Prospectus
HNTH-392: Honors Biology Junior Thesis Seminar II

Research Title: Role Circulation Biomarkers in Prostate Cancer Diagnosis

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ABSTRACT

SIGNIFICANCE

BACKGROUND AND LITERATURE REVIEW

Prostate cancer is a malignancy that develops in the small walnut sized gland that produces male seminal fluid. Brain-derived neurotrophic factor (BDNF) is a protein that is produced by nerve cells. Tropomyosin receptor kinase B (TrkB) works with BDNF to induce the survival of different cell populations (Our Better Health 2017).

Prostate cancer (PCa) is one the most frequently diagnosed cancer and in the top five of lethal cancers in men. The purpose of this study by Li T *et al*. (2020) was to identify molecular mechanisms underlying PCa progression and to investigate the roles of the brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) trail in PCa progression. In this study, a total of 42 patients with PCa endured radical prostatectomy from 2010 to 2015 at Union Hospital. The patients were placed into different categories based on the AJCC prostate cancer staging system and the D'Amico risk group. Additionally, the expression of- BDNF and TrkB were studied in several PCa cell lines by western blotting and qRT-PCR. There was a significant increase in expression of BNDF in PCa, which was determined by ELISA, enzyme-linked immunosorbent assay and elevated TrkB levels which are comparable with lymph node metastasis. As a result, epithelial-mesenchymal transition (EMT)- like transformation occurred where RNA causes TrkB diminution provoking reversion of EMT. In conclusion, the expression of BDNF and TrkB was undetected in nontumorigenic human prostate epithelial cell lines P69 and RWPE-1. Hence, a strategy to find a remedy for PCa can be researched with the information that BDNF/TrkB pathway is critical for PCa progression.

Tumor microenvironment plays an important factor in cancer metastasis and progression. In a study conducted by Li *et al.* (2018), the purpose was to decipher if the expression, prognostic value, and functional role of long non-coding RNA (lncRNA) brain-derived neurotrophic factor antisense (BDNF-AS) in PCa. In this study, patients with PCa had clinical tumor samples removed from them. By using qRT-PCR, the levels of endogenous BDNF-AS expression were assessed. In immortal PCa cell lines, the levels of BDNF-AS expression were also examined. Through lentiviral transduction, BDNF-AS was ectopically overexpressed in LNCaP and PC-3 cells. Both in vitro and in vivo evaluations of the roles that BDNF-AS overexpression plays in pca cell development were conducted. As a result, the short overall survival and poor prognosis of PCa patients were associated with low BDNF-AS expression. Lentivirus-driven BDNF-AS overexpression dramatically suppressed tumor growth in LNCaP and PC-3 cells by inhibiting cancer cell invasion and proliferation in culture as well as explant growth in vivo. In conclusion, A promising predictive biomarker for predicting a poor prognosis and survival in PCa patients is downregulated BDNF-AS.

Parotid gland cancer (PGC) is one of the rarest cancers in the salivary gland where researchers are having poor luck with understanding its molecular characteristics. The purpose of the experiment by Moriwaki *et al.* (2017) was to determine the role of the (BDNF)/TRKB cascade pathway in parotid gland cells (PGC) cells in the cancer-associated fibroblasts. In this study, there were a total of 23 patients, 14 men and 9 women aged between 19 and 76 years old, who all were diagnosed with PGC with no treatment but underwent surgery performed at Osaka Medical and Pharmaceutical University (OMPU) Hospital and their patient information such as tumor size, stage, recurrence, facial nerve paralysis, etc., was obtained. Immunohistochemistry

(IHC) of PGC specimens were performed using a BOND-MAX auto immunostainer. Horseradish peroxidase (HRP)-conjugated secondary antibodies and diaminobenzidine tetrahydrochloride (DAB) were used to obtain color development and lastly, to gather images, an automated quantitative pathology imaging system was used. The primary cell culture system showed an elevated level of TRKB expression suggesting that this expression may be a key prognostic marker in patients with PGC. In conclusion, these high levels were associated with aggressive features like poor prognosis which allowed scientists to believe that BDNF/TRKB pathway may be an appropriate therapeutic target for aggressive PGC with poor prognosis.

Non-small-cell lung cancer (NSCLC) makes up 80% of lung cancers. The purpose of the experiment by Ozono *et al.* (2017) was to explore the relationship between invasion/proliferation activities and tropomyosin-related kinase (Trk) expression using lung squamous cell carcinoma (SCC) cell lines to help clarify the biological significance of the Trk family (TrkA, TrkB, TrkC) in lung SCC. The sample size for this study was 99 SCC patients who underwent curative surgical resection at the Department of Surgery and Oncology at Kyusha University Hospital and the Department of Surgery at Shinkokura Hospital between January 1999 and January 2005, after being approved by the ethics committee. Paraffin tissue sections were stained by TrkA and TrkB, primary antibodies, at 4℃, followed by a 40–minute incubation with secondary antibodies. TrkC revival was done using a microwave that heated for 20 minutes with target retrieval solution (TRS) buffer. The proportion of immunoreactive cells on the entire sides were evaluated using the Allred score (AS). Out of the 99 cases of lung SCC and representative images, the high levels of TrkA, TrkB, and TrkC were seen in 33 cases, 43 cases, and 19 cases, respectively. The survival of patients with high TrkB expression was shorter than those with low TrkB expression.

In conclusion, TrkB displays poor prognosis in lung SCC, due to invasion of BDNF/TrkB signaling pathway.

BACKGROUND

Prostate cancer is a malignancy that develops in the small walnut gland known as the prostate. It is one of the most common forms of cancer. In certain patient cases, treatment does not ensure a long, healthier life (National Cancer Institute 2023).

Tropomyosin-related kinase B (TrkB) works alongside brain neurotrophic factor (BDNF) to produce cancers like breast cancer, lung cancer, esophageal cancer, etc. The purpose of this review by Serafim *et al.* (2020) was to promote the role of TrkB/BNDF axis in cancers, affect as a prognostic biomarker, and its responsibility in cancer cells. In this review, the search engine PUBMED was used to research articles on Trk's and BDNF dated during January 2014 and August 2019 where the criteria for the search were articles on the TrkB receptor and/or BDNF growth factor. The articles that were found were research on the following cancers: breast cancer, lung cancer, neuroblastoma, colorectal cancer, gallbladder cancer, renal cancer, leukemia, cervical, gallbladder, gastric, renal, ewing, sarcoma, esophageal, and head and neck cancer. In a graph from the article, it shows a comparison and contrast of the various cancers through characteristics by the high expression of the BDNF/TrkB axis. For example, invasion and migration is evident in lung cancer but absent in the testing for leukemia. In conclusion, the BDNF/TrkB axis is responsible for many different roles in the different cancers. Cell proliferation, resistance to apoptosis, resistance to anoikis, activation of phosphoinositide 3-kinase (PI3K)/akt pathway, regulation of tumor suppressor, etc. are all key drivers of BDNF/TrkB associated tumor progression. In conclusion, this gives indication to the possibility that BDNF/TrkB can be used as biomarkers.

BDNF is researched heavily by scientists in the mammalian brain. The purpose of this study by Colucci-D'Amato *et al.* (2020) was to fully depict the role of BDNF as a protective factor that is able to bestow protection against neurodegeneration. Various studies were

performed involving mice that were placed in an enriched environment. These mice were able to decrease the growth of intracranial growth, decrease proliferation, and invasion, increasing their survival rate. This enriched environment led to the synthesis of BDNF and interleukin-15 (IL-15). The synthesis of these two factors mitigate a change in the body from normal to an oncolytic environment. It was found the BDNF was responsible for affecting the synaptic function and cell survival through its synthesis with other cells and environment. Lastly, this factor was key to the production of brain tumors such as glioblastoma by foreseeing the environment and reorganizing it according to its best thriving point. It was also concluded that it does play a potent role in neuroprotection through signaling pathways that become resilient to neurodegeneration

TrkB serves as a growth factor and receptors for brain-derived neurotrophic factor BDNF. The purpose of this study by Junior *et al.* (2020) was to depict the role of TrkB/BDNF axis in several types of cancer, the use of a prognostic biomarker, and its role in cancer stem cells. During this study, a literature search was performed on PUBMED with the use of keywords like "receptor, TrkB, neoplasms, and cancer stem cell," from January 2014 to August 2019. However, this literature search was not successful in finding any sufficient evidence on the association of BDNF/TrkB in malignant disease. The research was extended to a 10-year time gap. It was concluded that BDNF/TrkB plays key roles in the many different types of cancers in regards to cell proliferation, resistance to apoptosis, resistance to anoikis, and activation of phosphoinositide 3-kinase, PI3K/Akt. BDNF/TrkB has been associated with inducing oncogenes processes such as invasion, migration, angiogenesis, and metastasis. As a result, BDNF/TrkB have been identified as a potential useful prognostic biomarker. Similarly, cancer stem cells (CSC) also produced poor prognosis biomarkers. However, studies have not proved that TrkB

has an effect on CSC's to allow them to have this scientific outcome. In the future, studies will be conducted using this information to assess the relationship between the two structures. This may lead to the construction of customized therapies.

Studies show that advances in diagnostic and therapeutic strategies in oncology have impacted the survival of cancer patients significantly. The purpose of this review by Lange *et al.* (2019) was to provide current research findings from PubMed searches between 2012 and 2019 which highlight key focus terms such as 'cognition,' 'cancer,' 'antineoplastic agents,' or 'chemotherapy.' The research data that was analyzed included imaging, clinical, pre-clinical data, and reports management strategies of cancer-cognitive impairment (CRCI). Unfortunately, reports of cognitive impairment are reported before and after treatment in cancer patients. Hormone therapies in breast and prostate seem to have lower impact on cognition. Studies regarding implementation of better assistance to cancer survivors with cognitive complaints are limited. Therefore, no pharmacological agents have been approved to reduce CRCI. Information was identified regarding predisposing factors, biological markers or brain functions that were associated with CRCI have improved. Additionally, factors such as age and genetic polymorphism of *apolipoprotein E, catechol-O-methyltransferase* and BDNF may predispose individuals to a higher risk of cognitive impairment. In conclusion, management of CRCI should be incorporated into clinical practice for patients with neurodegenerative disease because of its positive effect.

RESULTS

DISCUSSION

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