GLYCOSYLATED OLEIC ACID/VITAMIN D-BINDING PROTEIN SUPPRESSES HER2 ONCOGENE EXPRESSION IN HUMAN BREAST CANCER

Marco Ruggiero1,3, Jacopo J.V. Branca1,*, David Noakes1, Massimo Gulisano2, Gabriele Morucci3, Lynda Thyer1, and Stefania Pacini2

1Department of Experimental and Clinical Biomedical Sciences, University of Firenze, 50134 Firenze, Italy; 2Department of Experimental and Clinical Medicine, University of Firenze, 50134 Firenze, Italy; 3Immuno Biotech Ltd; GY1 6NB Guernsey, Channel Islands, UK.

Corresponding Author: Jacopo J. V. Branca (jacopo.branca@libero.it)

INTRODUCTION

The healthy properties of oleic acid (OA) in breast cancer have been known for centuries [1], and recent evidences suggest that these properties are amplified by association of OA with proteins such as α-lactalbumin and lactoferrins. These proteins form OA-protein complexes that exhibit highly selective anti-tumour activity in vitro and in vivo [2]. We recently demonstrated that also a serum protein with the capability to bind OA shows anticancer effects; this is the glycosylated vitamin D-binding protein also known as Gc-protein-derived Macrophage Activating Factor or GeMAF [3]. This protein binds both OA and vitamin D, and exerts its immune-stimulating and anticancer effects through cross-talk with the vitamin D receptor [4]. Here we report a clinical observation suggesting that OA-GeMAF, that is GeMAF complexed with OA, suppresses the expression of a major oncogene involved in human breast cancer that is the human epidermal growth factor receptor 2 (HER2).

RESULTS

Amplification or overexpression of HER2 plays an important role in the development and progression of breast cancer and has become an important biomarker and target of therapy [7] since it is strongly associated with increased disease recurrence and a poor prognosis [8]. Consistent with the aggressive nature of the cancer in this patient, pre-operative biopsy on four specimens collected under ultrasound guidance, showed significant positivity for HER2 assessed by polyclonal antibody A 0485, with > 10% of positivity and a score of 2+ (Fig. 1). After 3 weeks of OA-GeMAF treatment and subsequent mastectomy, analysis of the surgical specimen showed no positivity for HER2 expression (negative, score 0, Fig. 1), thus indicating complete suppression of oncogene expression.

The expression of progesterone receptor (PgR, clone 1E2) was consistent with such a reversal of the neoplastic phenotype. PgR expression in the biopsy was low (< 1%), a finding consistent with poor differentiation and aggressiveness. However, in the surgical specimen taken after the 3 weeks of treatment with OA-GeMAF, PgR expression was significantly increased to 20% (Fig. 1). The selectivity of these effects was confirmed by study of the expression of Ki67 and estrogen receptor (30% and 90% respectively) that did not show any change following OA-GeMAF treatment (Fig. 1).

DISCUSSION

These results demonstrate that OA-GeMAF, administered subcutaneously, seems to induce a functional food product, suppressed the expression of HER2, an oncogene which plays a key role in the aetiology, invasive progression and metastasis in breast cancer. This effect was paralleled by increase of PgR expression, thus indicating that OA-GeMAF treatment induced healthy differentiation of cancer cells. We hypothesize that these multifaceted effects on the regulation of gene expression in human breast cancer are due to the peculiar association of OA with GeMAF that is an association between two molecules endowed with anticancer properties. In fact, OA has been shown to down-regulate HER2 expression in cancer cell lines [9], and we demonstrated that GeMAF inhibits human breast cancer cell proliferation and reverses their malignant phenotype [10]. We hypothesize that OA-GeMAF, but not OA or GeMAF taken singularly, interacts with the HER2 protein through hydrophobic interaction between the amino-terminal of GeMAF and the extracellular region of HER2, and between the OA-binding region of GeMAF and the plasma membrane [4]. In fact, in the stretch of aminoisocaproic acid between position 17-46 of GeMAF, and position 243-273 of HER2, there is a high density of hydrophobic aminoisocaproic acids that may favour selective binding. Whatever the case, these results indicate that the effects of OA-GeMAF in cancer are due to a multiplicity of actions that include suppression of oncogene expression.

References