Chapter 1

Introduction

1.1 Background

One of the key hallmarks of cancer is sustained activation of proliferative signaling pathways. One of the major groups of regulators involved in this process is the receptor tyrosine kinases (RTKs), particularly the members of the Human Epidermal Growth Factor Receptor (HER/ErbB) family (Yan et al., 2015). The HER family consists of four members: EGFR/HER1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4, all of which regulate important cellular functions including proliferation, differentiation, survival, and migration (Ouyang et al., 2016). Dysregulation of HER signaling through receptor overexpression, amplification, or mutation is frequently associated with tumor initiation and progression in various epithelial cancers.

Among the HER family members, HER2 (ErbB2) has emerged as one of the most clinically important oncogenic drivers. Unlike other HER receptors, HER2 has no known direct ligand and exists in a constitutively open conformation that favors receptor dimerization (Barros et al., 2010). This unique structural property makes HER2 the preferred heterodimerization partner for other HER family receptors, particularly with EGFR and HER3, allowing it to amplify and stabilize downstream signaling cascades (Cheng, 2024). Upon dimerization, HER2 activates several oncogenic pathways, most notably the PI3K/AKT and MAPK pathways, which promote cell proliferation, survival, invasion, and resistance to apoptosis (Hsu & Hung, 2016). Due to its potent signaling capacity, HER2 overexpression or amplification is strongly associated with aggressive tumor behavior, poor prognosis, and increased metastatic potential in multiple cancers.

HER2 overexpression is observed in various types of cancer, which has led to the development of HER2-targeted therapies such as the monoclonal antibody trastuzumab (Galogre et al., 2023; Maadi et al., 2021). Trastuzumab exerts its effects through multiple mechanisms, including promoting HER2 degradation, inducing antibody-dependent cellular cytotoxicity (ADCC), and inhibiting downstream

signaling pathways such as PI3K/AKT and MAPK. These effects collectively reduce cell proliferation and survival, thereby slowing tumor growth (Vu & Claret, 2012). In addition to monoclonal antibodies, antibody-drug conjugates (ADCs) have been developed to improve therapeutic efficacy. These ADCs are conjugated with cytotoxic agents, such as topoisomerase inhibitors (e.g., deruxtecan, exatecan) or microtubule inhibitors (e.g., MMAE), allowing for targeted killing of HER2-positive cancer cells (Xie et al., 2026). However, despite these advances, many patients eventually develop resistance to HER2-targeted therapies, highlighting the need to better understand the underlying mechanisms of resistance.

One possible contributor to this resistance is the presence of other transmembrane proteins. As HER2 itself is a transmembrane receptor, interactions with other membrane-associated proteins may influence its function. Several studies have reported that certain transmembrane glycoproteins are overexpressed in various cancers and can enhance oncogenic signaling. For example, Mucin 4 (MUC4), a transmembrane glycoprotein, has been shown to affect trastuzumab sensitivity by masking the trastuzumab-binding site on HER2, thereby contributing to the drug resistance (Mercogliano et al., 2016; Wang et al., 2024).

Another transmembrane glycoprotein of interest is the carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6). CEACAM6 is a glycosylphosphatidylinositol (GPI)-anchored protein belonging to the CEA family within the immunoglobulin superfamily (Johnson & Mahadevan, 2015). It mainly plays a role in cell adhesion and epithelial integrity. Clinically, elevated CEACAM6 expression has been associated with poor overall survival, reduced recurrence-free survival, and resistance to chemotherapy and targeted therapies (Zhao et al., 2025). Mechanistically, CEACAM6 has been shown to modulate receptor tyrosine kinase signaling, particularly the EGFR pathway. Chiang et al. (2018) demonstrated that CEACAM6 interacts with EGFR within lipid rafts, stabilizing the receptor at the cell membrane and enhancing activation of downstream MAPK and PI3K/AKT signaling. These findings suggest that CEACAM6 may function as a membrane scaffold that sustains HER-family signaling.

Given the structural and functional similarities within the HER receptor family, as well as the tendency of EGFR and HER2 to form heterodimers, it is plausible that CEACAM6 may also influence HER2 receptor stability (Sassen et al., 2008). Moreover, since HER2 receptor stability is closely linked to the sensitivity of cancer cells to HER2-targeted therapies such as trastuzumab and HER2-directed ADCs, understanding this relationship is important.

1.2 Objective

This study aims to investigate whether CEACAM6 plays role in regulating HER2 receptor stability and HER2-targeted therapy response in cancer cells

1.3 Hypothesis

It is hypothesized that CEACAM6 stabilizes the HER2 receptor, hence enhancing cellular responsiveness to HER2-targeted therapy. Conversely, the loss of CEACAM6 is expected to reduce HER2 stability and decrease responsiveness to trastuzumab.