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.

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.² 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.²⁴ 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.\textsuperscript{12} In addition, leptin can promote transactivation of ErbB-2, and interacts in TNBC cells with IGF-1 to transactivate transactivation of ErbB-2, and interacts in TNBCs, respectively.\textsuperscript{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.\textsuperscript{17-20} Thus, we believe that physical activities and fasting and/or DR could be employed to reduce cancer mortality in the TNBCs 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.\textsuperscript{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-critical 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.

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