A network map of BDNF/TRKB and BDNF/p75NTR signaling system

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Abbreviations

BDNF - Brain-Derived Neurotrophic Factor
TRK - Tropomyosin-Related Kinase
NGF - Nerve Growth Factor
NT - Neurotrophin
p75NTR - p75 Neurotrophin Receptor
PPIs - Protein-Protein Interactions
PTMs - Post-Translational Modifications
BioPAX - Biological PAthway eXchange
SBML - Systems Biology Markup Language
PSI-MI - Proteomics Standards Initiative for Molecular Interaction

Introduction

Neurotrophic factors are growth factors, which play an essential role in the development and maintenance of nervous system. These include members of the nerve growth factor (NGF) family, known as neurotrophins. Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4 (NT4/5) and neurotrophin 6 (NT-6) constitute the family of neurotrophins (Barbacid 1995). The identification of neurotrophic factors began from the search for target-derived molecules, which act on neurons and promote their survival (Lindsay 1996). BDNF is one such essential survival factor.

BDNF was first isolated and purified from pig brain (Barde et al. 1982). BDNF, encoded by the *BDNF* gene, is the second member of the neurotrophin family after NGF (Timmusk et al. 1993). BDNF, like other neurotrophins, exists as a homodimer. It is synthesized as a precursor molecule, proBDNF (32 kDa), which is cleaved to form the mature and biologically active form of BDNF (~13 kDa) (Negro et al. 1994). It is expressed throughout the central nervous system (Leibrock et al. 1989) and also in peripheral tissues including muscle, liver, pancreas, colon, duodenum, lung, kidney and bladder (Lommatzsch et al. 1999).

The dimerized BDNF binds to the tyrosine kinase receptor, tropomyosin-related kinase B (TrkB), leading to activation of various signaling modules. Trk was first identified as an oncoprotein in human tumors (Martin-Zanca et al. 1986). The Trk family of receptors includes TrkA, which binds to NGF (Kaplan et al. 1991); TrkB, which is the receptor for BDNF and NT-4 (Klein et al. 1989); and TrkC, the receptor for NT-3 (Lamballe et al. 1991). TrkB is an 821 amino acid long glycoprotein, encoded by the *NTRK2* gene. It comprises of a signal peptide followed by an extracellular domain, a transmembrane domain and a cytoplasmic region consisting of the tyrosine kinase domain (Nakagawara et al. 1995). TrkB is expressed in the central and peripheral nervous system (Allen et al. 1994). Like other neurotrophins, BDNF also binds to nerve growth factor receptor (NGFR), also known as p75 neurotrophin receptor (p75NTR), albeit with a low-affinity (Chao et al. 1986). Binding of BDNF to TrkB results in the dimerization of the receptor and activation of its cytoplasmic kinase domain (Ohira et al. 2001, Wu et al. 1996), which results in the recruitment of adaptor proteins to the receptor, which in turn leads to the activation of intracellular signaling cascades including RAS/ERK pathway, PI3K/AKT pathway, PLC/PKC pathway and NFκB pathway.

BDNF/TrkB signaling is essential for growth, differentiation and survival of neurons. It is also important for neuronal morphogenesis and synaptic plasticity (Binder and Scharfman 2004). BDNF also plays a major role in other processes such as energy metabolism (Matthews et al. 2009), behavior, learning, memory (Hall et al. 2000), pain (Pezet et al. 2002) and apoptosis (Yeiser et al. 2004). BDNF is implicated in Alzheimer's disease (Ferrer et al. 1999), Huntington's disease (Zuccato et al. 2001), epilepsy (Takahashi et al. 1999) and bipolar disorder (Neves-Pereira et al. 2002). However, despite its biological significance, molecular events induced by either BDNF/TrkB or BDNF/p75NTR interactions, were not organized into a signaling network. As a part of the ongoing NetPath project, which aims at the development of a centralized resource for human signaling pathways (Kandasamy et al. 2010, Raju et al. 2011b), we have documented molecular reactions induced by several signaling systems by systematically reviewing published reports and assembled them in the form of signaling pathways. We have previously published molecular networks of signaling induced by prolactin (Radhakrishnan et al. 2012), oncostatin M (Dey et al. 2012); corticotropin releasing hormone (Subbannayya et al. 2013) and advanced glycation end-

products (Soman et al. 2012). Similarly, as BDNF signaling pathway is of immense biomedical interest, we analyzed literature pertaining to BDNF-induced signaling events and developed a graphical network map of BDNF/TrkB and BDNF/p75NTR signaling pathways.

Methods

Literature search pertaining to BDNF was carried out using search terms 'BDNF' and 'Brain-derived neurotrophic factor' in PubMed and Google Scholar. Articles were screened for information related to BDNF signaling such as molecular interactions, post-translational modifications (PTMs), activation and inhibition processes, translocation events and transcriptional gene regulation. The molecular reactions from the articles were documented using PathBuilder, a software utility developed by our group for annotation of signaling pathways (Kandasamy et al. 2009).

We have largely followed the annotation criteria that have been previously described in the generation of RANKL (Raju et al. 2011a), Leptin (Nanjappa et al. 2011), FSH (Telikicherla et al. 2011) and TSH (Goel et al. 2012) signaling pathways. Briefly, protein-protein interactions (PPIs) were categorized as either direct or complex interactions. For every PPI, data such as the gene identifiers, species of the interacting proteins, host organism, interaction location and the PubMed identifier of the article from which the reaction was taken were gathered. A brief comment on involvement of any PTM, domain or motif for every PPI was also included. Enzyme catalysis reactions were documented in the same way as PPIs. However, we mapped PTM site and residue to the longest isoform sequence of corresponding protein as provided by RefSeq before annotating it in PathBuilder. Transport of molecules from one subcellular compartment to the other upon stimulation with BDNF was entered under translocation events. The list of proteins, which were either activated or inhibited under influence of BDNF, was also provided. We have also cataloged genes, which were up- or down-regulated upon BDNF binding to its receptor. In addition, we documented known transcriptional regulators of genes controlled by BDNF. In addition to internal review system, each pathway reaction was also reviewed by the pathway authority, who is an expert in the field (RC, co-author in this article). BDNF signaling pathway information is made publicly available through NetPath (http://www.netpath.org) . The pathway map of BDNF signaling was drawn based on the NetSlim criteria, by selecting high confidence reactions from the gathered data. The molecules in the map were arranged using information from inhibition assays, mutation studies and review articles. The pathway map was designed using the visualization tool, PathVisio (van Iersel et al. 2008).

Results and Discussion

We have developed a pathway resource for molecular reactions that occur upon stimulation of cells by BDNF. By manually reviewing 140 articles, we documented 56 molecular associations, 93 enzyme-substrate reactions, 15 translocation events and 23 activation/inhibition events, which occur upon stimulation of TrkB and p75NTR with BDNF. We identified 261 differentially regulated genes upon BDNF treatment. We have depicted these pathway reactions as a signaling network (Figure 1). The BDNF pathway is accessible at http://www.netpath.org/pathways?path_id=NetPath_76.

The pathway map is also generated based on NetSlim criteria as mentioned earlier. We have included only 72 molecules in NetSlim map out of 129 molecules described in NetPath. NetSlim pathway diagram can be accessed at http://www.netpath.org/netslim/BDNF_pathway.html. The reactions in the map are provided

with citations linked to the research articles in PubMed. The molecules are linked to their respective molecule pages in NetPath and HPRD (Goel et al. 2012) and the genes to their corresponding gene pages in NCBI.

BDNF signaling is triggered when it binds to the tyrosine kinase receptor TrkB (Klein et al. 1991). Subsequently, the tyrosine residues in the kinase domain of TrkB undergo autophosphorylation (Wu et al. 1996), which leads to the recruitment of molecules such as SHP2 (*PTPN11*) (Yamada et al. 1999), SHC (*SHC1*) and PLC-gamma (*PLCG1*) (Yamada et al. 2002). These molecules further interact with their downstream targets and lead to activation of various signaling modules such as PI3K/AKT pathway (Araki et al. 2000), RAS/ERK pathway (Ou and Gean 2006), PLC/PKC pathway (Groth and Mermelstein 2003), AMPK/ACC (Matthews et al. 2009) and NFκB pathway (Burke and Bothwell 2003). BDNF stimulation of PI3K/AKT signaling cascade is essential for proliferation, protection and survival of neuronal cells (Yamada et al. 2001). BDNF also leads to neuronal survival through ERK5/MEF pathway (Shalizi et al. 2003). Activation of PI3K/AKT further activates mTOR pathway and subsequently protein synthesis (Takei et al. 2004). BDNF through activation of ERK1/2 (*MAPK3*/*MAPK1*) plays major role in various cellular processes including growth (Sugimoto et al. 2001), differentiation (Yin et al. 2010), cell invasion (Zhang et al. 2010), calcification (Kajiya et al. 2008), protection of neuronal cells (Szatmari et al. 2007) and release of neurotransmitters (Jovanovic et al. 2000). Other than activation of PKC, PLC also leads to release of intracellular calcium and phosphorylation of CREB (*CREB1*) (Finkbeiner et al. 1997), neuronal migration (Zhao et al. 2009) and maintenance of synaptic plasticity (Groth and Mermelstein 2003). BDNF also maintains synaptic plasticity through cAMP/PKA signaling (Thakker-Varia et al. 2001). cAMP/PKA module is also involved in BDNF induced secretion of BDNF in an autocrine manner (Cheng et al. 2011). BDNF regulates axonal growth and branching through phosphorylation of catenin-beta (*CTNNB1*) (David et al. 2008).

BDNF induces neurite outgrowth through activation of JAK/STAT (Lin et al. 2006), RAC (*RAC1*) and cell division cycle 42 (*CDC42*) pathways (Miyamoto et al. 2006). It enhances oxidation of fat through AMPK-dependent inhibition of ACC (*ACACB*) (Matthews et al. 2009). It also mediates microtubule assembly through inhibition of GSK3-beta (*GSK3B*) (Namekata et al. 2012). BDNF leads to oxidative neuronal necrosis through activation of p47-PHOX (*NCF1*) and p67- PHOX (*NCF2*) (Kim et al. 2002). BDNF also regulates the surface expression of AMPA and NMDA receptors (Wu et al. 2004). Further, BDNF regulates the expression of genes leading to processes such as differentiation of dendrites and calcification of cementoblast-like cells (Kajiya et al. 2008). BDNF induces ubiquitination of TrkB receptor through TRAF6 (*TRAF6*) (Jadhav et al. 2008). TRAF6 also mediates phosphorylation of c-Jun (*JUN*) through activation of JNK, which leads to apoptosis (Yeiser et al. 2004). BDNF/p75NTR signaling through NFκB pathway leads to production of nitric oxide (Burke and Bothwell 2003). Activation of JNK3 (*MAPK10*) by BDNF leads to proteolytic cleavage of p75NTR (Kenchappa et al. 2010).

The pathway data is freely available in various data exchange formats such as PSI-MI version 2.5 (Hermjakob et al. 2004), BioPAX version 3.0 (Demir et al. 2010) and SBML version 2.1 (Hucka et al. 2003). The NetSlim version can be downloaded in .gpml, .png and .pdf formats. The pathway is also made available through WikiPathways (http://www.wikipathways.org/index.php/Pathway:WP2380) to the scientific community. We will constantly update the BDNF pathway as and when more published literature becomes available.

Conclusions

BDNF is an essential neurotrophin involved in neuroprotection and survival. BDNF signaling has significant clinical implications in many neurological disorders. We have gathered experimental data related to BDNF signaling from the published literature and integrated into a bioinformatics resource, which will facilitate future bioinformatics analyses and scientific investigations using high-throughput experiments. Freely available BDNF signaling pathway will find its way into gene set enrichment analysis software utilities. Such a development will increase the chances of identifying the role of BDNF signaling in normal and disease physiology in humans.

Conflict of interests

The author(s) declared no conflicts of interests.

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Figure Legend

Figure 1: Schematic representation of the BDNF signaling network.

The BDNF signaling pathway map contains 129 molecules for which the PPIs, PTMs, translocation and activation/inhibition reactions are experimentally proven in BDNF signaling. The major signaling modules activated by BDNF include PI3K/AKT, RAS/ERK, PLC/PKC, AMPK/ACC and JAK/STAT pathways. These signaling events in neurons lead to various context-specific processes such as growth, cell proliferation, differentiation, maintenance of synaptic plasticity, microtubule assembly, fat metabolism, protection, survival, calcification, production of nitric oxide and apoptosis. This pathway map is made publicly available at (http://www.wikipathways.org/index.php/Pathway:WP2380). A high confidence version of this map is available at http://www.netpath.org/netslim/BDNF_pathway.html.