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A Linkage Between Oncoprotein Erbb2 Expression and Tumor-Associated Pro-Coagulant Properties of Breast Cancer Cells is Mediated by the Pi3k/Akt Signaling Pathways

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ABSTRACT

Abbreviations: VTE: Venous Thromboembolism; TF: Tissue Factor; CSC: Cancer Stem Cell; MUC1: Transmembrane Mucin 1; HER2: Human Epidermal Growth Factor Receptor 2

Introduction

Venous thromboembolism (VTE) and cancer are strongly associated, as the local or systemic activation of blood coagulation can be produced by tumor products and favours tumor spread. The occurrence of thrombosis is often the first indicator of an underlying malignancy and patient data also demonstrates a close association between tumour progression and the development of a procoagulant profile, supporting the hypothesis that the activation of the blood coagulation system contributes to tumour aggressiveness and vice versa [1]. Although the mechanisms underlying this association are not completely understood, the blood coagulation system is now known to have an influence on a wide range of differing aspects of tumor cell biology that are associated with clotting factor dependent signaling within the tumor cell. Receptor tyrosine-protein kinase ERBB-2 (HER2 - human epidermal growth factor receptor 2) is considered as a marker of aggressiveness in the case of breast cancer in primary tumours as well as in corresponding metastases.

In particular, the overexpression of ERBB2 enhances the properties of tumour cells associated with increased cancer metastasis (invasiveness, angiogenicity, enhanced survival). The enhancement in metastatic properties was also found to occur via activation of ERBB2 receptor signaling pathways [2]. Therefore, in recent years, this protein has become an important biomarker and target of therapy for around a third of breast cancer patients [3]. It has been proposed that oncogenes (EGFR (ERBB), MET) and tumor suppressors (PTEN, TP53) may also be capable of altering the vesicular release of tissue factor (TF) from cells [4-6]. In addition, it has also been shown that the level of fibronectin, a blood clotting associated protein is significantly increased in ERBB2-overexpressing MDA-MB231 cells [7]. These reports led us to consider as a working hypothesis whether the

overexpression of ERBB2 is able to establish a procoagulant disorder in cancer.

To investigate a possible modulatory role of ERBB2 in the procoagulant status of breast cancer cells, a line of ERBB2 overexpressing human breast cancer MCF-7 cells (MCF-7 ERBB2+) and human normal mammary MCF-12a cells (MCF-12a ERBB2+) respectively, were established by transfection with an ERBB2 plasmid (Addgene, Cambridge, USA) in our lab. The effect of over expression on the synthesis and activities of selected blood coagulation proteins was determined as well as relevant signaling pathways. Meantime ERBB2 inhibitors were also used for further confirmation. It was observed that overexpression of ERBB2 was able to modulate the level of several coagulation proteins, including protein C, Factor-X and TF, and the activities of TF and thrombomodulin, as well as the rate of clotting and thrombin activity. Such effects were found to be mediated by PI3k/Akt signaling pathways since the increased these ERBB2 sensitive coagulation proteins in a way that was commensurate with the activity of p-ERK and p-Akt.

In line with this conclusion it was also observed that the expression of coagulation proteins corresponded with the level of expression of ERBB2 in three 'native' breast cancer cell lines (human enriched breast cancer stem cell (CSC), MDA-MB231 and MCF-7). The finding is the first time shown pro-tumour gene ERBB2 enable to modulate coagulation protein expression and clotting kinetics in breast cancer cells, it is via the PI3k/Akt pathways, which further supports the proposal that the state of the coagulation system in cancer is directly influenced by oncogenic transformation.

There are considerable evidences suggested that a hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate the coagulation system. During the thrombophilic state observed in cancer patients of different origins, the presence of circulating TF-bearing MVs in plasma has been used to explain why cancer patients may present a thromboembolic event distant from the location of tumour development [1]. The transmembrane mucin 1 (MUC1) oncoprotein is aberrantly overexpressed in breast cancer cells and associates with HER2. Targeting the MUC1-C oncoprotein downregulates HER2 activation [8]. Our other recent work also found MUC1 is a potential modulator for thrombin activity. Downregulation MUC1 gene significantly altered the procoagulant characteristics of breast cancer cells, along with modulation of a wide range of cell signaling pathways, including a reduction in both p-HER2/ERBB2 and PI3k/Akt activities [9]. The expression of ERBB2 also found is associated with the pro-coagulant properties of breast cancer cells which mediated by the PI3k/Akt pathways.

Taken together these findings that each of the individual oncoproteins, occurring locally within in a tumour bearing organ, may contribute to the hyper-coagulable state of cancer patients. The co-operative effects of individual oncoprotein, such as MUC1 and ERBB2, may also via their effects on signaling cascades produce and secrete procoagulant / fibrinolytic substances and inflammatory cytokines in cancer. Our work further supports the proposal that the state of the coagulation system in cancer is directly influenced by oncogenic transformation, and presents a view that different oncoproteins could co-operate each with the other and contribute to the pro-coagulant properties resulting in tumor-associated thrombosis. Such considerations could provide a vision to help further fundamental understanding of tumor-associated pro-coagulation pathophysiology. As a key tumour marker / target protein, the molecular mechanisms underlying the relationship between the pro-coagulant phenotype and ERBB2 expression merits further investigation.

References

1. Lima LG, Monteiro RQ (2013) Activation of blood coagulation in cancer: implications for tumour progression. Biosci Rep 33(5): e00064.
2. Yu D, Hung MC (2000) Overexpression of ErbB2 in cancer and ErbB2-targeting strategies. Oncogene 19(53): 6115-6121.
3. English DP, Roque DM, Santin AD (2013) HER2 expression beyond breast cancer: Therapeutic Implications for Gynecologic Malignancies. Mol Diagn Ther 17(2): 85-99.
4. Milsom CC, Yu J L, Mackman N, Micallef J, Anderson G M, et al. (2008) Tissue factor regulation by epidermal growth factor receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. Cancer Res 68(24): 10068-10076.
5. Yu J L, May L, Lhotak V, Shahrzad S, Shirasawa S, et al. (2005) Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. Blood 105(4): 1734-1741.
6. Rong Y, Post D E, Pieper R O, Durden D L, van Meir E G et al. (2005) PTEN and hypoxia regulate tissue factor expression and plasma coagulation by glioblastoma. Cancer Res 65(4): 1406-1413.
7. Jeon M, Lee J, Nam SJ, Shin I, Lee JE, et al. (2015) Induction of fibronectin by HER2 overexpression triggers adhesion and invasion of breast cancer cells. Exp Cell Res 333(1): 116-126.
8. Raina D, Uchida Y, Kharbanda A, Rajabi H, Panchamoorthy G, et al. (2014) Targeting the MUC1-C oncoprotein downregulates HER2 activation and abrogates trastuzumab resistance in breast cancer cells. Oncogene 33(26): 3422-3431.
9. Chen Y, Scully M (2022) Tumour-associated Mucin1 correlates with the procoagulant properties of cancer cells of epithelial origin. Thrombosis Update 9.

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