Am J Cancer Res 2025;15(9):3947-3956
www.ajcr.us /ISSN:2156-6976/ajcr0167326

Original Article

Characterization of TrkB autoantibodies reveals an agonist binding region in breast cancer

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Received July 9, 2025; Accepted August 19, 2025; Epub September 15, 2025; Published September 30, 2025

Abstract: The neurotrophin receptor TrkB has been increasingly implicated in the progression, metastasis, and drug resistance of breast cancer. While its natural ligand, brain-derived neurotrophic factor (BDNF), activates TrkB signaling to promote tumor cell proliferation and survival. In this study, we identified that certain patient-derived antibodies can function similarly as agonists, we investigated their binding region and functional activities using a reporter cell assay and a combination of epitope mapping. Our results reveal distinct binding patterns associated with agonistic activity and identify a key activation site targeted by these antibodies. These findings suggest that TrkB agonist autoantibody mediated modulation of this region may influence cancer cell signaling and providing a potential basis for further investigation into immune-related mechanisms in breast cancer.

Keywords: Autoantibody, TrkB, NTRK2, cancer, agonist antibody

Introduction

The immune system primarily functions to defend the body against pathogens and abnormal cells. However, under certain pathological conditions, it can paradoxically support cancer progression [1-3]. Within the dynamic and complex tumor microenvironment (TME), diverse immune cells play pivotal roles, including tumor-infiltrating B cells. These cells secrete antibodies, that recognize tumor-associated antigens [4, 5]. Cancer cells often present mutated, overexpressed, or aberrantly glycosylated surface antigens that may break immune tolerance and stimulate autoantibody production [6]. Some of these autoantibodies are not mere bystanders; rather, they can function as ligand mimetics [7]. The presence of autoantibodies in cancer has gained increasing attention due to their potential to modulate tumor biology. Tumor cells often display aberrantly expressed or mutated surface proteins, which can become immunogenic and elicit an autoimmune response. Currently, it seems that the impact of autoantibodies on the progression of malignancies is dependent on the context [8]. Some of them are associated with active cancer surveillance, thus preventing cancer progression, whereas others may serve as accelerators and thus promote cancer initiation and progression. The recent study showed that certain autoantibodies targeting nucleic acids can activate the cytoplasmic pattern recognition receptor cyclic GMP-AMP synthase (cGAS), thereby triggering immune signaling and inducing cGAS-dependent cytotoxic responses [9]. Among these autoantibodies, some have been shown to functionally mimic natural ligands of growth factor receptors, acting as agonists or antagonists and influencing tumor progression, proliferation, and immune evasion. It has been reported that tumor-infiltrating B cells and antibody-secreting cells (ASCs) contribute to both antitumor and pro-tumor responses [10]. Intratumoral antibodies often exhibit class switching, high somatic hypermutation rates, and autoreactivity [11, 12]. These autoantibodies show the immunity and immune response. In fact,

https://doi.org/10.62347/ECCZ9749

studies have reported autoantibodies targeting tumor-associated antigens such as HER2, p53 [13], NY-ESO-1, and MET in a substantial portion of cancer patients [8, 13-16]. Notably, some of these antibodies are associated with favorable therapeutic outcomes, while others correlate with more aggressive disease, underscoring the dual nature of humoral immunity in cancer.

Breast cancer is the most common cause of cancer-related deaths, driven by complex signaling pathways that promote tumor growth, spread, and resistance to treatment. The discovery of new therapeutic strategies and the improvement of patient outcomes are essential [17-19]. Traditionally linked to neurodevelopment, brain-derived neurotrophic factor (BDNF) and its receptor TrkB encoded by *NTRK2* have emerged as oncogenic players in this context. Breast cancer is molecularly classified by hormone receptor (HR) status, estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, reflecting its clinical heterogeneity. Emerging evidence indicates that TrkB signaling contributes to tumor growth via PI3K/AKT and MAPK/ERK, promoting survival and proliferation [20-22]. The reports also show TrkB signaling significantly increases cell migration, EMT, and resistance to anoikis, contributing to cell survival during chemotherapy [23-25]. In this study, we were guided by our previous studies [26-28], breast cancer patients have autoantibodies against TrkB, and we identified two patient-derived antibodies against TrkB that exhibit distinct functional activities. One antibody promotes breast cancer cell growth by mimicking ligand-induced signaling, while the other has inhibitory effects. We sought to investigate the binding specificity for this agonist antibody. Through gene expression analysis, cellular assays, and structural modeling, we show that these antibodies recognize epitopes within the extracellular domain of TrkB. Our findings show that TrkB autoantibodies binding region and may provide a framework for studying TrkB signaling in diseases.

Materials and methods

Antibody expression

Two antibodies (93 and 641) were isolated from breast cancer patients exhibiting high TrkB expression [27]. The variable regions were sequenced and cloned for recombinant expression. Antibody expression vectors were transiently transfected into Expi293F cells using the ExpiFectamine 293 transfection reagent. Supernatants were harvested five days post-transfection. Antibodies were purified by affinity chromatography using a HiTrap Protein A HP column (GE Healthcare, #17-0403-03) on an ÄKTA purifier 100 system (GE Healthcare). Elution was carried out with glycine buffer (pH 2.7), and the eluates were immediately neutralized using Tris buffer. Buffer exchange to PBS was performed using Ultracel 30 kDa centrifugal filters (Merck Millipore). Antibody concentrations were quantified using the Qubit Protein Assay Kit (Thermo Fisher Scientific).

Expression and purification of recombinant TrkB proteins

The coding sequences of human NTRK2 (UniProt ID: Q16620) corresponding to two fragments of the TrkB extracellular domain (amino acids 32-426 and 197-426) were amplified and cloned into a pcDNA expression vector containing a C-terminal His-tag to facilitate purification. The resulting constructs were transiently transfected into Expi293F™ cells (Thermo Fisher Scientific) using the ExpiFectamine™ 293 Transfection Kit according to the manufacturer's protocol. Five days post-transfection, culture supernatants were collected by centrifugation and filtered through a 0.22 μm membrane. His-tagged recombinant proteins were purified by immobilized metal affinity chromatography (IMAC) using HisTrap™ HP columns (Cytiva) under native conditions. Purified proteins were analyzed by SDS-PAGE and stored at -80°C until use.

Bioinformatics and structural modeling

Publicly available datasets were utilized to evaluate the expression profile and clinical significance of TrkB (NTRK2) across various cancer types. Gene expression data for NTRK2 were retrieved from the UCSC Xena platform (https://xena.ucsc.edu/public), encompassing pan-cancer analyses. Mutational landscapes of NTRK2 were assessed via the cBioPortal for Cancer Genomics (https://www.cbioportal.org/), with 32 breast cancer datasets selected to investigate mutation frequencies and patterns. Kaplan-Meier survival analyses were performed using the KMplot database (https://

kmplot.com/), focusing on breast cancer patient data linked to NTRK2 expression (probe ID: 207152_at), to determine prognostic implications. For structural analysis, 93, 641 antibody and TrkB complexes were modeled using AlphaFold3 (https://alphafoldserver.com). The resulting structures were visualized and analyzed using PyMOL (https://www.pymol.org/), enabling identification of binding epitopes contacts. To estimate the binding affinity of the 93, 641 antibody TrkB-D5 complexes, we used HADDOCK PRODIGY (https://rascar.science.uu.nl/haddock2.4/), which predicts Kd values based on the interface properties of the modeled complexes.

TrkB reporter cell assay

TrkB-CRE-bla 293 reporter cells were stimulated with either BDNF or anti-mtTrkB antibodies for 5 hours. Following incubation, adherent cells were loaded with the CCF4-AM substrate, detached using Accutase, and analyzed by flow cytometry. Upon activation, beta-lactamase expression led to cleavage of CCF4, disrupting FRET. Consequently, excitation at 405 nm yielded a blue fluorescent signal at 450 nm, accompanied by a reduction in green fluorescence at 520 nm.

Western blotting

TrkB-overexpressing 293T cells were serum-starved overnight in culture medium lacking fetal bovine serum (FBS). Cells were then stimulated with BDNF or antibodies for 10 minutes at 37°C. Following treatment, cell lysates were harvested and subjected to Western blot analysis to assess total and phosphorylated levels of AKT and ERK using antibodies purchasing from Cell Signaling Technology.

ELISA binding assay

Microwell plates (Nunc) were coated overnight at 4°C with 100 ng per well of either recombinant TrkB ectodomain or neutravidin pre-bound with biotinylated peptides. The next day, plates were blocked with PBS containing 0.1% Tween-20 and 5% non-fat milk for 1 hour at room temperature. After washing with PBS/0.1% Tween-20, wells were incubated for 1 hour at 37°C with HRP-conjugated anti-human Fc antibodies. For assays using biotinylated peptides, Streptavidin-HRP was used. Plates were then washed thoroughly, and 50 μl of ABTS substrate solution was added to each well. After a 30-minute incubation, the reaction was stopped by adding 50 μl of 2 M H_2SO_4, and absorbance was measured using a microplate reader.

Results

NTRK2 expression and clinical correlation in breast cancer

To investigate the NTRK2 in breast cancer, we analyzed its expression across different molecular subtypes. Understanding how NTRK2 varies among subtypes may provide insight into its functional significance and therapeutic potential. We analyzed NTRK2 expression in the TCGA database and the results (**Figure 1A**) show that NTRK2 is differentially expressed across breast cancer subtypes. Its expression is lowest in HER2 and LumB subtypes, indicating limited involvement in these tumor types. In contrast, Basal and LumA subtypes exhibit significantly higher NTRK2 expression, with a broader range observed in Basal tumors and a more consistent elevation in LumA. To assess the prognostic relevance of NTRK2, we investigated the mRNA expression levels of NTRK2, using the clinical Kaplan-Meier Plotter database. The results (**Figure 1B**) show that breast cancer patients with high expression of NTRK2 had significantly lower overall survival than those with low expression (hazard ratio [HR]: 1.46, P=0.04). NTRK2 expression and the survival rate of TNBC breast cancer, and found that the median survival for TNBC patients with low expression of NTRK2 is 38 mo and 24.31 mo for those with high NTRK2 expression. Taken together, these findings suggest that NTRK2 may play subtype-specific roles, particularly in basal-like and LumA tumors. Higher TrkB levels correlated with a poor overall survival rate. In addition, we explored mutational analysis (**Table 1**) revealed that several mutations, including V53M, P56L, N67S, V87D, R136H, D230N, A284T, and D386N, were frequently observed in breast cancer patients. Moreover, C607W, C623W, V673M, and V689M were also identified in intracellular domain. These mutations may contribute to abnormal TrkB function and autoantibody generation. Taken together, these findings show NTRK2 was associated with breast cancer and higher expression is associated with poor survival rate in TNBC.

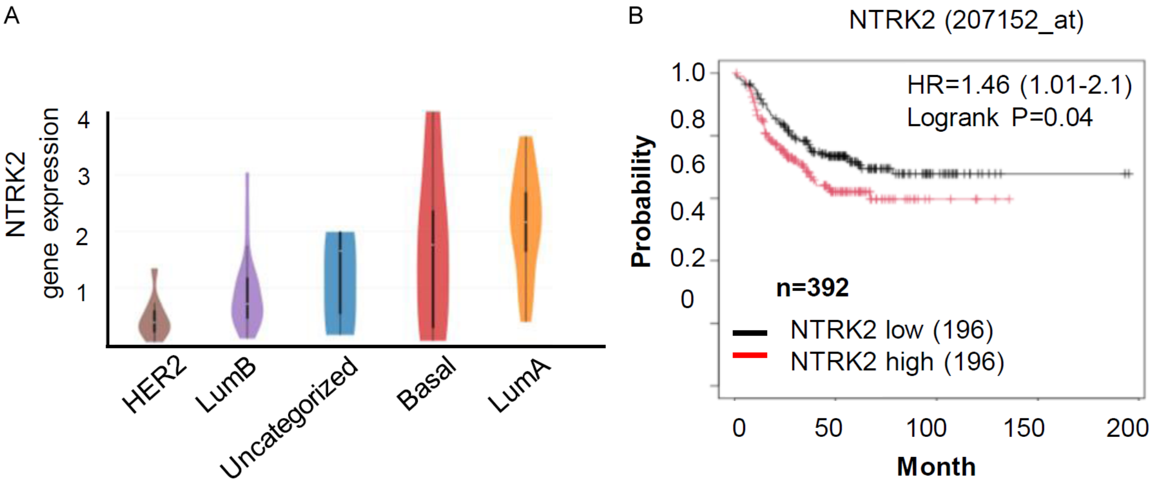


Figure 1. NTRK2 expression and survival curves in breast cancer patients. A. TCGA database Violin plot depicting NTRK2 expression across various breast cancer subtypes (LumA, LumB, HER2+, Basal). B. Kaplan-Meier analysis of NTRK2 mRNA in TNBC patient samples shows the probability of survival with high (red) or low (black) expression of NTRK2 mRNA. Hazard ratio (HR), 95% confidence intervals (CI), breast cancer patients (n=196).

Table 1. NTRK2 protein change/mutation in breast cancer patient sample retrieved data by cBioPortal for cancer genomics

Protein Change	Cancer Type	Study of Origin
V53M	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
P56L	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
N67S	Breast Invasive Ductal Carcinoma	The Metastatic Breast Cancer Project (Provisional, December 2021)
V87D	Breast Invasive Ductal Carcinoma	Breast Cancer (MSK, Cancer Cell 2018)
R136H	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
D230N	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
A284T	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
D386N	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
C607W	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
C623W	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
V673M	Breast Invasive Lobular Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)
V689M	Breast Invasive Ductal Carcinoma	Breast Invasive Carcinoma (TCGA, PanCancer Atlas67)

TrkB antibody characterization and structural prediction

Two patient-derived antibodies, 93 and 641, both of which specifically bind to the TrkB receptor [27]. The antibody 93 was found to promote breast cancer cell growth and antibody 641 was shown the inhibition of tumor growth. These findings prompting us to investigate whether these antibodies trigger distinct downstream signaling events and the binding region of TrkB. First, we used two TrkB reporter cell lines, TrkB-NFAT-CHOK1 and TrkB-CRE-293 cells to study 93 and 641 Ab signaling. The results (**Figure 2A**, **2B**) showed that antibody 93 significantly enhanced TrkB-mediated reporter activity, suggesting an agonistic function, whereas 641 did not show the signal. To further validate these observations, we conducted Western blot analysis to examine phosphorylation of key downstream signaling proteins. TrkB-overexpressed 293 cells were incubated with BDNF, antibody 93 or 641. The result shown in **Figure 2C**, antibody 93 induced pAKT and pERK phosphorylation of TrkB, resembling the activation pattern triggered by the natural ligand BDNF. In contrast, antibody 641 showed minimal induction of phosphorylation, especially in ERK. These results demonstrate that although both antibodies target TrkB, they exert opposing functional effects on receptor signaling. Antibody 93 acts as a TrkB agonist, promoting downstream activation and potentially enhancing tumor cell growth.

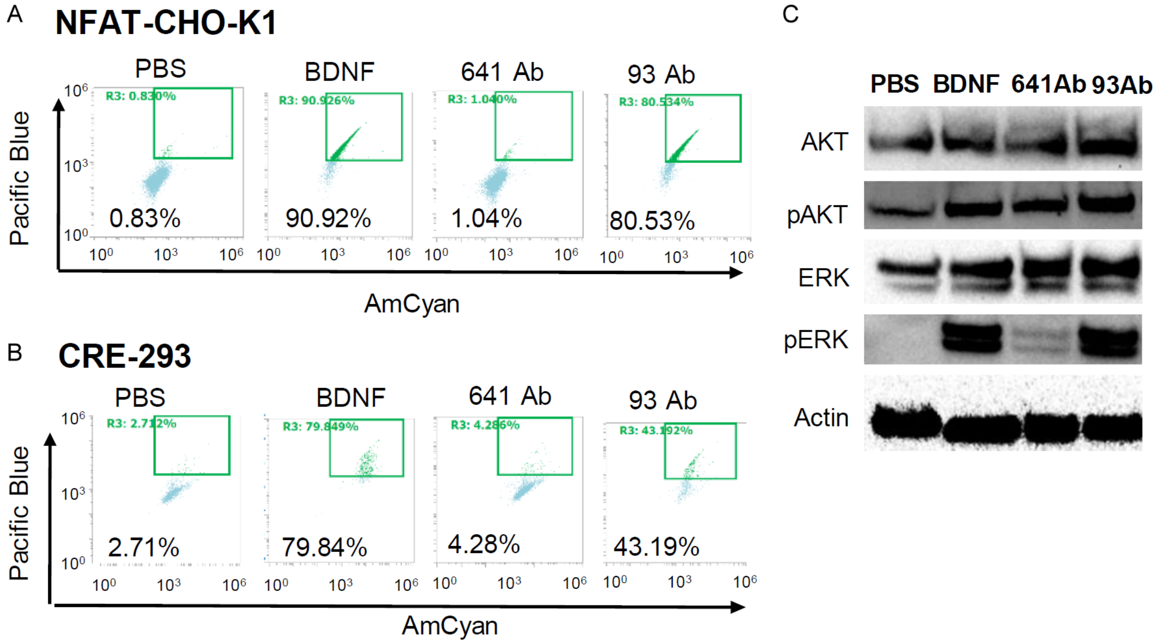


Figure 2. Characterization the TrkB antibodies 93 and 641. A. TrkB-NFAT-bla CHO-K1 reporter. B. TrkB-CRE-bla 293 reporter cell lines were used and treated with BDNF (100 ng/mL), antibody 93 or 641 at 10 μg/mL or isotype antibody for 5 h. Cells were incubated with the CCF4-AM substrate and subjected to FACS based on the FRET signal. C. TrkB-overexpressed 293 cells were incubated with BDNF, antibody 93 or 641. After a 10-min incubation at 37 °C, cell lysates were prepared and analyzed for the total and phosphorylated AKT, and ERK.

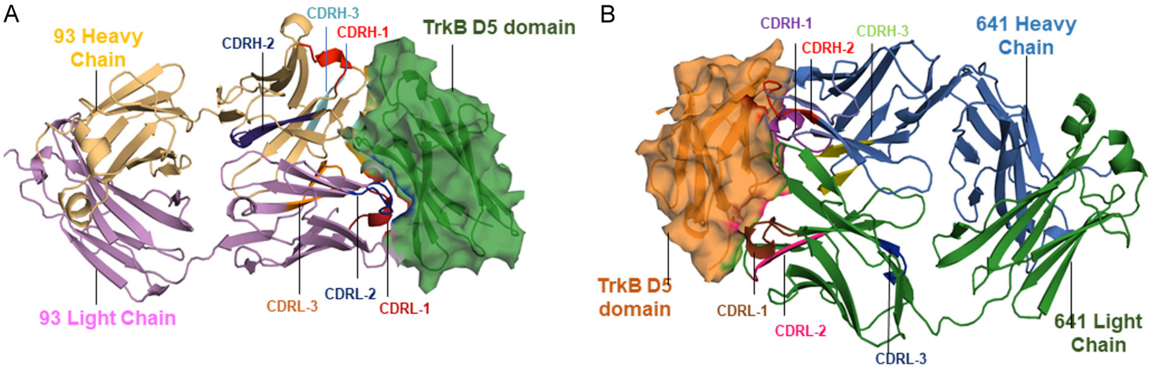
To further explore the structural basis of these functional differences, we employed AlphaFold3 modeling to predict the TrkB-antibody complexes. The predicted structures (**Figure 3A-C**) showed that 93 and 641 major interact with TrkB D5 domain via CDRH1 and CDRH2. We found that agonist 93 Ab and 641 Ab binding to different amino acid residues in D5 domain of Trkb which results in epitope overlapping. This binding orientation may contribute to its agonist activity of 93 and antagonist activity of 641. We also further measured the Kd value of both the complex. We observed that 93 Ab has better Kd value than 641 Ab to D5 domain as shown in **Table 2**.

The validation and epitope mapping of TrkB antibodies

To investigate the specific binding region of TrkB-targeting antibodies, we first expressed two recombinant fragments of the TrkB extracellular domain. One spanning amino acid 32-426 and the other 197-426. Domain-specific ELISA showed that both antibodies, 93 and 641, preferentially bind to the 197-426 fragment, indicating their epitopes is located within this region (**Figure 4A**). To further refine epitope mapping, we synthesized a panel of overlapping peptides spanning amino acids 211-420 of the TrkB extracellular domain, with each peptide overlapping by 10 amino acids to ensure comprehensive coverage of potential binding epitopes. ELISA assays were performed using antibodies 93 and 641 to determine their specific binding patterns. As shown in **Figure 4B**, **4C**, both 93 and 641 Ab demonstrated binding to TrkB peptides; however, 93 Ab displayed noticeably stronger binding to peptides number 13-15 compared to 641 Ab. In contrast, antibody 641 showed weaker and broader binding, suggesting a different or more conformationally sensitive epitope. These results identify the binding site of antibody 93 within peptides 13-15 and suggest this region may be involved in receptor activation and functional signaling.

Discussion

Breast cancer remains a leading cause of cancer-related mortality, driven by complex signaling networks that regulate tumor initiation, growth, metastasis, and therapeutic resistance [29, 30]. Among these, BDNF and its receptor TrkB encoded by *NTRK2*, which are traditionally associated with neurodevelopment but are in-



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CDR Regions (IMGT Numbering)	Interacting residues of 93 Fab region	Interacting residues of Trkb D5 domain
CDRH-1	Arg 31	Phe 305, Thr 306, Cys 302, Cys 345
CDRH-1	Asn 33	Asp 298, His 300
CDRH-2	Asp 54	Lys 333
CDRH-2	Ser 56	Lys 333
FR-3	Asn 74	His 335
CDRL-1	Arg 34	Phe 378
CDRL-1	Tyr 36	Ser 297
CDRL-2	Arg 51	Ser 297
CDRL-2	Ser 56	Trp 381

CDR Regions (IMGT Numbering)	Interacting residues of 641 Fab region	Interacting residues of Trkb D5 domain
CDRH-1	Asn 28	Thr 306
CDRH-1	Asn31	Cys 302, Cys 345, Gly 344, Phe 305
CDRH-1	Tyr 32	Glu 293
CDRH-1	Asn 35	Asp 298
CDRH-2	Asp 56	Lys 333
CDRH-3	Gln 99	Thr 296
CDRL-1	Arg 34	Ser 297, Phe 378
CDRL-1	Tyr 36	Ser 297
CDRL-2	Arg 51	Ser 297
CDRL-2	Ser 56	Gly 380

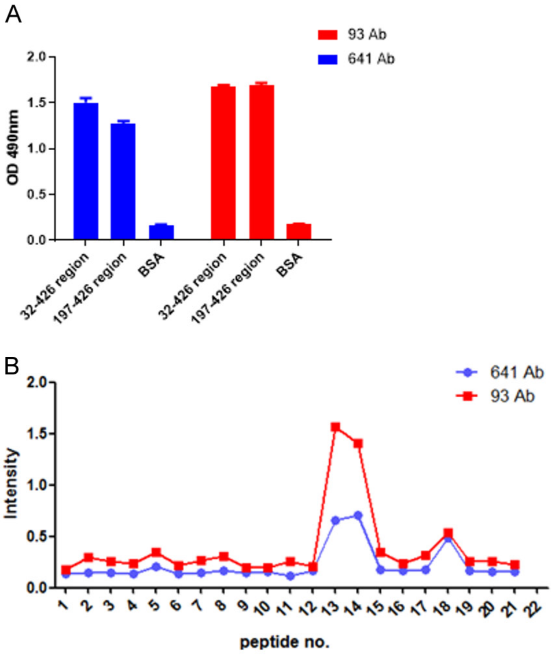
Figure 3. AlphaFold 3 predicted structural model of the anti-TrkB antibody bound to the TrkB receptor. A. Predicted complex of TrkB with the 93 antibody. TrkB is displayed as green surface, while the heavy and light chains of the 93 antibody are shown as yellow and violet cartoons, respectively. B. Predicted complex of TrkB with the 641 antibody. TrkB is shown as an orange surface, with the heavy and light chains of the 641 antibody depicted in green and blue color cartoon, respectively. C. Summary of the interaction interfaces between the Fab regions of 641 and 93 antibodies and the TrkB epitope.

Table 2. The predicted binding affinities for TrkB antibodies-TrkB D5 domain

Antibody	TrkB Receptor	K_D (nM)
93	D5 domain	0.051 nM
641	D5 domain	0.93 nM

Table presenting the predicted binding affinities (Kd values) for each antibody - TrkB interaction, as estimated using the PRODIGY web server.

creasingly implicated in oncogenesis. The immune system, while primarily a defense mechanism, can paradoxically support tumor progression under pathological conditions. Tumor cells often present mutated, overexpressed, or aberrantly glycosylated surface antigens that may break immune tolerance and stimulate autoantibody production. Some of these autoantibodies are not mere bystanders; rather, they can function as ligand mimetics. A classic example of pathogenic autoantibodies is the thyroid-stimulating autoantibody found in patients with Graves' disease. These antibodies bind to the thyroid-stimulating hormone (TSH) receptor, leading to excessive synthesis and unregulated release of thyroid hormones [31, 32]. Similarly, our previous work and that of others have shown that autoantibodies targeting TrkB can exhibit either agonistic or antagonistic activity, with direct consequences for tumor cell behavior. In this study, we were guided by our previous study and were curious that from two patient-derived antibodies that both bind to TrkB have opposing functional effects. Antibody 93 mimics BDNF by activating TrkB signaling pathways, enhancing phosphorylation of downstream effectors, and promoting breast cancer cell proliferation. In contrast, antibody 641 shows no agonistic activity and inhibits tumor cell growth, functioning more like an antagonist. These functional differences were traced to their binding orientations, as revealed



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Peptide no.	Sequence	Region
1	Blank	
2	GKSITLSCSVAGDPVPNMYW	211-230
3	AGDPVPNMYWDVGNLVSKHM	221-240
4	DVGNLVSKHMNETSHTQGSL	231-250
5	NETSHTQGSLRITNISSDDS	241-260
6	RITNISSDDSGKQISCVAEN	251-270
7	GKQISCVAENLVGEDQDSVN	261-280
8	LVGEDQDSVNLTVHFAPTIT	271-290
9	LTVHFAPTITFLESPTSDHH	281-300
10	FLESPTSDHHWCIPFTVKGN	291-310
11	WCIPFTVKGNPKPALQWFYN	301-320
12	PKPALQWFYNGAILNESKYI	311-330
13	GAILNESKYICTKIHVTNHT	321-340
14	CTKIHVTNHTEYHGCLQLDN	331-350
15	EYHGCLQLDNPTHMNNGDYT	341-360
16	PTHMNNGDYTLIAKNEYGKD	351-370
17	LIAKNEYGKDEKQISAHFMG	361-380
18	EKQISAHFMGWPGIDDGANP	371-390
19	WPGIDDGANPNYPDVIYEDY	381-400
20	NYPDVIYEDYGTAANDIGDT	391-410
21	GTAANDIGDTTNRSNEIPST	400-420

Figure 4. Epitope mapping and validation of TrkB antibody binding regions for 93 and 641 antibodies. A. Binding activity of antibodies 93 and 641 against two recombinant fragments of the TrkB extracellular domain: residues 32-426 and 197-426. BSA was used as a negative control. B. A panel of overlapping synthetic peptides covering amino acids 211-420 of the TrkB extracellular domain was synthesized, with each peptide overlapping by 10 amino acids to ensure complete coverage. For ELISA assays, biotinylated peptides were immobilized on streptavidin-coated 96-well plates. Antibodies 93 and 641 were added at a concentration of 10 μg/mL, followed by HRP-conjugated anti-human Fc antibodies (1:5000 dilution). C. Peptide sequence list. Amino acid sequences of the overlapping peptides used for epitope mapping in (B).

by AlphaFold3 modeling and peptide mapping, which showed that 93 and 641 interact with overlapping but distinct epitopes within the TrkB D5 domain. Importantly, we also identified a previously uncharacterized activation interface on TrkB. This discovery may provide a direction in which we can use engineered antibodies to selectively contact or block this activation site to inhibit oncogenic TrkB signals or, conversely, to activate TrkB in a clinical setting.

In this study, our finding highlight the clinical relevance of *NTRK2* in breast cancer. Analysis of TCGA datasets revealed that TrkB expression varies across subtypes, with particularly high expression in basal-like and luminal A tumors. In particular, higher TrkB expression correlated with poor survival in triple-negative breast cancer (TNBC) patients, suggesting that TrkB is not only a marker of aggressive disease but also a potential driver. In addition, mutational profiling uncovered recurrent alterations in the extracellular domain (e.g., P56L, D230N, A284T), which may further modulate receptor activity and antigenicity, potentially contributing to autoantibody generation in the tumor microenvironment. Importantly, it is not clear that the relationship between these mutated in TrkB and autoantibodies. The further studies will be necessary to investigate whether these TrkB mutations can function as neoantigens in patients and whether they influence the generation or binding of TrkB-targeting autoantibodies. These findings suggest that certain autoantibodies, such as antibody 93, may mimic the natural ligand BDNF and activate TrkB signaling pathways, including PI3K/AKT and MAPK/ERK as illustrated in the proposed model (**Figure 5**). In the context of cancer, activation of TrkB promotes cell survival, proliferation, migration, and invasion. Thus, agonistic autoantibodies may play an unexpected tumor-promoting role by sustaining TrkB-mediated oncogenic signaling.

In summary, we defined the epitope recognized by TrkB agonist antibody 93 and identified the

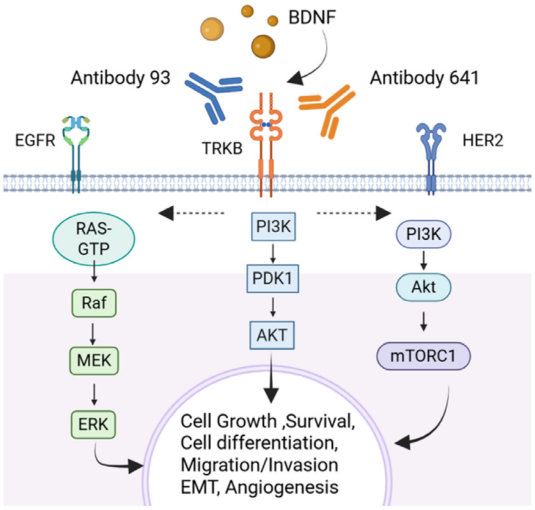

Figure 5. Proposed model of TrkB activation and downstream signaling in breast cancer. TrkB autoantibodies may activate PI3K/AKT and MAPK/ERK pathways similar to the natural ligand BDNF, thereby promoting cancer cell growth and survival. This model illustrates a potential mechanism by which agonistic autoantibodies contribute to TrkB-mediated oncogenic signaling in the tumor microenvironment.

activation site on the receptor. Future studies should aim to more precisely characterize the kinetics and signaling duration of antibody 93 and BDNF. A deeper understanding of these dynamics will be essential for elucidating their roles in downstream immune modulation and therapeutic efficacy. These findings extend our understanding of the role of TrkB autoantibodies in breast cancer and TrkB receptor function. We currently do not have direct evidence demonstrating that high TrkB expression leads to the breakdown of immune tolerance, however, previous studies have shown that overexpression of membrane receptors such as EGFR, HER2, MET, can elicit autoantibody responses in cancer patients. Similarly, autoantibodies specific to estrogen receptor also has been reported to associated with humoral immune activation. These precedents support the possibility that elevated TrkB expression, particularly in aggressive breast cancer subtypes, may trigger a similar immune response contributes to the breakdown of immune tolerance and the generation of autoantibodies could be further study. The potential role of TrkB in disrupting immune tolerance and promoting autoantibody generation warrants further investigation.

Acknowledgements

This work was supported by the China Medical University Yingcai Scholar Fund CMU110-YTY-03, and “Cancer Biology and Precision Therapeutics Center, China Medical University” from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

Disclosure of conflict of interest

None.

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