Breast Cancer Research and Treatment (2019) 173:751–752
https://doi.org/10.1007/s10549-018-5051-0

LETTER TO THE EDITOR

Clinical implication of E-cadherin deficiency in lobular breast cancer

Giovanni Corso[1,2] · Gabriella Pravettoni[2,3] · Viviana Galimberti[1] · Paolo Veronesi[1,2]

Received: 4 November 2018 / Accepted: 13 November 2018 / Published online: 17 November 2018

We read with high interest the recent results published by Teo and Colleagues [1].

E-cadherin plays a crucial role in the maintenance of epithelial cell polarization; the deficiency of this molecule is responsible of cancer metastasis due to the loss of the cell–cell adhesion, with a concomitant increased cell motility that causes spreading in blood and lymphatic vessels [2].

Also, E-cadherin is considered an invasion suppressor, and its deregulation is often found in advanced cases of some epithelial carcinoma [3].

The mechanisms of somatic E-cadherin inactivation are multiple and controversial. In human gastric cancer with diffuse histotype, the frequency of E-cadherin somatic mutations is between 3% and greater than 50%. Loss of heterozygosis at the *CDH1* locus (the gene that encodes of E-cadherin protein) ranges from 11 to 46%. Epigenetic silencing through *CDH1* promoter hypermethylation has been reported in frequencies that vary from 50 to 83%. Patients affected by primary gastric cancer carrying any somatic *CDH1* inactivation present a worse prognosis [4]. In lobular breast cancer, E-cadherin is well documented, due to the scarce expression in this specific subtype [5]. However, no data are available about lobular breast cancer prognosis and the frequency of somatic *CDH1* alteration status. Generally, patients with lobular breast cancer present a poor prognosis in particular in specific subtype as "mixed" and "non-classic" lobular tumors [6]. Often management of lobular breast cancer is a clinical burden, because response to primary chemotherapy is lower in terms of pathologic complete remission (0–3%) in locally advanced invasive lobular carcinoma compared to invasive ductal carcinoma, maybe due to a significantly higher expression of steroid hormone receptors in lobular breast cancer. In fact, adjuvant endocrine therapy is the preferred treatment for this specific breast cancer [7]; but endocrine treatment is not sufficient in high-risk conditions (as the presence of distant metastasis and/or lymph nodes axillary invasion). Novel targeted therapies are required.

Recently, important novel E-cadherin cross-talk mechanisms are described. In the current study, Teo and Colleagues demonstrated that growth factor signals are hyperactivated upon E-cadherin loss, regardless of somatic activating mutations in downstream effectors. In particular, the PI3K/Akt pathway is activated upon E-cadherin loss in absence of specific oncogenic mutations. Current oncologic management indicates that targeted therapies are not indicated in absence of oncogenic mutations; interestingly, the Authors demonstrated that lobular breast cancer cells in vitro are sensitive to pharmacological inhibition of Akt, using ATP competitor AZD5363 and two allosteric inhibitors, MK2206 and VIII. The strongest reduction in term of growth and survival for cancer cells was observed for MK2206 Akt inhibitor [1].

The heterodimer E-cadherin/EGFR complex is a second attractive therapeutic target. The presence of extracellular mutations of E-cadherin disturb the stability of E-cadherin/EGFR heterodimers, allowing receptor activation by the ligand and consequent activation of RhoA signalling pathway, accompanied by enhanced cell motility. Upon interaction with EGFR, E-cadherin exerts an inhibitory function modulating the kinase activity of the receptor in an adhesion-independent manner. The extracellular E-cadherin mutants, by reducing its affinity for EGFR, increase the fraction of unbound EGFR, which can thus be activated resulting in enhanced cell motility. This effect is transmitted through the activation of RhoA [8]. It remains to clarify the role of HER2 in this pathway and the effect of targeted treatment using HER2 inhibitor (i.e., Trastuzumab).

Mateus et al. demonstrated in gastric cancer cells that upon treatment of E-cadherin extracellular mutant cells with the EGFR inhibitor (Tyrphostin AG 1478), the increase of

✉ Giovanni Corso
giovanni.corso@ieo.it

[1] Division of Breast Surgery, European Institute of Oncology IRCCS, via G. Ripamonti 435, 20141 Milan, Italy

[2] Department of Oncology and Onco-Hematology, Faculty of Medicine, University of Milan, Milan, Italy

[3] Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology, Milan, Italy

RhoA activation is abrogated and accompanied by decreased migratory behavior [9].

There are some studies in vitro demonstrating that E-cadherin is not only the "hallmark" to distinguish breast cancer with different histotypes (i.e., lobular versus ductal carcinoma), but also it represents more than an attractive argument for novel targeted therapies, also in absence of oncogenic mutations.

Acknowledgements This manuscript was supported by the Italian Ministry of Health (Project Code: GR-2016-02361655. "Understanding how CDH1 germline mutations affect hereditary lobular breast cancer").

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Informed consent Not necessary for this study.

References

1. Teo K, Gómez-Cuadrado L, Tenhagen M, Byron A, Rätze M, van Amersfoort M et al (2018) E-cadherin loss induces targetable autocrine activation of growth factor signalling in lobular breast cancer. Sci Rep 8(1):15454. https://doi.org/10.1038/s41598-018-33525-5
2. Christofori G, Semb H (1999) The role of the cell-adhesion molecule E-cadherin as a tumour-suppressor gene. Trends Biochem Sci 24(2):73–76
3. Takeichi M (1993) Cadherins in cancer: implications for invasion and metastasis. Curr Opin Cell Biol 5(5):806–811
4. Corso G, Carvalho J, Marrelli D, Vindigni C, Carvalho B, Seruca R et al (2013) Somatic mutations and deletions of the E-cadherin gene predict poor survival of patients with gastric cancer. J Clin Oncol 31(7):868–875. https://doi.org/10.1200/JCO.2012.44.4612
5. Berx G, Cleton-Jansen AM, Nollet F, de Leeuw WJ, van de Vijver M, Cornelisse C et al (1995) E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. EMBO J 14(24):6107–6115
6. Iorfida M, Maiorano E, Orvieto E, Maisonneuve P, Bottiglieri L, Rotmensz N et al (2012) Invasive lobular breast cancer: subtypes and outcome. Breast Cancer Res Treat 133(2):713–723. https://doi.org/10.1007/s10549-012-2002-z
7. Colleoni M, Russo L, Dellapasqua S (2011) Adjuvant therapies for special types of breast cancer. Breast 20(Suppl 3):S153–S157. https://doi.org/10.1016/S0960-9776(11)70315-0
8. Mateus AR, Simões-Correia J, Figueiredo J, Heindl S, Alves CC, Suriano G et al (2009) E-cadherin mutations and cell motility: a genotype-phenotype correlation. Exp Cell Res 315(8):1393–1402. https://doi.org/10.1016/j.yexcr.2009.02.020
9. Mateus AR, Seruca R, Machado JC, Keller G, Oliveira MJ, Suriano G et al (2007) EGFR regulates RhoA-GTP dependent cell motility in E-cadherin mutant cells. Hum Mol Genet 16(13):1639–1647