Towards a comprehensive understanding of p75 neurotrophin receptor functions and interactions in the brain

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Abstract

The role of neurotrophins in neuronal plasticity has recently become a strong focus in neuroregeneration research field to elucidate the biological mechanisms by which these molecules modulate synapses, modify the response to injury, and alter the adaptation response. Intriguingly, the prior studies highlight the role of p75 neurotrophin receptor ($p75^{NTR}$) in various injuries and diseases such as central nervous system injuries, Alzheimer's disease and amyotrophic lateral sclerosis. More comprehensive elucidation of the mechanisms, and therapies targeting these molecular signaling networks may allow for neuronal tissue regeneration following an injury. Due to a diverse role of the $p75^{NTR}$ in biology, the body of evidence comprising its biological role is diffusely spread out over numerous fields. This review condenses the main evidence of $p75^{NTR}$ for clinical applications and presents new findings from published literature how data mining approach combined with bioinformatic analyses can be utilized to gain new hypotheses in a molecular and network level.

Key Words: bioinformatics; brain injury; data mining; neuron; neurotrophins; $p75^{NTR}$; plasticity; regeneration

Introduction

Tropomyosin receptor kinases (Trk-family) bind neurotrophins, which are growth factors in the central nervous system. neurotrophins like nerve growth factor, brain derived neurotrophic factor (BDNF), neurotophin-3 and neurotrophin-4 promote neuronal growth, surviving and plasticity (Park and Poo, 2013). They are synthesized from pro-neurotrophins into mature neurotrophins, which both can bind to Trk-receptors. Neurotrophins, and especially pro-neurotrophins, can also bind to p75 neurotrophin receptor ($p75^{NTR}$) (Park and Poo, 2013). Activation of $p75^{NTR}$ leads to the enzyme-mediated cleavage of the receptor: the extra cellular domain of $p75^{NTR}$ is cleaved by the metalloproteinase TNFα-converting enzyme (TACE, also known as ADAM17) and the transmembrane domain by γ-secretase complex (Chao, 2016). As a result, intracellular domain of $p75^{NTR}$ is released. The intracellular domain of $p75^{NTR}$ is then translocated in the nucleus where it regulates a wide range of cellular functions, including neuronal apoptosis, axonal growth and degeneration, myelination, cell proliferation and synaptic plasticity (Park and Poo, 2013; Chao, 2016). Some of these functions are activated by the neurotrophin binding to $p75^{NTR}$ but in others, $p75^{NTR}$ acts as a co-receptor associated with other neurotrophin receptors, for example Trks, sortilin, Lingo-1 and Nogo (Park and Poo, 2013).

$p75^{NTR}$ in Neurological Diseases

Many prior studies highlight the central role neurotrophins and $p75^{NTR}$ play in response to central nervous system injury such as traumatic brain injury, subarachnoid hemorrhage, intracranial hemorrhage, and ischemic stroke (Ploughman et al., 2009; Meeker and Williams, 2015; Lee et al., 2016). It is shown among others that pharmacological inhibition of $p75^{NTR}$ reduced 20% of the brain lesion volume in experimental TBI model (Sebastiani et al., 2015). Additionally, the pathobiology of $p75^{NTR}$ has notable similarities with the biology of amyloid precursor protein in Alzheimer's disease (AD) as AD patients show increased levels of $p75^{NTR}$ and proBDNF in hippocampal tissue samples (Bai et al., 2008; Fleitas et al., 2018). AD patients also have a greater proBDNF/BDNF ratio in cerebrospinal fluid, which may disrupt the delicate balance between death and survival counter-regulation mechanisms (Fleitas et al., 2018). Interestingly, cleavage of $p75^{NTR}$ seems to be linked to Alzheimer's disease as well through α-secretase, γ-secretase and TACE enzymes (Chao, 2016). In addition, amyotrophic lateral sclerosis (ALS) patients have also greater $p75^{NTR}$ ectodomain concentrations in urine when compared to healthy controls (Shepheard et al., 2014). High concentrations of $p75^{NTR}$ ectodomain have been reported to correlate with the progression of amyotrophic lateral sclerosis (Shepheard et

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al., 2014). As a result of these mechanistic studies, therapeutic and clinical interests into neurotrophins concentrate on their ability to regulate the process of neuronal and synaptic regeneration following either acute or chronic brain injury. As such, the role of neurotrophins in neuronal plasticity has recently become a strong focus of research in an attempt to elucidate the biophysiological mechanisms by which these molecules modulate synapses, modify the response to injury, and alter the adaptation response (Meeker and Williams, 2015). Following clear elucidation of these mechanisms, therapies targeting these molecular signaling networks may allow for healthy neuronal tissue regeneration following injury.

Can We See a Big Picture?

It is clear that p75^{NTR} is involved in various diseases due to its central role in response to injury, and as a result the body of evidence comprising its true biological role is diffusely spread out over numerous fields. A thorough and analytic review that would combine these prior articles and establish connections in one place may yield interesting insights by connecting the dots. There is a possibility to identify new connections, pathways, and mechanisms that were previously not identified because certain elements were only characterized in isolation from other data. Our recent study attempted to solve this specific dilemma regarding incorporating the existing current knowledge by using a large dataset approach that would increase the overall understanding of complex p75^{NTR} functions and molecular interactions (Sajanti et al., 2020). We first identified *p75^{NTR}* and its related genes using a data mining approach (**Figure 1**). A total of 2041 peer-reviewed articles related to p75^{NTR} and published in the past 20 years, comprised the large database for further querying. Using this approach, we identified 235 genes associated with *p75^{NTR}* and its role in neuronal signaling. Furthering our analyses using a machine learning educated linkage gene approach, our research group aimed to identify new gene and protein candidates that may be involved in a network with *p75^{NTR}*, but have not been widely identified or established as possible targets in the literature regarding response to cellular injury. Additionally, these 235 genes related to *p75^{NTR}* were also investigated using hierarchical genome-wide pathways. The results from these pathway analyses provide a general overview of the functions of *p75^{NTR}* in a network with its closely related genes neatly tying together a core summary of what is known about *p75^{NTR}* in the literature, while also purporting new networks and possible therapeutic targets.

The primary goal of this study was therefore to shed some light on what the existing data is revealing about the role of p75^{NTR} when considering the literature together, as well as whether there are hidden factors that are not seen until putting the whole puzzle together. The results obtained from genome-wide cluster and pathway analyses validated the current understanding of p75^{NTR} reinforcing his role in various pathways including programmed cell death, immune system modulation, signal transduction, developmental biology, gene expression regulation, and extracellular matrix organization (Lee et al., 2001; Nalbandian and Djakiew, 2006; Schecterson and Bothwell, 2010; Park and Poo, 2013). The most enriched pathways that were identified also validated the roles of previous studies, such as p75^{NTR} being highly expressed in human cancers including melanoma (Nalbandian and Djakiew, 2006; Boiko et al., 2010). Notably, this link of p75^{NTR} to cancer pathophysiology is particularly interesting given the complex interactions that cancer progression has with immune modulation, matrix remodeling, and cellular adaptation (Nalbandian and Djakiew, 2006; Boiko et al., 2010; Park and Poo, 2013). Currently, however, there are no studies suggesting a significant role of p75^{NTR} with regards to immune response modulation in cancer, nor in acute or chronic brain disease, suggesting this area may warrant further investigation. In addition, MAPK1/ERK2 and MAPK3/ERK1 pathways were identified in relation to p75^{NTR} with well documented roles in apoptosis, neuronal repair, and axonal growth (Lad and Neet, 2003). The large existing body of knowledge on MAPK further supports that these significant connections involving p75^{NTR} should be further investigated in relation to these pathways.

Further, we combined the gene network analyses with a focused subnetwork analysis using linkage genes that identified functionally related genes that were not part of the original data-mined *p75^{NTR}* identified genes. This essentially

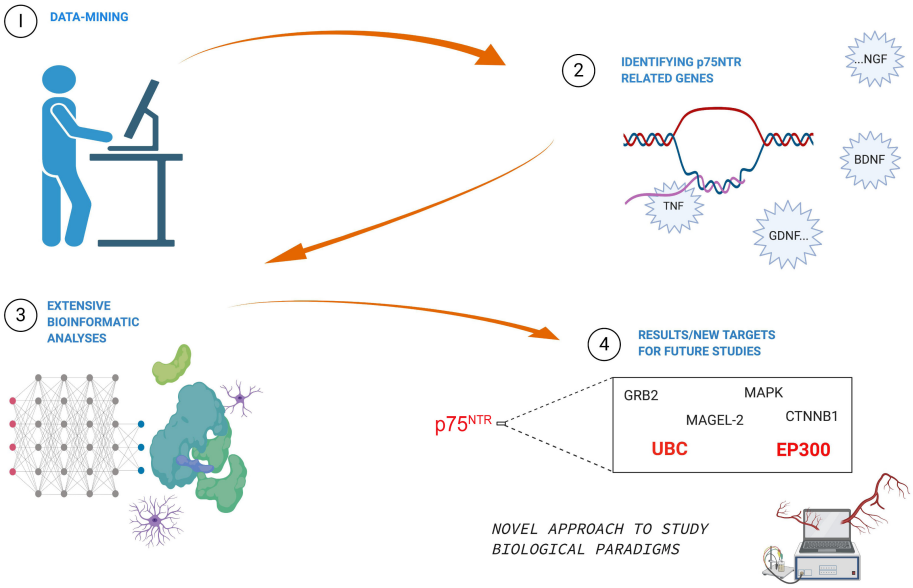

Figure 1 | Illustration of study approach and results.
The PubMed database was queried with specified search terms and subsequently was mined resulting in target genes associated with the p75 neurotrophic receptor (p75^{NTR}). Network analyses were performed using a highly reliable algorithm extracted from multiple human-curated pathways. Network analyses were followed by pathway enrichment analysis with hypergeometric testing. The approach integrated vast amount of research data that was diffusely spread out over numerous fields and identified new targets for future studies. Furthermore, the data mining approach can be applied to other studies as well – it is not restricted to only p75^{NTR} studies.

allows for novel identification of genes that are not apparent from each study separately. For example, GRB2 has previously been shown to act directly downstream of *TrkA* as a signaling adaptor protein, however, there were no previous links with *p75^{NTR}* until this analysis was performed (MacDonald et al., 2000). Supporting this novel direct link was the observation that in scrapie-infected rodent brain tissue the protein levels of BDNF, TrkB, phospho-TrkB, GRB2 and p75^{NTR} were all significantly down-regulated (Wang et al., 2016). Considering the degenerative nature of scrapie disease, it is interesting to consider the possible interplay of GRB2 and p75^{NTR} in other neurodegenerative diseases such as AD, although it arises from a different unclear etiology.

Another novel linkage gene identified was *UBC*, which is the gene for polyubiquitin precursor protein that plays a significant role in proteasome degradation (Caldeira et al., 2014). Conjugation of ubiquitins is well recognized to be highly important for protein degradation and its larger roles in cellular processes such as DNA repair, cell cycle regulation, kinase modification, and the endocytosis system, while dysfunction of this system results in various pathologies. Loss of *UBC* is associated with the pathophysiological molecular factors of AD via decreased proteasome degradation system, which may be a result of decreased recycling of malfunctioning, damaged, and old proteins (Latina et al., 2018). These connections with *p75^{NTR}* highlight its possible important role in AD's pathophysiology (Shen et al., 2019). It is important to note, however, that the role of *p75^{NTR}* in AD pathophysiology is probably only a model for which *p75^{NTR}* acts as a central protein signaler in response to various types of cellular damage.

Several other interesting genes such as *SRC*, *CTNNB1*, and *EP300* were also identified in the same linkage gene network with *p75^{NTR}*. Inhibition of SRC family kinases has previously been shown to improve cognitive function in rats after intraventricular hemorrhage, suggesting they may play a role in cellular recovery after injury (Liu et al., 2017). As a result, these observations combined with the known functions of p75^{NTR} in neuronal recovery suggest it likely plays a significant role following hemorrhagic insult as another form of pathological damage. Similarly, *CTNNB1* encodes a β-catenin protein that increases precursor form of nerve growth factor leading to p75^{NTR} activation ultimately promoting neuronal growth. Examining this relationship in rat models of intracerebral hemorrhage showed that modulation of β-catenin pathway is neuroprotective following a hemorrhagic event (Zhao et al., 2019). The role of p75^{NTR}, however, has not previously been considered in this regard. Our recently published results suggest an association between *CTNNB1* and *p75^{NTR}* thus positing there may be a substantial role for p75^{NTR} in response to hemorrhage.

It is well recognized that p75^{NTR} plays a significant role in neuronal development, and some of the linkage genes identified further shed light on this role. *MAGEL2*, which belongs to the same melanoma-associated antigen (MAGE) family as NRAGE, was also identified in our analysis. Similar to how NRAGE is involved in the p75^{NTR} mediated programmed cell death, *MAGEL2* is linked to neurodevelopmental disorders such as Prader-Willi syndrome and Schaaf-Yang syndrome, thereby suggesting significant importance of *MAGEL2* in human neuronal development. Previous animal studies have also shown that mTOR and autophagy pathways are dysregulated in *Magel2* null mice models, further highlighting that these dysregulated processes may be the underlying pathological changes that result in altered neuronal development (Crutcher et al., 2019). In our analysis, *MAGEL2* was directly linked to transcription factor *E2F1*, which was directly linked to p75^{NTR}. This suggests a role of necdin-related MAGE proteins in p75^{NTR} functions, which is supported by previous preclinical observations and suggests this may be a fruitful area for future study (Kuwako et al., 2004).

Interestingly, two of the seven subnetwork linkage genes identified, *UBC* and *EP300*, have not been extensively studied in the context of brain plasticity. These two linkage genes and their encoded proteins could be important targets for future studies to explore their involvement in patients with acute brain injury or neurodegenerative diseases. However, this underscores the benefit of the methodological approach undertaken in our study: combing a large-scale dataset through data mining we can construct an overview of the interactions that may exist between different studies but have not previously been discovered due to the inability to consistently combine all elements of literature into a new single paper in isolation. It is important to note, that this approach is limited to *in silico* analyses and results are based on mined data further analyzed by bioinformatical software-tool built on mathematical predictions and information acquired from previously published studies. Getting the most of this approach, it is necessary to perform biological validation in order to make further conclusions, but generating new hypotheses and finding new candidate molecules or genes is the potentiality of this approach.

Conclusion

Most importantly, this systematic data mining approach is not restricted to only p75^{NTR} studies, but can be applied to study other diseases, mechanisms, and networks as well. With the approach used herein, researchers may be able to provide utilizable large-scale gene and functional network libraries in regards to a research question in interest. These results not only discover new possible target genes for further investigation, but also validate previously conducted research that identified pathways, genes, and clusters which highlighted biological functions of primary hypothesis. Here the methods were applied to p75^{NTR}, and it is clear that more studies are needed to understand and validate the biological complexity of p75^{NTR} with its related genes and pathways. Furthermore, the same need is present in other fields of biomedical research suggesting that this methodology should be applied to gleam new insights from the vast amounts of pre-existing data.

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