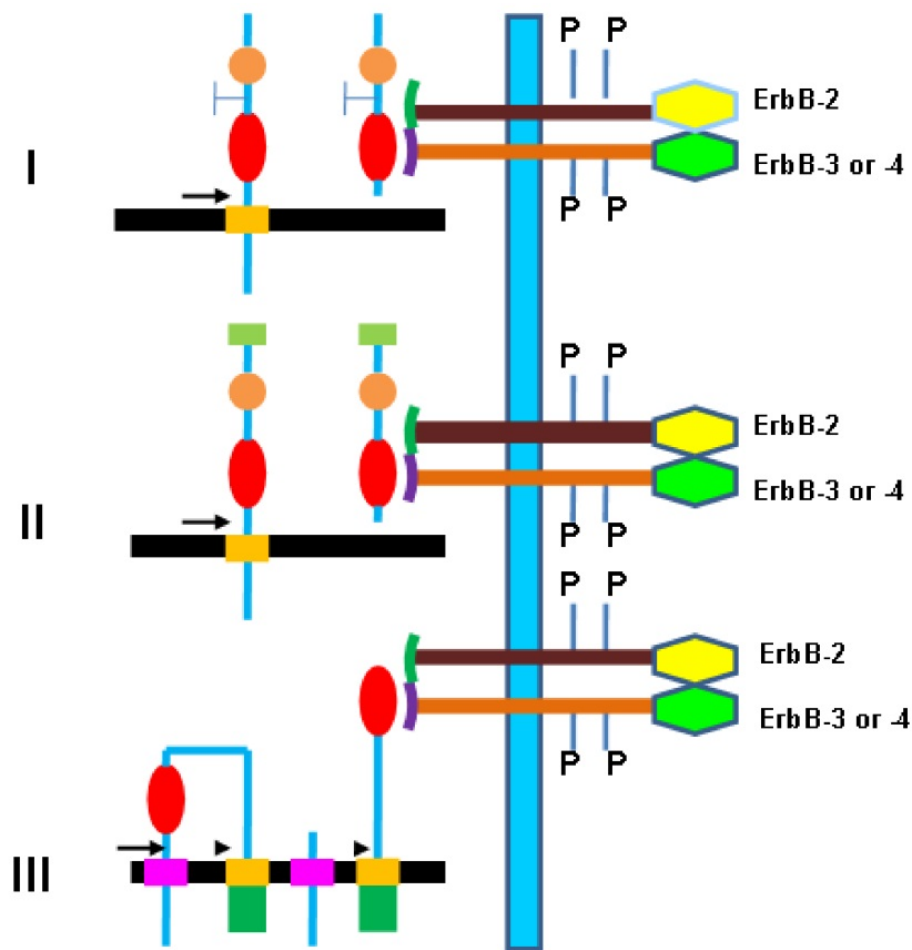
Figure 2. **Schematic of type I- III Nrg1 interaction with their receptors.** The initial proteolysis site was indicated by the arrow, and the site for second proteolysis was indicated by the arrow head.

2. Endogenous expression of Nrg1 in the anterior pituitary and rat lactosomatotroph GH3 cells

2.1. Expression and localization of Nrg1 and its receptor in the anterior pituitary of rat and non-human primates

The Nrg1-ErbB signaling pathway has a critical role in organ development, cell differentiation and tumorigenesis. Neuregulins have previously been described in the nervous system, especially in the cortex, spinal cord and hypothalamus. In the hypothalamus, ARIA (or Nrg1α and β) was expressed in neurons with processes projecting to the posterior pituitary gland but not in those without these projections, suggesting that hypothalamus-derived Neuregulin regulates certain functions of the pituitary (Bernstein et al., 2006; Corfas et al., 1995). Furthermore, Nrg1 receptors were reported to be expressed in hypothalamic astrocytes, where their activation as a result of paracrine Nrg1 stimulation is essential for stimulating secretion of luteinising hormone-releasing hormone (LHRH), intrapituitary gonadotrophin secretion and normal sexual puberty (Bernstein et al., 2006; Prevot et al., 2003).

Neuregulin has also been reported to be expressed in the endocrine organs, including the adrenal gland and the adult pancreas (Harari et al., 1999; Orr-Urtreger et al., 1993). Additionally, thyroid-derived cell lines and corresponding papillary carcinomas also express Nrg1 and ErbB receptors ErbB2 and ErbB4 (Fluge et al., 2000; Mincione et al., 1998). By contrast, Nrg1 expression and localization, as well as its role in the adenohypophyseal structure, have not been fully defined for a long time. Recently, exogenous Nrg1 has been reported to modulate PRL mRNA expression and PRL secretion from the rat lactosomatotroph GH3 cells, where the ErbB3 receptor was shown to correlate with malignant transformation of prolactinomas (Vlotides et al., 2009). Thus, it is essential to elucidate (i) whether the anterior pituitary gland endogenously expresses Nrg1, (ii) whether intrahypophyseal Nrg1∕ErbB receptor can regulate PRL secretion and (iii) its relevance to the development of prolactinoma.

2.1.1. Multiple Nrg1 isoforms are expressed in the anterior pituitary and GH3 cells

Based on a domain RT-PCR method systematically used by Cote et al. (2005), multiple isoforms of Nrg1 were amplified. In our work, we first amplified a 392-bp band from the rat cortex and anterior pituitary cDNA, corresponding to the spacer domain (SP)-containing Ig-EGFα segment in type I Nrg1 **(Fig 3A)**. When primers spanning the Ig-like domain and the EGFβ domain were used, a band at 401 bp was amplified from the cortex, hypothalamus and anterior pituitary cDNA, representing type I Nrg1β. A 299-bp band was amplified from the cortex and hypothalamus, but not from the anterior pituitary cDNA, which represents the SP free Ig- EGFβ segment exclusively contained in type II Nrg1 **(Fig 3B)**. With primers specific to both the Ig domain and S1, S3 or S4, we found that S1 and S3 are present in type I Nrg1 in rat cortex, hypothalamus and anterior pituitary **(Fig 3C-E)**. When primers against the CRD-EGFα domain was employed, an 833-bp band was weakly amplified from the cortical cDNA and strongly amplified from the anterior pituitary and GH3 cells **(Fig 3G)**. Using primers against the CRD-EGFβ domain, an 842-bp band was amplified in all tested samples **(Fig 3H)**. With primers specific to CRD and S1, S3 or S4, we found that S1 and S3 are present in both forms of type III Nrg1 in rat cortex, hypothalamus, anterior pituitary and GH3 cells **(Fig 3I, J)**, whereas S4 was present in rat cortex and undetectable in the other samples tested **(Fig 1K)**. GAPDH signals were equal in each group, suggesting the equal loading of samples **(Fig 3F)**. To confirm the expression of membrane-anchored Nrg1, transmembrane segments were amplified by using primers specific to the different types of cytoplasmic domains. All samples tested showed two similar bands, in which the upper band represents the TM-cytoplasmic a tail segment and the lower band represents the TM-cytoplasmic b tail segment **(Fig 3L)**.

By contrast to previous studies depicting type II Nrg1 (GGF I-III) expression in the pituitary (Goodearl et al., 1993), other studies do not support this idea as a result of the absence or extremely low levels of GGF mRNA in rat pituitary with in situ hybridization (ISH) or RT-PCR (Marchionni et al., 1993). In line with the letter, the rat anterior pituitary expresses both type I Nrg1α∕β and type III Nrg1α∕β, whereas the GH3 cells only express type III Nrg1α∕β (**Tab 1**). This suggests that Nrg1 may have specific functions there. Furthermore, the

presence of both membrane-tethered Nrg1 and soluble Nrg1 may function in an autocrine∕ paracrine manner.

Type	sample	α	β	S1	S3	S4	ICD-a	ICD-b	ICD-c
I	AP	+	+	+	+	−	+	+	+
	GH3	−	−	−	−	−	−	−	−
II	AP	−	−	−	−	−	−	−	−
	GH3	−	−	−	−	−	−	−	−
III	AP	+	+	+	+	−	+	+	+
	GH3	+	+	+	+	−	+	+	+

Table 1. Nrg1 domain identification in the anterior pituitary (AP) and GH3 cells (GH3) based on domain RT-PCR. α, EGF-like domain α; β, EGF-like domain β; S, stalk domain; ICD, intracellular domain.
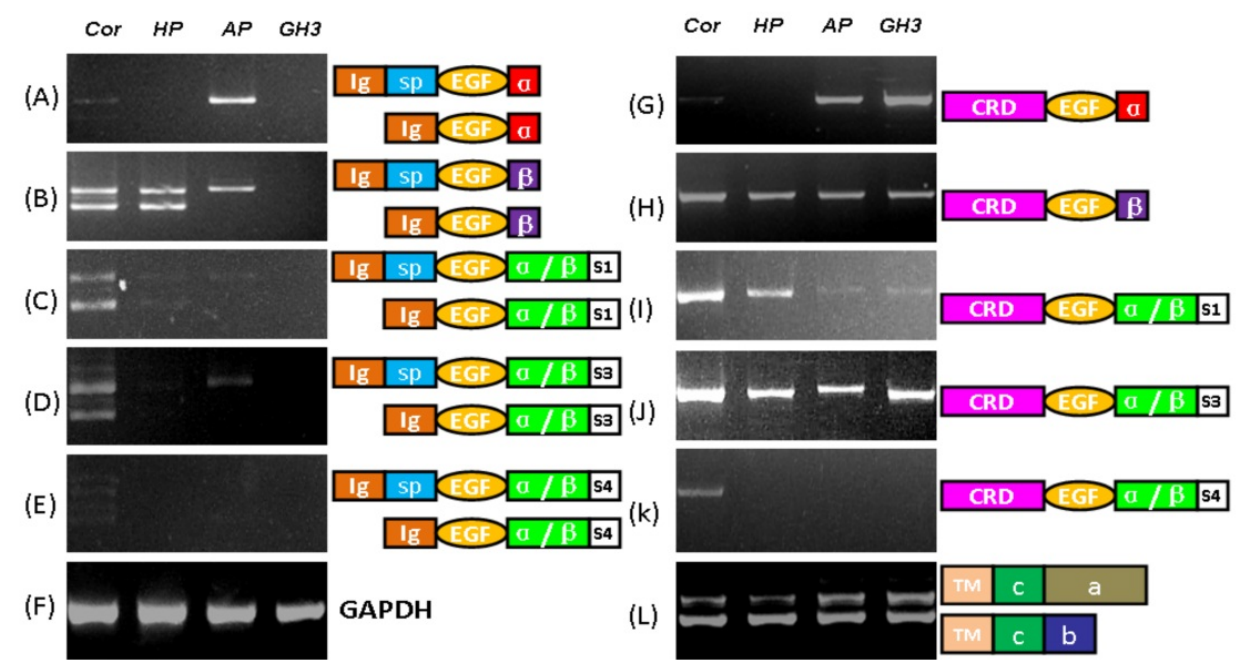

Figure 3. Domain RT-PCR for multiple Nrg1 isoforms in the rat cortex, hypothalamus, anterior pituitary and GH3 cells. Reverse transcriptase-PCR with several sets of domain specific primers amplified the expression of Nrg1 isoforms in the hypothalamus (HP) and anterior pituitary (AP) and GH3 cells (GH3). Rat cortex (Cor) serves as positive control. D-Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used to indicate the equal loading of samples. The schematic diagrams right to the RT-PCR results indicate domains that the RT-PCR products contain. α, EGF-like domain α; β, EGF-like domain β; s, stalk domain; CRD, cysteine-rich domain; ICD, intracellular domain; TM, transmembrane domain. (Zhao et al., 2011a)

At the protein level based on Western blot, the anterior pituitary give rise to a group of bands with a wide range of molecular weights as a result of alternative splicing and post-translational modification such as hyperglycosylation. In the anterior pituitary cell lysates, bands at 140, 110, 95 and 90 kDa, representing the main Nrg1 precursors, were observed, whereas, in the hypothalamus cell lysates, a weak band at 110 kDa was observed. Soluble

Nrg1s at 36 and 30 kDa were detected in the anterior pituitary, whereas only the 36 kDa Nrg1 was detected in the hypothalamus.

In the anterior pituitary, Nrg1$\alpha\beta$ was co-localized with Nrg1α, further confirming the domain RT-PCR and western blotting results and indicating that Nrg1α is the predominant intrapituitary Nrg1. However, Nrg1$\alpha\beta$ was not co-localized with S-100, GH and ACTH, which serve as markers for folliculo-stellate cells, somatotrophs and corticotrophs, respectively. Notably, neighbouring localization of Nrg1 with PRL was observed, suggesting a potential interaction between lactotrophs and Nrg1 positive cells. In addition, Nrg1 was weakly detected in partial PRL positive lactotrophs. Further immunofluoresecence investigation demonstrated Nrg1$\alpha\beta$ were co-stained with FSH or LH, both of which are markers for gonadotrophs. Significant co-localization of Nrg1$\alpha\beta$ with either FSH or LH was noted in the transition zone between pars tuberalis and pars distalis. However, in the pars distalis, such co-localization was relatively weak. This suggests that gonadotrophs in the pars tuberalis adjacent to the pars distalis are the major source of intrapituitary Nrg1α/β (**Fig 4**) (Zhao et al., 2011a).
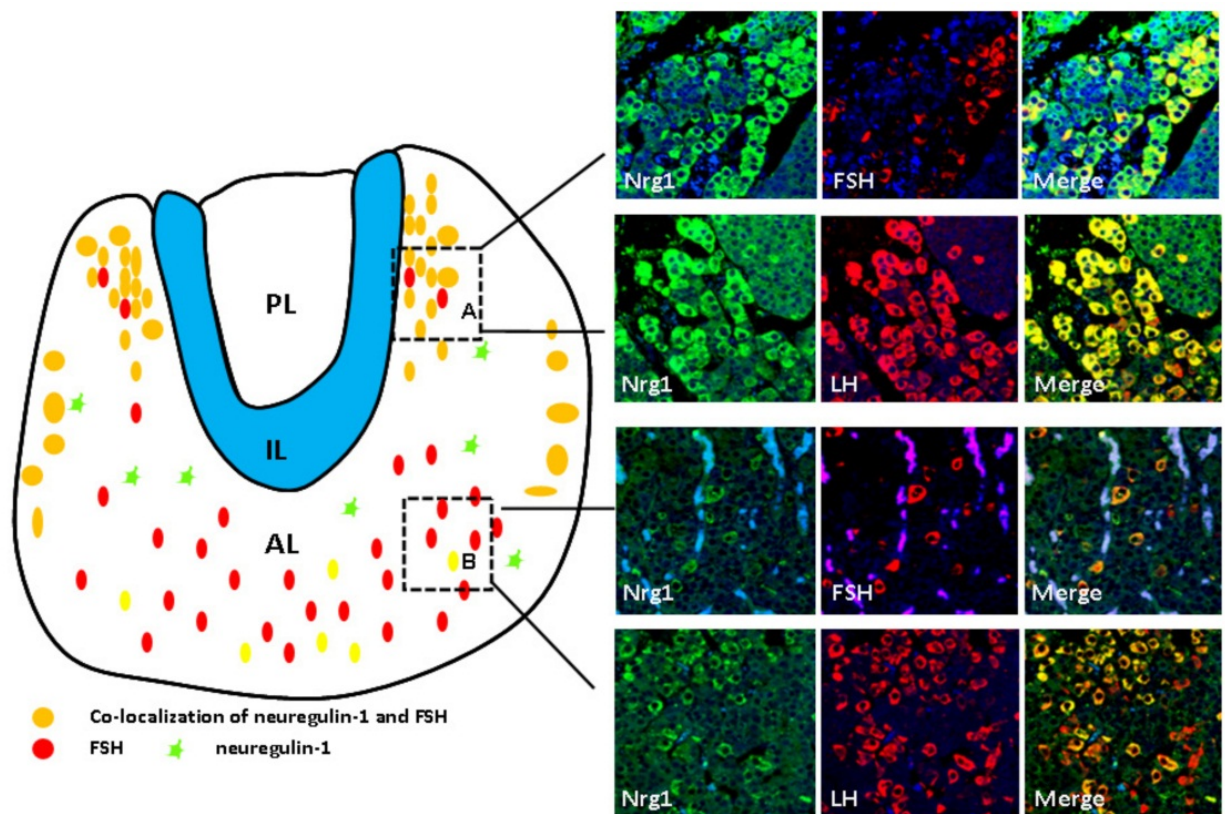

Figure 4. Gonadotrophs are the main source of Nrg1 in the anterior pituitary. PL, posterior lobe; IL, intermediate lobe; AL, anterior lobe. A, pars tuberalis; B, pars distalis. (Zhao et al., 2011a)

In addition, RT-PCR demonstrated varying expression patterns of Nrg 1 isoforms at the mRNA level during the estrous cycle. Type I Nrg1α was expressed at a low level during the proestrous (PE) phase and at a constant level in other phases. In contrast, low levels of type I Nrg1β were observed in the metestrous (ME) and diestrous (DE) phases. Type II Nrg1 was

expressed at the highest level during the E1 phase. Both type III Nrg1α and type III Nrg1β were expressed at higher levels during the E1 and E2 phases, when an estrogen surge occurred in response to hypophyseal gonadotrophic hormones. At the protein level, the expression of both 110 kDa and 95 kDa Nrg1s in the anterior pituitary were significantly higher in E1 and E2 phases. No similar expression pattern was observed in the posterior pituitary (Zhao et al., 2011c). In spite of these observations, it is still unclear whether Nrg1 functions in an sex-dependent manner or not in the anterior pituitary, and unfortunately, little is known about the sex-specific expression and function of Nrg1 in the brain (Taylor et al., 2012).

2.1.2. Localization of Nrg1 and ErbB4 receptor in the anterior pituitary of male Rhesus monkeys

In male Rhesus monkeys aged 5-7 years, the existence of Nrg1 and ErbB4 was observed, which showed a partial adjacent pattern, suggesting the existence of Nrg1/ErbB4 juxtacrine signaling in the anterior pituitary in non–human primates (See Figure 5) (Zhao et al., 2011c).

Green: Neuregulin-1
Red   : ErbB-4
Blue : DAPI
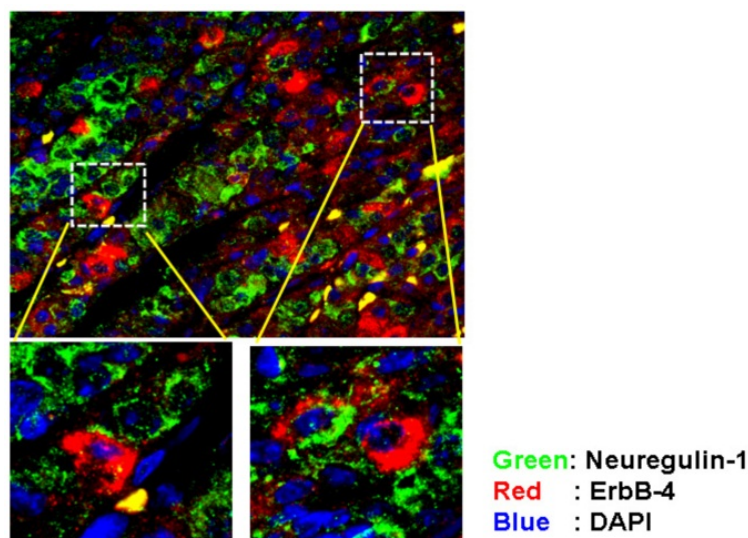
Figure 5. Nrg1 and ErbB4 receptor are expressed in the anteior pituitary of the rhesus monkey. The anterior pituitary of Rhesus monkey was subjected to immunofluorescence staining for both Nrg1 and ErbB4 (Green: Nrg1; Red: ErbB4; Blue: DAPI).

2.2. Expression and Localization of Nrg1 in GH3 cells

Exogenous Nrg1 was first shown to increase PRL mRNA expression and PRL secretion from GH3 cells by activating the ErbB3 receptor and intracellular AKT. In addition, the ErbB3 receptor has been shown to correlate with the malignant transformation of prolactinomas (Vlotides et al., 2008, 2009).

Subsequent investigation demonstrated that administration of siRNA against Nrg1 reduced the expression of multiple isoforms, including the 110-, 60-, 36-, 33-, and 30-kDa proteins, indicating that these bands potentially represented alternatively spliced Nrg1 gene

products, post-translationally modified forms, and/or the shed ectodomains from their initial precursors. Immunofluorescence staining also demonstrated the reduced expression of Nrg1α/β in GH3 cells. Nrg1 was detected, with the ErbB2 receptor partially expressed in some human prolactinoma samples. This suggests the existence of Nrg1/ErbB receptor autocrine/paracrine signaling during the development of prolactinoma.

In addition, type III Nrg1 (SMDF) is distinct from the other two types of Nrg1 and contains an extra N terminal transmembrane structure. In type III Nrg1, initial proteolysis frees the EGF-like domain from the membrane, leading to juxtacrine signalling characterised by reciprocal intercellular communication (Bao et al., 2003; Hancock et al., 2008). Further cleavage releases a shorter EGF-like domain-containing peptide, which functions in autocrine / paracrine interactions. Indeed, high levels of ErbB4 receptor and Nrg1 have also been reported to be expressed in K-ras transformed thyroid Kimol and A6 cells, where Nrg1 signals through the ErbB2/ErbB4 heterodimeric complex in an autocrine manner (Mincione et al., 1998). Although Nrg mRNA was present in both tumor and non-tumor tissue, Nrg precursor isoform immunohistochemically showed nuclear immunostaining in most human papillary carcinomas but not in normal thyroid tissue. Cytoplasmic Nrgα, β1 and β3 were also exclusively detected in papillary carcinomas (Fluge et al., 2000). Significant expression of the ErbB2, ErbB3 and ErbB4 receptors, in addition to Nrg1 isoforms, was also detected in the developing murine fetal pancreas, where they potentially contribute to islet development and regrowth (Kritzik et al., 2000). The strong expression of Nrg1 in lactosomatotroph GH3 tumor cells was in sharp contrast with that observed in the anterior pituitary, where Nrg1 was almost undetectable in the prolactotroph (Zhao et al., 2011b). Thus, overexpression of Nrg1 may play a vitally functional role in prolactinoma development.

3. Autocrine/juxtacrine modulation of prolactin (PRL) secretion via Nrg1/ErbB receptor pathway

3.1. Modulating role of Nrg1 on PRL secretion in the anterior pituitary

Previous studies have described the morphological relationship between prolactotrophs and gonadotrophs, which is characterised by conditional gap junctions, and have reported the functional roles of LH on PRL secretion in response to GnRH (Andries et al., 1995; Denef et al., 1983). More recently, Henderson et al. (2008) described GnRH-induced PRL release independent of gonadotrophins.

FSH positive gonadotrophs can form contacts with ErbB3 positive cells and ErbB3 was also shown to be localized on the prolactotroph membrane. These observations, altogether, raised the hypothesis that Nrg1 present in gonadotrophs may function by modulating lactotrophs by interacting with ErbB3 receptor on the membrane. Thus, intrapituitary gonadotrophs and prolactotrophs may partially use gap junctions to form contacts, allowing the binding of gonadotroph-derived membrane-tethered type III Nrg1 to ErbB3 receptors on the prolactotrophic membrane. In addition, both prolactotrophs and gonadotrophs may

form contacts through cell adhesion molecules widely distributed in the anterior pituitary, including L1 cell adhesion molecule and neural cell adhesion molecule (Zhao et al., 2010). These molecules may increase the interaction between Nrg1 and ErbB receptors, such as ErbB3 and ErbB4, a process that may activate a series of intracellular signals and also increase enzymatic cleavage of the PRL precursor.

In one study, type I and type III Nrg1$\alpha\beta$ as well as membrane-tethered type III Nrg1 were able to be identified using domain-specific primers-based RT-PCR in the mouse gonadotroph αT3-1 cells. Using Western blot assays with an anti-Nrg1 antibody, a cluster of proteins were observed with molecular weights in the range 30–114 kDa. Proteins at 70, 60 and 45 kDa were also detected in serum-free culture medium conditioned by αT3-1 cells. However, commonly recognized soluble Nrg1 with molecular weight ranging from 40–25 kDa were rarely observed, suggesting the precursor is the main form of Nrg1 in this gonadotroph cell line, which may be the base for juxtacrine interaction between Nrg1 and its cognate receptors. Subsequently, PRL and GH secreting GH3 cells were co-cultured with gonadtroph αT3-1 cells pretreated with siRNA against Nrg1. Administration of siRNA against mouse Nrg1 significantly reduced the staining intensities of intracellular Nrg1$\alpha\beta$, as well as their co-localization, as observed with immunofluorescence assays. Nrg1 reduction in αT3-1 cells reduced PRL expression in co-cultured GH3 cells. Co-culturing of GH3 cells with αT3-1 cells treated with siRNA against Nrg1 significantly reduced the secretion of an 18 kDa form of PRL from GH3 cells at 48 h, although it had no significant effect on the secretion of 23-kDa PRL and 22-kDa GH. This result, coupled with the observation that membrane-tethered type III Nrg1 is mainly expressed in the gonadotrophs, suggests the existence of a type III Nrg1-mediated juxtacrine mechanism that affects secretion of a subset of PRL, a process that may also occur in the normal anterior pituitary.

Cleaved full-length PRL has been reported to be a vascular function modulator mainly in the 16-kDa form (Clapp et al., 2006, 2008; Macotela et al., 2006). However, an 18- kDa form was also reported as an intermediate form of the final cleavage product in vitro (Lkhider et al., 2004; Nicoll et al., 1997). We reported that Nrg1 can modulate the release of an 18-kDa cleavage form of PRL, which is typical to GH3 cells. This process may be related to the modulation of Nrg1 on enzymes specific for PRL cleavage, such as cathepsin D and matrix metalloprotease (MMP) family members (Clapp et al., 2006, 2008; Macotela et al., 2006). Indeed, Nrg1 has been shown to promote the expression of MMP-7 and -9 in an ErbB receptor dependent manner in cancer cells (Ueno et al., 2008; Yuan et al., 2006).

3.2. Modulating role of Nrg1 on PRL secretion in rat lactosomatotroph GH3 cells

In one study, siRNA method was used to investigate the autocrine/paracrine effect of Nrg1 on PRL secretion. siRNA of Nrg1 significantly downregulated the release of a soluble form of 36 kDa Nrg1 into the conditioned culture medium. Western blotting analysis showed significantly reduced secretion of both the 23-kDa and the 18-kDa PRLs into the conditioned culture medium in response to the reduced secretion of 36 kDa Nrg1, and a reduction in

ErbB3 receptor activation was also observed. However, downregulation of Nrg1 has no effects on GH secretion. Thus, Nrg1 may modulate PRL secretion from GH3 cells in an autocrine, paracrine/juxtacrine manner (See Fig 6).
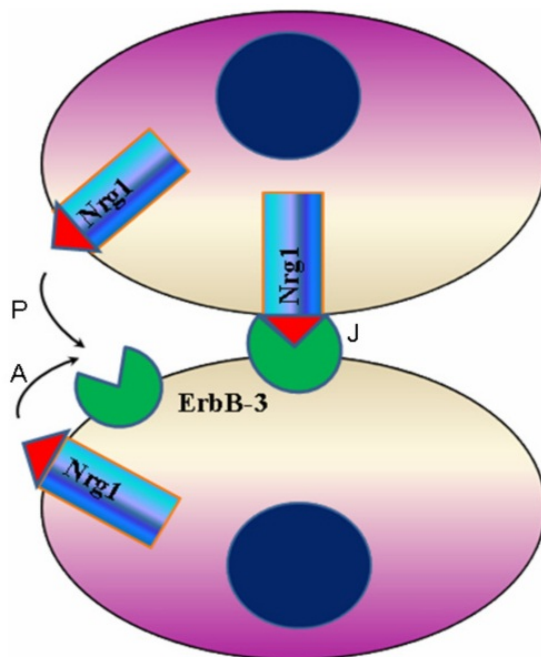
Figure 6. Schematic diagram illustrating the hypothesized model for Neuregulin-1 (Nrg1) on PRL regulation. A, autocrine; P, paracrine; J, juxtacrine.

4. Nrg1/ErbB receptor inhibition as a potential clinical management of prolactinoma

The role of Nrg1-mediated autocrine, paracrine, or juxtacrine signaling in several aspects of cancer biology suggests that it is a potential target for tumor therapy. Success with a combined therapeutic antibody and sheddase inhibitor treatment has been demonstrated in the mammary cancer MCF- 7 cell line, in which the administration of INCB7839 (a second generation sheddase inhibitor) with Lapatinib prevents the growth of ErbB2 positive BT474-SC1 human breast cancer xenografts in vivo (Witters et al., 2008). Gefitinib, a tyrosine kinase inhibitor, has also been reported to suppress Nrg1-mediated ErbB2/ErbB3 signaling to PRL (Vlotides et al., 2008, 2009). A recent investigation has also revealed that Lapatinib, an ErbB2 inhibitor, possesses additional effects in the suppression of PRL expression, and oral Lapatinib treatment triggers the shrinkage of estrogen-induced prolactinomas in rats (Fukuoka et al., 2010). Thus, the co-localization of Nrg1 with ErbB2 in partial prolactinomas suggests that inhibiting Nrg1 expression or abolishing its binding ability might also have similar effects in inhibiting Nrg1-dependent ErbB receptor activation and prolactinoma progression. In one of our studies, five human prolactinoma tissues were stained for both Nrg1 and ErbB2. All samples demonstrated positive staining for Nrg1, and co-expression of both molecules was observed in one sample (Zhao et al., 2011b). Additional prolactinoma samples should be recruited to stress further the role of Nrg1/ErbB receptor singling in

future investigations. The findings regarding the endogenous expression of Nrg1 and an Nrg1-mediated autocrine/paracrine mechanism in GH3 cells have expanded previous results and reveal Nrg1 as a potential diagnostic serological marker for prolactinoma. In addition, a therapeutic approach involving the direct functional inhibition of Nrg1 might be a viable clinical treatment for PRL-secreting pituitary tumors.

5. Conclusions and perspectives

Among a series of regulators of PRL, the emerging role of Nrg1 is rather new, but important. Overexpression of Nrg1 and its cognate receptor ErbB2, as well as their co-localization provides the promising therapeutic method to control prolactinoma and hyperprolactinemia. Such a clinical purpose can be achieved by 1) Nrg1 receptor inhibitor, such as Erlotinib, Lapatinib et al.; 2) neutralizing antibody against Nrg1 and 3) their combination. Additionally, Nrg1-mediated autocrine/paracrine mechanism in GH3 cells have expanded previous results and reveal Nrg1 as a potential serological marker not only for prolactinoma diagnosis, but for prognosis evaluation post operation. In addition, a therapeutic approach involving the direct functional inhibition of Nrg1 might be a viable clinical treatment for PRL-secreting pituitary tumors. To avoid the side effects, such as affecting the physiological function of circulating Nrg1 brought by intravenous administration of anti-Nrg1 antibody, the therapeutic hypothesis may be established by intratumoral (i.t.) injection of the therapeutic antibody in patients, whose prolactinomas are highly resistant to chemotherapy or in whom the tumor location can lead to high surgery risk. It has recently been reported that experimental i.t. injections with ErbB2 targeted gold nanoparticles (AuNPs) resulted in high tumor retention with low systemic exposure and represents an attractive delivery strategy (Chattopadhyay et al., 2012).

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Acknowledgement

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