Short Communication

Aspirin inhibits breast cancer progression via the switch of epithelial-mesenchymal into mesenchymal-epithelial event

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ABSTRACT

Metastatic breast cancer disease is one of the leading causes of cancer-related death among women worldwide. Meanwhile, it is well-established that the epithelial-mesenchymal transition (EMT) is a major event in the development of cancer metastases. On the other hand, recent studies revealed that Aspirin could play an important role in preventing cancer development and its progression. Herein, we explored the effect of aspirin on breast cancer cells and EMT. We found that aspirin-treatment initiates mesenchymal to epithelial transition, which is the opposite event of EMT; thus, aspirin-treatment can potentially inhibit cancer invasion and metastasis. These data suggest that aspirin could be useful to prevent breast cancer progression as well as other human carcinomas and their metastases.

Key words: Aspirin, breast cancer, cancer progression, differentiation, mesenchymal to epithelial transition

Breast cancer is the most common type of malignant disease in women worldwide. Currently, breast cancer is the second leading cause of death due to cancer in women.[1] It is estimated that more than 90% of cancer deaths are the result of metastasis, either directly due to tumor involvement of critical organs or indirectly due to complications of therapy to control tumor growth and spread. In view of the limited success of available treatment modalities for metastatic cancer including breast, alternative and complementary preventive strategies need to be explored. Herein, we investigated the effect of aspirin on the epithelial-to-mesenchymal transition (EMT) event, which is considered as a dedifferentiation switch between polarized epithelial cancer cells and motile mesenchymal cells during cancer progression and metastasis; the EMT is characterized by a decrease in the expression of proteins that enhance cell-cell adhesion such as the E-cadherin/catenin complex, as well as an increase in the expression of mesenchymal markers such as vimentin and N-cadherin as well as the activity of certain matrix metalloproteinases.[2]

Aspirin (acetylsalicylic acid [ASA]) is widely used to manage pain, arthritis, and cardiovascular diseases. Epidemiological studies, randomized control trials, and experimental investigation suggest the beneficial effect of ASA in the prevention, progression, and metastatic growth of various cancers, including colon, gastrointestinal cancer, prostate, and breast cancers.[3] The major mechanism is the anti-inflammatory action through the inhibition of COX-1/COX-2 and modulation of the NFκB or STAT3 pathways.[3] In addition, aspirin may activate AMPK, thus affecting

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notch, Wnt/β-catenin and other signaling pathways.[4,5] This is particularly significant since the Wnt/β-catenin signaling pathway is a major regulator of EMT.[2]

Herein we report, for the 1st time, that ASA induces a mesenchymal-epithelial transition (MET) of MCF7 and BT20 breast cancer cells, which could consequently inhibit cell invasion and cancer metastasis. MET is considered as the opposite event of EMT, which can be accompanied by an up-regulation and restoration of the expression patterns of the E-cadherin/catenin complex as well as other cell-cell adhesion proteins. MCF7 and BT20 cells were treated with 5 μM and 10 μM ASA for 2 days. In the absence of treatment, MCF7 and BT20 cells displayed a fibroblast-like (mesenchymal) morphology and formed multilayered disorganized cells. In contrast, as indicated in Figure 1, ASA-treatment led to a substantial phenotypic conversion from fibroblast-like (mesenchymal) to epithelial phenotype. Cells became more flattened in appearance, and showed an increase in cell-cell contact in comparison with untreated cells and dimethyl sulfoxide (DMSO)-treated cells [Figure 1], which was used to dissolve the ASA (Sigma Chemical Co.). Recently Maity *et al.*[6] reported that ASA treatment of MCF7 and MDA231 breast cancer cell lines induce a down-regulation of mesenchymal marker (i.e., vimentin), and an up-regulation of epithelial markers (i.e., keratin-19 and E-cadherin); thus blocking cell invasion ability of these cell lines. Accordingly, we demonstrated clearly that ASA initiate MET of MCF7 and BT20 cancer cells.

Regarding the mechanism of ASA MET induction, we believe that the AMPK and Wnt/β-catenin signaling pathways could be the main routes of this effect. We previously reported that SKI-606, a Src/Abl kinase inhibitor, induce MET, of HeLa and SiHa cervical cancer cells, and consequently reduce cell invasion ability of these cell lines *in vitro*; this was accompanied by a re-localization of E-cadherin and β-catenin expression patterns from the cytoplasm and nucleus, respectively, to the undercoat cytoplasmic membrane;[7] in addition, we revealed that Src activation converts β-catenin's role from a cell-cell adhesion molecule to a transcriptional regulator via its interaction with the Tcf/Lef family of transcription factors.[7] Based on this investigation and recent study of Maity *et al.*,[6] we assume that ASA could dephosphorylate Src and consequently β-catenin, via its interaction with receptor tyrosine kinases such as ErbB family members and VEGF-receptor,[8,9] which is largely expressed in human carcinomas including breast. Thus, ASA can restore the expression pattern of β-catenin to the undercoat membrane to act as a cell-cell molecule, and regulate several genes including epithelial and mesenchymal markers, thereby blocking cell invasion and metastasis via the conversion of EMT into MET. Accordingly, we firmly believe that ASA can be used to prevent human carcinomas progression including breast as well as other malignancies; however, we consider that more molecular and cellular studies are necessary to elucidate the exact mechanistic function of ASA in the conversion of EMT into MET from, which can have a major role to identify new and efficient targets to prevent and/or manage metastatic cancers.

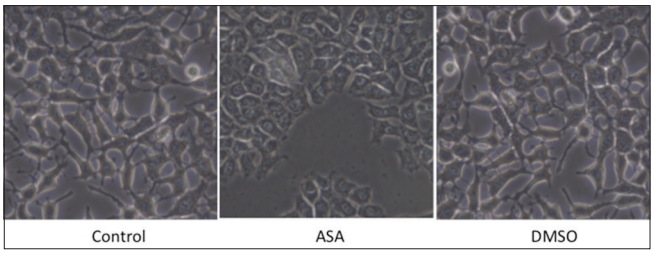

Figure 1: ASA induces morphological changes in MCF7 cells. Untreated (control) cells possess a fibroblast-like (mesenchymal) cell phenotype, whereas 48 h treatment with ASA (5 μM) significantly induces a mesenchymal-epithelial transition of these cells in comparison with DMSO-treated cells, which was used to dissolve the ASA

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Conflict of interest

There are no conflict of interest.

REFERENCES

1. Green VL. Breast cancer risk assessment, prevention, and the future. Obstet Gynecol Clin North Am 2013;40:525-49.
2. Al Moustafa AE, Achkhar A, Yasmeen A. EGF-receptor signaling and epithelial-mesenchymal transition in human carcinomas. Front Biosci (Schol Ed) 2012;4:671-84.
3. Alfonso L, Ai G, Spitale RC, Bhat GJ. Molecular targets of aspirin and cancer prevention. Br J Cancer 2014;111:61-7.
4. He Z, Peng Y, Duan W, Tian Y, Zhang J, Hu T, *et al.* Aspirin regulates hepatocellular lipid metabolism by activating AMPK signaling pathway. J Toxicol Sci 2015;40:127-36.
5. Deng L, Hu S, Baydoun AR, Chen J, Chen X, Cong X. Aspirin induces apoptosis in mesenchymal stem cells requiring Wnt/beta-catenin pathway. Cell Prolif 2009;42:721-30.
6. Maity G, De A, Das A, Banerjee S, Sarkar S, Banerjee SK. Aspirin blocks growth of breast tumor cells and tumor-initiating cells and induces reprogramming factors of mesenchymal to epithelial transition. Lab Invest 2015 Apr 13. doi: 10.1038/labinvest.2015.49.
7. Yasmeen A, Alachkar A, Dekhil H, Gambacorti-Passerini C, Al Moustafa AE. Locking Src/Abl tyrosine kinase activities regulate

cell differentiation and invasion of human cervical cancer cells expressing E6/E7 oncoproteins of high-risk HPV. J Oncol 2010;2010. pii: 530130. doi: 10.1155/2010/530130.
8. Cho M, Kabir SM, Dong Y, Lee E, Rice VM, Khabele D, *et al*. Aspirin blocks EGF-stimulated cell viability in a COX-1 dependent manner in ovarian cancer cells. J Cancer 2013;4:671-8.
9. Sato T, Amano H, Ito Y, Eshima K, Minamino T, Ae T, *et al*. NSAID, aspirin delays gastric ulcer healing with reduced accumulation of CXCR4(+)VEGFR1(+) cells to the ulcer granulation tissues. Biomed Pharmacother 2013;67:607-13.