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Epithelial-mesenchymal transition and its regulators are major targets of triple-negative breast cancer

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Triple negative breast cancers (TNBCs) represent a distinct subtype of breast cancers that are associated with early recurrence and an aggressive metastatic progression of the disease and consequently poor outcome. Recently, it was reported that c-Met growth factor receptor is overexpressed in around 52% of TNBCs. On the other hand, it is known that c-Met signaling pathways initiate the epithelial–mesenchymal transition (EMT) phenomenon, which is described as a crucial event during cancer metastasis. Herein, we discuss the association between c-Met and EMT in the TNBC group.

Keywords: EMT, c-Met, IGF-1, Leptin, triple negative, breast cancer, metastasis & cancer mortality

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Triple-negative breast cancers (TNBCs), a subgroup of breast cancer, are characterized by the absence of estrogen and progesterone receptors and the lack of ErbB-2 overexpression, which represent 10–20% of all breast cancer cases and are associated with the most aggressive metastatic behavior. Presently, no efficient targeted therapy is available for the treatment of patients with TNBCs. Based on this fact, Zagouri et al.[1] has recently investigated the expression of c-Met growth factor in a cohort of 170 TNBC tissues. They reported that c-Met is overexpressed in 52% of these cancer samples. In addition, their data showed clearly that recurrence-free and overall survival is shorter in TNBC patients with high tumor c-Met expression than in patients with low tumor c-Met expression. This statement is consistent with several previous investigations regarding c-Met expression in breast cancer.[2-4] Therefore, these data suggest that the c-Met pathway could be exploited as a significant target for TNBCs. We want to congratulate the authors for their contribution to the literature on this very important topic of breast cancer.

On the other hand, cancer progression and subsequent invasion of cancer cells into the surrounding stroma marks a vital step toward metastases, which is the major cause of cancer mortality. Cancer metastasis is governed by epithelial–mesenchymal transition (EMT) phenomena, which is a distinctive morphological change whereby the epithelial cancer cells switch from a well-differentiated phenotype to an invasive mesenchymal (fibroblast) one.[5] In addition, numerous studies including ours have shown that several receptor tyrosine kinases (RTKs), such as epithelial growth factor-receptors (EGF-Rs), c-Met, insulin-like growth factor-1 receptor (IGF-1R), and non-RTK c-Src activations, induce EMT and consequently cancer progression through PI3k/Akt/mTOR and RAF/MEK/ERK1/2 pathways as well as the phosphorylation and transcriptional activation of β-catenin.[5-9] In parallel, recently it has been demonstrated that leptin and its receptor (OB-R) initiate EMT and consequently cancer invasion and metastasis of breast cancer cells via PI3k/Akt signaling pathway and β-catenin.[10] Leptin can also activate the MAPK pathway by inducing ERK1 and ERK2 phosphorylation, which could lead to EMT initiation and cancer progression.[11] On the other hand, it was reported that Leptin induce cell growth of breast cancer cells through activation of Jak/STAT3 and can mediate angiogenesis by inducing the expression of

VEGF.[12] In addition, leptin can provoke transactivation of ErbB-2, and interacts in TNBC cells with IGF-1 to transactivate the EGF-R1, thus promoting invasion and migration probably by EMT initiation.[12-14] In this context, it is evident that cancer progression and invasion of human carcinomas including TNBC occurs through the "crosstalk" or cross-signaling pathways between growth factor receptors particularly OB-R, IGF-1R, and c-Met via EMT initiation.

Earlier studies reported that leptin and its receptor as well as IGF-1R are overexpressed in 86%, 92%, and 41.9% of TNBCs, respectively.[15,16] Meanwhile, it was demonstrated that physical activities and fasting and/or dietary restriction (DR) greatly reduce secretion of both leptin and IGF-1 in the body.[17-20] Thus, we believe that physical activities and fasting and/or DR could be employed to reduce cancer mortality in the TNBC's group through the inhibition of EMT initiation.

In conclusion, it is clear that c-Met, leptin, and IGF-1 play important roles in the initiation of TNBCs invasion and metastasis, and therefore cancer mortality, through EMT progression. Thus, we totally agree with Zagouri et al.[1] that c-Met represent one of the major important targets in the treatment of TNBCs. Meanwhile, we think that leptin and IGF-1 can be considered as co-crucial targets in this subgroup of aggressive breast cancers. We believe that it is important to encourage cancer patients and especially TNBCs' patients to pursue an adequate program of physical activities and DR during and after their treatment in order to prevent metastatic initiation, which is responsible for the majority of cancer-related deaths.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Dedication

I dedicate this work to the memory of my beloved Naima, she passed away because of TNBC.

References

1. Zagouri F, Bago-Horvath Z, Rössler F, Brandstetter A, Bartsch R, Papadimitriou CA, Dimitrakakis C, Tsigginou A, Papaspyrou I, Giannos A, et al. High MET expression is an adverse prognostic factor in patients with triple-negative breast cancer. Br J Cancer 2013; 108:1100-5; PMID:23422757; http://dx.doi.org/10.1038/bjc.2013.31
2. Nakopoulou L, Gakiopoulou H, Keramopoulos A, Giannopoulou I, Athanassiadou P, Mavrommatis J, Davaris PS. c-met tyrosine kinase receptor expression is associated with abnormal beta-catenin expression and favourable prognostic factors in invasive breast carcinoma. Histopathology 2000; 36:313-25; PMID:10759945; http://dx.doi.org/10.1046/j.1365-2559.2000.00847.x
3. Tolgay Ocal I, Dolled-Filhart M, D'Aquila TG, Camp RL, Rimm DL. Tissue microarray-based studies of patients with lymph node negative breast carcinoma show that met expression is associated with worse outcome but is not correlated with epidermal growth factor family receptors. Cancer 2003; 97:1841-8; PMID:12673709; http://dx.doi.org/10.1002/cncr.11335
4. Lengyel E, Prechtel D, Resau JH, Gauger K, Welk A, Lindemann K, Salanti G, Richter T, Knudsen B, Vande Woude GF, et al. C-Met overexpression in node-positive breast cancer identifies patients with poor clinical outcome independent of Her2/neu. Int J Cancer 2005; 113:678-82; PMID:15455388; http://dx.doi.org/10.1002/ijc.20598
5. Al Moustafa AE, Achkhar A, Yasmeen A. EGF-receptor signaling and epithelial-mesenchymal transition in human carcinomas. [Schol Ed]. Front Biosci (Schol Ed) 2012; 4:671-84; PMID:22202084; http://dx.doi.org/10.2741/S292
6. Hung CM, Kuo DH, Chou CH, Su YC, Ho CT, Way TD. Osthole suppresses hepatocyte growth factor (HGF)-induced epithelial-mesenchymal transition via repression of the c-Met/Akt/mTOR pathway in human breast cancer cells. J Agric Food Chem 2011; 59:9683-90; PMID:21806057; http://dx.doi.org/10.1021/jf2021489
7. Sivakumar R, Koga H, Selvendiran K, Maeyama M, Ueno T, Sata M. Autocrine loop for IGF-I receptor signaling in SLUG-mediated epithelial-mesenchymal transition. Int J Oncol 2009; 34:329-38; PMID:19148466
8. Shirakihara T, Horiguchi K, Miyazawa K, Ehata S, Shibata T, Morita I, Miyazono K, Saitoh M. TGF-β regulates isoform switching of FGF receptors and epithelial-mesenchymal transition. EMBO J 2011; 30:783-95; PMID:21224849; http://dx.doi.org/10.1038/emboj.2010.351
9. Guarino M. Src signaling in cancer invasion. J Cell Physiol 2010; 223:14-26; PMID:20049846
10. Yan D, Avtanski D, Saxena NK, Sharma D. Leptin-induced epithelial-mesenchymal transition in breast cancer cells requires β-catenin activation via Akt/GSK3- and MTA1/Wnt1 protein-dependent pathways. J Biol Chem 2012; 287:8598-612; PMID:22270359; http://dx.doi.org/10.1074/jbc.M111.322800
11. Catalano S, Mauro L, Marsico S, Giordano C, Rizza P, Rago V, Montanaro D, Maggiolini M, Panno ML, Andó S. Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor alpha in MCF-7 cells. J Biol Chem 2004; 279:19908-15; PMID:14985328; http://dx.doi.org/10.1074/jbc.M313191200
12. Cirillo D, Rachiglio AM, la Montagna R, Giordano A, Normanno N. Leptin signaling in breast cancer: an overview. J Cell Biochem 2008; 105:956-64; PMID:18821585; http://dx.doi.org/10.1002/jcb.21911
13. Davis AA, Kaklamani VG. Metabolic syndrome and triple-negative breast cancer: a new paradigm. Int J Breast Cancer 2012; 2012:809291; PMID:22295251; http://dx.doi.org/10.1155/2012/809291
14. Spina A, Di Maiolo F, Esposito A, D'Auria R, Di Gesto D, Chiosi E, Sorvillo L, Naviglio S. Integrating leptin and cAMP signalling pathways in triple-negative breast cancer cells. [Landmark Ed]. Front Biosci (Landmark Ed) 2013; 18:133-44; PMID:23276914; http://dx.doi.org/10.2741/4092
15. Otvos L Jr., Kovalszky I, Riolfi M, Ferla R, Olah J, Sztodola A, Nama K, Molino A, Piubello Q, Wade JD, et al. Efficacy of a leptin receptor antagonist peptide in a mouse model of triple-negative breast cancer. Eur J Cancer 2011; 47:1578-84; PMID:21353530; http://dx.doi.org/10.1016/j.ejca.2011.01.018
16. Law JH, Habibi G, Hu K, Masoudi H, Wang MY, Stratford AL, Park E, Gee JM, Finlay P, Jones HE, et al. Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. Cancer Res 2008; 68:10238-46; PMID:19074892; http://dx.doi.org/10.1158/0008-5472.CAN-08-2755
17. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med 2003; 54:131-52; PMID:12525670; http://dx.doi.org/10.1146/annurev.med.54.101601.152156
18. Rock CL, Pande C, Flatt SW, Ying C, Pakiz B, Parker BA, Williams K, Bardwell WA, Heath DD, Nichols JF. Favorable changes in serum estrogens and other biologic factors after weight loss in breast cancer survivors who are overweight or obese. Clin Breast Cancer 2013; 13:188-95; PMID:23375717; http://dx.doi.org/10.1016/j.clbc.2012.12.002
19. Al Moustafa A. Fasting inhibits human cancer progression via the epithelial-mesenchymal transition process: Important evidence unraveled. Clin Cancer Investig J 2012; 1:181-3
20. Al Moustafa AE. Insulin-like growth factor-1 enhances mortality risk in women with breast cancer through epithelial-mesenchymal transition initiation. Clin Cancer Investig J 2013; 2:175-7