COMPARISON OF THE AUTOANTIBODY REACTIVITY OF THE EXTRACELLULAR AND INTRACELLULAR DOMAINS OF THE TUMOR ANTIGEN HER2 IN BREAST CANCER DIAGNOSIS

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SUMMARY

The autoantibody reactivity of the extracellular (ECD) and intracellular (ICD) domain of HER2 was investigated in normal, newly diagnosed primary invasive breast cancer (PBC) and advanced breast cancer (ABC) to determine their potential to diagnose/detect recurrence in breast cancer.

Autoantibody assays specific for HER2 may have a significant role to play in breast cancer diagnosis.

INTRODUCTION

Detection of breast cancer at an early stage can increase the five year survival rate from 26% to 98%. Autoantibodies produced by the immune system against tumor markers such as HER2 (Human Epidermal growth factor Receptor-2) have the potential to be a novel diagnostic tool.

The subclass I superfamily of receptor tyrosine kinases consists of four members – HER-1, -2, -3 and-4. HER2, a 185kDa transmembrane phosphoglycoprotein, has an ECD with no known ligand and due to alterations in the 4 regions, constantly resembles the active state of the other family members, suggesting autoactivation and a high level of constitutive activity. Despite this, it still homo- or hetero-dimerizes with one of the other family members before downstream signalling occurs. Its ICD has tyrosine kinase activity and activates pathways such as PI3-K, MAPK and PLC, involved in cell growth, differentiation, motility, adhesion and apoptosis.

HER2 is overexpressed in 25-30% of invasive ductal carcinomas and 60% of ductal carcinoma in-situ[1], providing growth and survival advantage. It is associated with poor prognosis and a shorter time to relapse[2].

Previous studies have shown that HER2+ breast tumors can produce autoantibodies to both domains[3] but their predictive potential in breast cancer has not been investigated.

METHODS

Serum was used from 111 PBC and 48 normals and 107 ABC and 75 normals. Analysis showed samples had to be age-matched because autoantibody signal deteriorates with age. The HER2 status was unknown. Autoantibodies to ECD and ICD were measured using indirect ELISA with microtitre plates coated with recombinant antigen according to in-house protocols (patent pending). A small-tag-only protein acted as a negative control. Serum samples were run in triplicate and repeated 3 times. The Mann Whitney U Test was used to determine statistical significance between normal and cancer autoantibody results.

References and Acknowledgements

1. Latta, E.K., Tjan, S., Parkes, et al., (2002). Modern Pathology 15(12), 1318-25.
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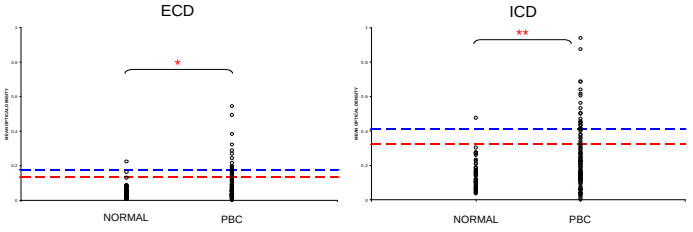
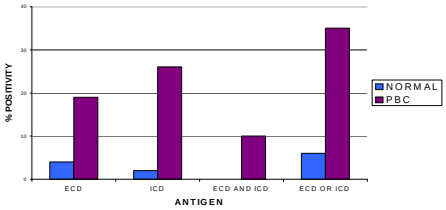
PRIMARY BREAST CANCER

Distribution of mean optical density (OD) readings, specificity and sensitivity for autoantibodies to ECD and ICD in normal vs PBC. Cut-off = mean OD of normal population + 2SD (---) or 3SD (---). PBC population significantly different from normal population against ECD (* P=0.0134) and ICD (** P=0.0013).

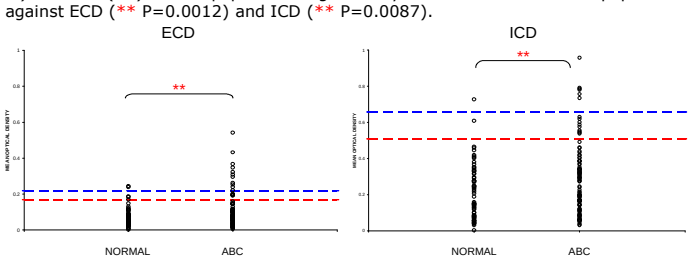


Percentage of each patient group. Positivity defined as value > than mean OD of normal population + 2SD (95% CI).

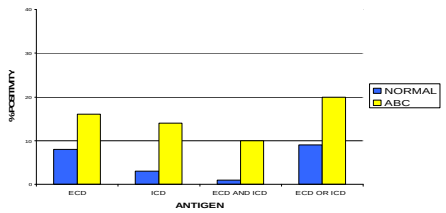


ADVANCED BREAST CANCER

Distribution of mean optical density (OD) readings, specificity and sensitivity for autoantibodies to ECD and ICD in normal vs ABC. Cut-off = mean OD of normal population + 2SD (---) or 3SD (---). ABC population significantly different from normal population against ECD (** P=0.0012) and ICD (** P=0.0087).



Percentage of each patient group. Positivity defined as value > than mean OD of normal population + 2SD (95% CI).



DISCUSSION

Autoantibodies to HER2 can be detected in nearly 40% of individuals with primary invasive breast cancer but only 20% of individuals with metastatic disease. A greater proportion of PBC patients had autoantibodies to the internal domain (26%) than the external domain (19%) and 26% of those with autoantibodies to HER2, had antibodies to BOTH domains.

Detection of autoantibodies to both domains of HER2 greatly increases their diagnostic potential.

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