Neutrophil Elastase and Trastuzumab Responsiveness

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Dear Editors,

There are three well-characterized mammalian elastases. The best characterized is the porcine pancreatic elastase I, which is a serine protease secreted in a zymogen form by pancreatic acinar cells. The second class of mammalian elastases is neutrophil elastase (NE), the neutral protease found in granules of human neutrophils. A third mammalian elastase is a metalloprotease, secreted by inflammatory macrophages. Of these elastases, NE is the only neutral protease that is able to degrade insoluble elastin. NE can also hydrolyze other extramatrix proteins, including fibronectin, proteoglycans, and type IV collagen. Since the invaded tissues of tumor consist mainly of these components, we could guess that cancer cells might produce NE. In order to verify this hypothesis, an in vitro experiment has been conducted using breast cancer cell lines; we first demonstrated that immunoreactive NE was produced by breast cancer cells per se [1]. Furthermore, immunoreactive NE concentration in tumor extracts is an independent prognostic factor in patients with primary breast cancer [2], suggesting that tumor NE may play an active role in tumor progression that leads to metastasis in human breast cancer.

How does the increased NE in cancer cells make the cancer more malignant? Recently, some researchers have clarified the signaling structure of NE [3, 4]; NE can split cell surface epidermal growth factor (EGF) or transforming growth factor (TGF)- α from the cell membrane. Thus, it is conceivable that the splitting EGF or TGF- α from cancer cells may send signals to their own EGF receptors, making the cancer cells more malignant, because many cancer cells have EGF receptors in abundance, including breast cancer cells.

Trastuzumab is a recombinant humanized antihuman epidermal growth factor receptor 2 (HER2) monoclonal antibody engineered from a cloned human IgG framework and the antigen-binding residues of the murine monoclonal antibody

4D5. HER2 gene encodes a 185-kDa transmembrane glycoprotein receptor (p185^{HER2}), which is amplified in 25–30% of human breast cancers. When amplified, the gene produces high levels of HER2 surface receptor expression. Patients with breast cancer whose tumors demonstrate HER2 gene amplification and protein overexpression have an aggressive form of the disease with shortened disease-free and overall survival. Recent randomized clinical trials provide evidence that trastuzumab is an active and well-tolerated option for first-line treatment of women with HER2-overexpressing metastatic breast cancer [5, 6]. However, their objective response rates were at most 20–30%; thus, there is a need for markers to identify those patients who respond to trastuzumab.

Recently, we have treated 11 patients with metastatic breast cancer with first-line weekly trastuzumab monotherapy at patient request (they declined receiving cytotoxic chemotherapy). Their tumor HER2 status determined by immunohistochemistry (IHC) was IHC3+ (interpreted according to the manufacturer's test kit protocols). The response to treatment was evaluated according to the criteria of the Japan Mammary Cancer Society. We noticed that trastuzumab-responsive tumors contained much higher concentrations of NE (table 1).

At present, the ligand that binds to HER2 is unknown. However, DiCamillo et al. [3] presented the novel finding that NE-initiated EGF signaling in lung fibroblasts is induced via cell surface EGF molecules directly released by NE in an autocrine loop fashion. Thus, in breast cancer with both HER2 overexpression and abundant NE, this proteolytic enzyme may trigger HER2 activation by releasing soluble form(s) of EGF-like molecule(s) and recruiting HER2 into signal transduction, causing these breast cancer cells to be responsive to trastuzumab. These preliminary findings suggest that NE in the primary tumor predicts responsiveness to trastuzumab treatment in patients with HER-2-overexpressing metastatic breast cancer.

Table 1. Relation between immunoreactive neutrophil elastase concentration in tumor extracts and response to trastuzumab treatment

Trastuzumab responsiveness, n				Immunoreactive neutrophil elastase μg/100 mg protein
CR	PR	NC	PD	
1	4	0	0	12.31 ± 5.22 ^a
0	0	3	3	2.36 ± 2.14

CR = Complete response; PR = partial response; NC = no change; PD = progressive disease; CR + PR = responders; NC +PD = nonresponders.

^ap < 0.001 vs. nonresponder.

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