UDC 616-006.6:577.1:615.277:612.017.3 *https://doi.org/10.7124/FEEO.v36.1724*

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STRUCTURAL ORGANIZATION OF HER2-HER3 HETERODIMERS AND AN APPROACH TO THE THERAPY OF BREAST AND LUNG CANCERS

Breast cancer remains one of the most common carcinomas worldwide and is the leading cause of cancer-related death in women. A subset of these tumors – approximately 15% to 20% –are characterized by overexpression of HER2 receptor. Humanized monoclonal antibodies as therapeutic agents have significantly improved clinical outcomes targeting HER2. However, in many cases, the presence of multiple mutations such as substitutions, deletions, and insertions makes HER2 undetectable to these agents, even in HER2-HER3 complexes. ***Aim.*** In this study, we explore alternative sites on the ECD region of the HER2 and HER3 receptor proteins that may be potential epitopes for humanized monoclonal antibodies to treat these HER2-HER3-positive cancers. ***Methods.*** Analyses were performed on HER2 and HER3 sequences collected from the AlphaFold DB, EMBL-EBI UniProt, and NCBI PBD databases using NCBI BLAST, Print and ScanProsite, and PyMOL tools. ***Results.*** Comparative alignment of HER2 proteins revealed multiple deletion and/or insertion mutations where therapeutic agents bind the receptor protein. Further searching and analysis of the ECD region of both receptors revealed conserved residues and motifs on HER2 outside the pertuzumab and trastuzumab binding sites, as well as in the cysteine-rich region of HER3. ***Conclusions.*** Exploring and Understanding of these conserved residue organizations of HER2 and HER3 as a motifs may be used as alternative sites for the development of future therapeutic agents.

Keywords: ErbB receptors, heterodimerization, breast cancer, targeted therapy, humanized antybodies.

The human epidermal growth factor receptor 2 and 3 (HER2 and HER3) are a members of the epidermal growth factor receptor (ErbB) family of tyrosine kinases, which consists of four structurally related receptors. HER2 and HER3 are composed of several key regions that contribute to their function: an extracellular domain with two ligand-binding subdomains and cysteine-rich motifs crucial for receptor dimerization; a single transmembrane segment; a cytoplasmic tyrosine kinase domain; and a tyrosine-rich C-terminal tail that undergoes phosphorylation. The ErbB family receptors can form a variety of dimer pairs up to 28 different homo- or heterodimeric configurations [1]. These receptor dimers trigger multiple intracellular signaling pathways involved in fundamental biological functions, including cell proliferation, motility, adhesion, and resistance to programmed cell death [2].

The HER2 gene is located on the long arm (q22 region) of chromosome 17 [3]. The unglycosylated protein has a molecular weight of approximately 140 kDa, but glycosylation increases this to around 185 kDa. Unlike other members of the ErbB receptor family, HER2 does not possess any known ligand, which precludes it from undergoing ligand-dependent homodimerization. Instead, it preferentially forms heterodimers with other ErbB receptors or homodimerizes spontaneously when overexpressed. This inherent property makes HER2 a central amplifier of intracellular signaling, often leading to hyperactivation of pathways such as RAS/RAF/MEK/ERK/MAPK and PI3K/AKT/mTOR-both of which are key contributors to tumorigenesis in HER2-driven cancers, including breast malignancies [1].

Among the possible dimer configurations, the HER2-HER3 heterodimer is particularly significant due to its exceptional signaling potency. This complex acts as a major activator of the PI3K-AKT cascade, leveraging nearly all available HER2 and HER3 receptors, while simultaneously boosting RAS-ERK signaling [4]. Strong clinical and experimental evidence links this dimer with the aggressive behavior of HER2-positive tumors. As such, therapeutic strategies that disrupt HER2-driven signaling or circumvent associated resistance mechanisms are crucial for improving clinical outcomes [5].

The emergence of monoclonal antibodies targeting receptor tyrosine kinases has revolutionized breast cancer treatment. These biologics, primarily directed at the EGFR/HER family and VEGF receptors, have significantly improved therapeutic responses. Trastuzumab and pertuzumab remain the cornerstone monoclonal antibodies used in treating HER2-positive breast cancer.

In tumor cells exhibiting HER2 gene amplification, spontaneous dimerization and activation of HER2 are common. Additionally, HER3 can mediate HER2 activation through ligand-induced mechanisms, primarily involving heregulin. Although HER2 does not bind heregulin or any other HER ligands directly, its kinase activity is greatly enhanced upon heterodimerization, facilitating stronger and more sustained downstream signaling. HER3, despite its lack of intrinsic kinase function, becomes phosphorylated by HER2 and subsequently activates the PI3K/AKT pathway–an axis HER2 alone cannot trigger efficiently [6].

Pertuzumab and Trastuzumab, are humanized monoclonal antibody that bind specifically to domain II and IV respectively of HER2's extracellular domain (ECD) region [7]. This binding interferes with receptor dimerization and halts downstream signaling. Despite initial responsiveness in about one-third of HER2-positive breast cancer patients, resistance commonly develops over time [8]. Longitudinal studies have revealed that while one year of trastuzumab therapy significantly lowers recurrence and mortality rates, extending treatment to two years does not further enhance survival, emphasizing the challenges posed by resistance [9].

In this study, we explore alternative sites on these receptors that could be used as potential epitopes for the production of humanized monoclonal antibodies against HER2-HER3-positive cancers.

Material and methods

To collect HER2 and HER3 sequence data, AlphaFold DB, EMBL-EBI UniProt, and NCBI protein bioinformatics databases and resources were used as research material. Sequence analyses were performed using online tools such as NCBI Protein BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Conserved residues and motifs were analyzed using Print and ScanProsite tools at https://prosite.expasy.org/scanprosite/.

The study analyzed more than 10 human HER2 protein sequences (splice form, mutation, insertion or deletion) and 2 HER3 protein sequences.

Localization of motifs in the three-dimensional structure was performed using PyMOL (https://www.pymol.org/pymol).

Results and discussion

In the analysis 10 splice forms of HER2 with accession numbers of AAA75493.1 wild type, 1255 aa), NP_001369721.1 (1243 aa), NP_001369719.1 (1254 aa), NP_001369718.1 (1262 aa), NP_001369717.1 (1265 aa), NP_001369720.1 (1252 aa), NP_001369716.1 (1280 aa), NP_001369714.1 (1289 aa), NP_001369713.1 (1294 aa), NP_001369715.1 (1282 aa) were used. The BLAST search and computer alignment revealed insertions and deletions in the ECD region of HER2 protein (Fig. 1).

As shown in the figure, the ECD of HER2 receptor protein isoforms are mutated with insertion and/or deletion in the amino acid sequence. This makes the ECD region of certain isoforms inaccessible to monoclonal antibodies used as therapeutic agents.

Targeting HER2 with Therapeutic Antibodies

Pertuzumab and Trastuzumab are monoclonal antibodies that bind to domain II and IV of the HER2 receptor, which are essential for dimerization. By interfering with this regions, Pertuzumab and Trastuzumab separately block the formation of HER2-containing dimers [11, 12], including the potent HER2-HER3 heterodimers, thereby disrupting oncogenic signaling [13]. When combined the Pertuzumab with trastuzumab together–which targets a different extracellular site on HER2–this dual antibody therapy yields synergistic inhibition of HER2 activity and has demonstrated superior clinical outcomes in HER2-positive patients [10]. How-

ever, the binding sites of both of these antibodies are often subject to deletions or insertions, making them difficult for the antibody to recognize, leading to hetero- (and sometimes homo-) dimerization and persistent unnecessary signaling (Fig. 1).

A search of a wide range of HER2 and HER3 receptor databases and analysis of the data revealed that there are certain motifs and/or residues that may play a critical role in receptor dimerization (Fig. 2). In HER2, the cysteine-rich residues 266-L- to -K-333 extend beyond the pertuzumab binding site and residues 520-C- to –C-600 extend beyond the trastuzumab binding site are more stable and important for mono- or heterodimerization of the receptor. In HER3, the cysteine-rich motif 183C- to -C259 and residues 510W- to G598 are more important for dimerization, likely with HER2.

In both receptors the conserved motifs are located on domains II and IV, and the localization of these residues in the crystal structure facing the outside of the globular structure indicates that these residues in both HER2 and HER3 are important for dimerization (Fig. 3), and blocking these residues or regions could potentially block receptor dimerization and hence downstream signaling.

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AAA75493.1      1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369721.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369719.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369718.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369717.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369720.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQ---EV  77
NP_001369716.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369714.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369713.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80
NP_001369715.1  1    MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEV  80

AAA75493.1      81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369721.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369719.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369718.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369717.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369720.1  78   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  153
NP_001369716.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE[25]ILKGGVLIQ  181
NP_001369714.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369713.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156
NP_001369715.1  81   QGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTE    ILKGGVLIQ  156

AAA75493.1      157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369721.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369719.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369718.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369717.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369720.1  154  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  233
NP_001369716.1  182  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  261
NP_001369714.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369713.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236
NP_001369715.1  157  RNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCC  236

AAA75493.1      237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369721.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369719.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369718.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369717.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369720.1  234  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  313
NP_001369716.1  262  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  341
NP_001369714.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369713.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
NP_001369715.1  237  HEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCP  316
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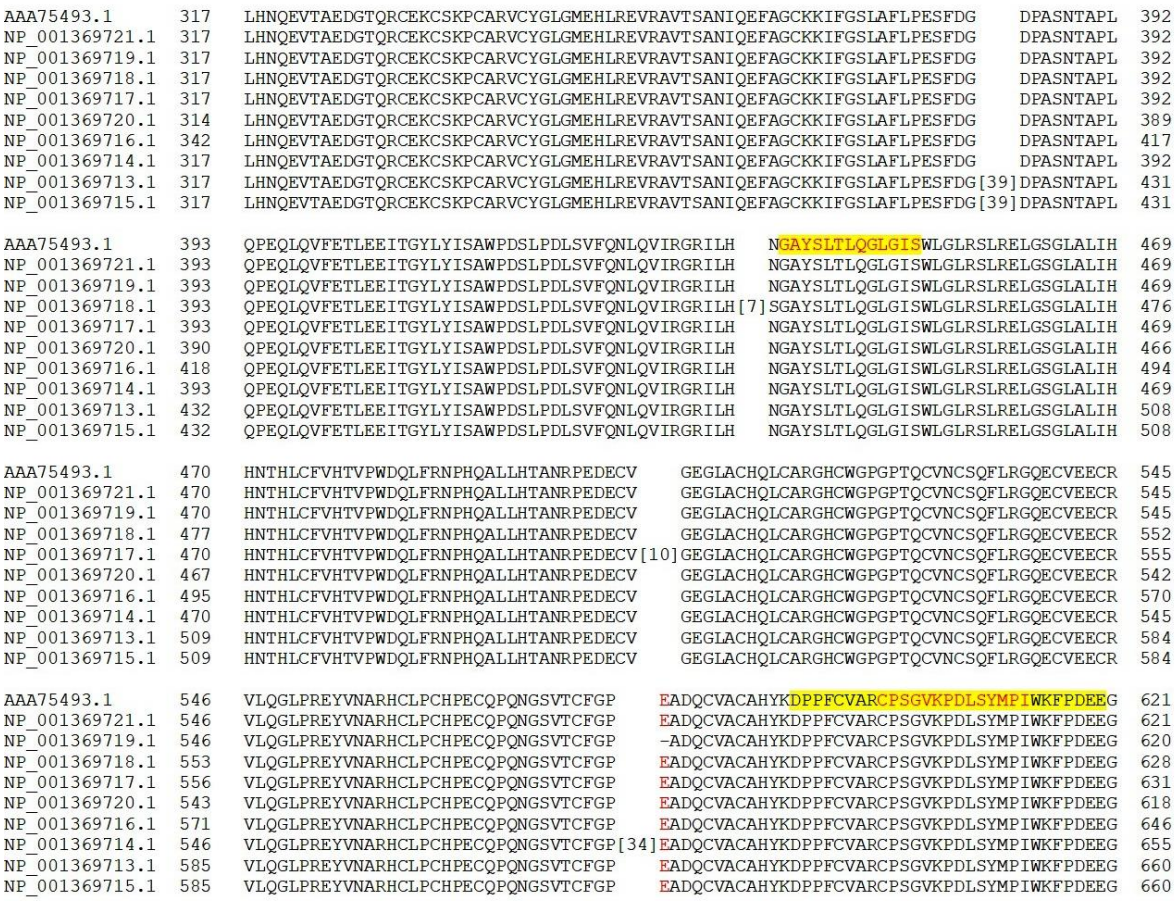

Fig. 1. The computer alignment of the ECD region of HER2 isoforms. These isoform are differed with insertion and/or deletion mutation in amino acid sequence.

Fig. 2. Conserved motifs and residues of HER2 and HER3 ECD regions. Red coloured sequences are the motifs potentially carrying certain functions. Residues with blue background important residues for functioning of ECD region and current motif. Underlined regions in HER2 are binding sites for known humanized monoclonal antibodies Pertuzumab and Trastuzumab. The remains of the transmembrane helical zone are shown in bold.

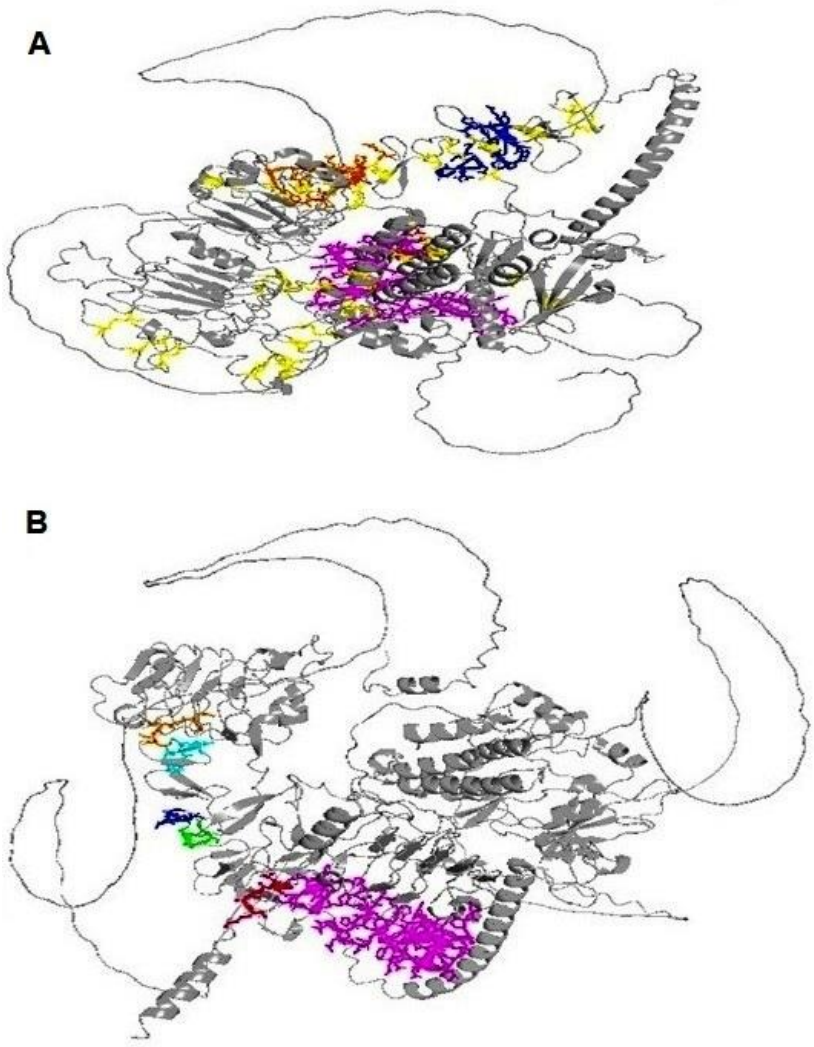

Fig. 3. The model depicts the ECD regions of HER2 (A) and HER3 (B), as well as the localization of motifs and regions of interest in both receptors. In HER2 (A) magenta 266–333, orange 520–545, and blue 576–600 residues. All Cys residues in HER2 ECD are shown in yellow. In HER3 (B) magenta 183–259, orange 515–520, green 527–532, blue 561–566, yellow 569–574, red 592–597. The figure is generated by PyMOL (https://www.pymol.org/pymol).

Conclusions

The HER2-HER3 heterodimer plays a pivotal role in the pathogenesis of both breast and lung cancers, serving as a potent driver of oncogenic signaling through the PI3K/AKT and MAPK pathways. Its unique structural and functional characteristics distinguish it from other ErbB receptor combinations, offering specific targets for therapeutic intervention. Despite the clinical success of HER2-targeted agents such as trastuzumab and pertuzumab, resistance remains a significant challenge. Understanding the conserved residue organizations of HER2 and HER3, and their role in signal transduction will facilitated the development of next-generation therapies, including bispecific antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates. Furthermore, innovative diagnostic tools are enhancing our ability to identify patients who are most likely to benefit from these targeted treatments.

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СТРУКТУРНА ОРГАНІЗАЦІЯ ГЕТЕРОДИМЕРІВ HER2-HER3 І ПІДХІД ДО ТЕРАПІЇ РАКУ МОЛОЧНОЇ ЗАЛОЗИ ТА ЛЕГЕНЬ

Рак молочної залози залишається однією з найпоширеніших карцином у світі та є основною причиною смерті від раку у жінок. Підгрупа цих пухлин – приблизно від 15% до 20% – характеризується надмірною експресією рецептора HER2. Гуманізовані моноклональні антитіла, як терапевтичні засоби, значно покращили клінічні результати, спрямовані на HER2. Однак у багатьох випадках наявність множинних мутацій, таких як заміни, делеції та інсерції, робить HER2 невиявним для цих агентів, навіть у комплексах HER2-HER3. ***Мета.*** У цьому дослідженні ми вивчаємо альтернативні ділянки в області ECD білків рецепторів HER2 та HER3, які можуть бути потенційними епітопами для гуманізованих моноклональних антитіл для лікування цих HER2-HER3-позитивних видів раку. ***Методи.*** Аналізи були проведені на послідовностях HER2 та HER3, зібраних з баз даних AlphaFold DB, EMBL-EBI UniProt та NCBI PBD, за допомогою інструментів NCBI BLAST, Print and ScanProsite та PyMOL. ***Результати.*** Порівняльне вирівнювання білків HER2 виявило множинні делеції та/або вставки мутацій, де терапевтичні агенти зв'язуються з рецепторним білком. Подальший пошук та аналіз ECD-ділянки обох рецепторів виявив консервативні залишки та мотиви на HER2 поза сайтами зв'язування пертузумабу та трастузумабу, а також у багатій на цистеїн ділянці HER3. ***Висновки.*** Дослідження та розуміння цих консервативних організацій залишків HER2 та HER3 як мотивів може бути використано як альтернативні сайти для розробки майбутніх терапевтичних агентів.

Ключові слова: рецептори ErbB, гетеродимеризація, рак молочної залози, таргетна терапія, гуманізовані антитіла.