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LETTER TO THE EDITOR

Downregulation of miRNA-21 and cancer stem cells after chemotherapy results in better outcome in breast cancer patients

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Abstract

Epigenetic modifications have been observed as a decline in miRNA-21 expression and breast cancer stem cell (CSC) population after 3 cycles of standard chemotherapy. The epigenetic response (miRNAs expression) and CSCs are also correlated in patients with Breast Cancer. In patients who tolerated chemotherapy well, miRNA-21 (non-coding RNA) expression decreased significantly after three cycles of chemotherapy. The miRNA-21 expression in breast cancer tissue was quantified by quantitative PCR (real-time PCR) using the standard protocol. In addition, breast CSCs (CD44+/CD24-) were also decreased in these patients. The miRNA-21 regulates cell division, proliferation, and autophagy of cancerous cells (as it targets phosphatase and tensin homolog/AKT/transcription factor EB/programmed cell death 4/autophagy-related protein 5 and chemotherapy also produces similar effects), thereby contributing to these benefits. Therefore, when all of the targets on genes have been explored by mimic miRNA, chemotherapy combined with anti-miRNA21 therapy may prove useful in the care of cancer patients.

Key Words: Epigenetic modification; miRNA-21; Breast carcinoma; Autophagy;

Chemotherapy; Breast cancer stem cells

Core Tip: Epigenetic modification by non-coding RNAs (miRNA), along with the discovery of a cancer stem cell (CSC) database for all cancer types, has revolutionized oncology. The hallmarks of cancer include six capabilities acquired during the development of human tumors. These include sustaining proliferative signaling, evading growth suppressors, resisting cell death, facilitating replicative immortality, promoting angiogenesis, and promoting invasion and metastasis. These hallmarks are primarily manifestations of genome instability, which facilitates their acquisition, epigenetic modifications, and CSCs (Heterogenic tissue populations), which play vital roles in nurturing multiple hallmark functions. These alterations can be explored and targeted for better cancer management.

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TO THE EDITOR

The article by Mandhair *et al*[1] provides an excellent review of the mechanisms behind autophagy, commonly known during cancer progression for its function as an oncolytic and adaptive signaling pathway. Additionally, the authors discussed various epigenetic modifications such as methylation, acetylation, non-coding RNA (miRNAs), and cancer stem cells (CSCs), which influence genomic diversity and promote carcinogenesis. The relentless work by scientists and clinicians on carcinogenesis has proposed a few hallmarks of cancer, including maintaining proliferative signaling, evading growth suppressors, avoiding cell death, inducing angiogenesis, and activating invasion and metastasis[2].

The author provided an excellent, well-organized description of transcriptional factors expression that are crucial for stemness behavior of CSCs, as well as the contribution of epigenetic modulation, which is involved in regulation of autophagy through various transcriptional factors and signaling pathways. Apoptosis (established hallmark) is regulated by autophagy through the degradation of NOXA (Phorbol-12-myristate-13-acetate-induced protein 1), while inhibiting autophagy increases NOXA protein levels by extending the protein half-life. NOXA accumulation inhibits tumor cell growth by inducing apoptosis, which is further enhanced when p53 is present[3].

The authors have successfully provided an in-depth understanding of autophagy in cancer and its modulation, even though we liked the idea that transcriptional factors, methylations, and non-coding microRNAs have diverse crossroads that affect other indicators of cancer and interfere with them[2]. Similarly, cancer treatment strategies such as chemotherapy and radiation therapy have also been found to interfere with and affect various transcriptional factors and epigenomic milieus of cancers.

Chemotherapy affects autophagy, and the cell cycle in well-tolerated and chemosensitive patients, resulting in better outcomes[4]. We also find, in patients with breast carcinoma (unpublished work), that miR-21 (non-coding RNA) was decreased significantly after three cycles of chemotherapy in those patients who had well tolerated the chemotherapy. Quantitative real-time PCR was used to assess miR-21 expression from breast cancer tissue using the established standard protocol[5].

The breast CSC populations (CD44+/CD24-) also declined in these breast cancer patients. The breast CSC populations (CD44+/CD24) were counted by Flow-cytometer using corresponding antibodies[5]. The miR-21 is one of the most consistently highly expressed onco-miRs in several cancers, where it regulates multiple stemness parameters. Suppression of apoptosis is one of the key roles of miR-21.

Few cancer types appear to be highly affected by epigenetic modifications that modulate miR-21 expression. As a result of treatment with the demethylating agent 5-aza-2′-deoxycytidine, several miRNAs such as miR-21 were strongly induced in the ovarian cell line OVCAR3 (Human ovarian cancer cell lines). In this study, hypomethylation may be responsible for promoting its *in vivo* overexpression. miR-21 inhibits apoptosis by targeting the FASL and by inhibiting an entire network of onco-suppressor genes, including tumor protein p53 (TP53), transforming growth factor β, *PTEN* (phosphatase and tensin homolog), and PDCD4 (programmed cell death 4)[6,7]. In addition, it is also known that tumor suppressor gene PDCD4 inhibits the expression of autophagy-related gene autophagy-related protein 5 (ATG5)[8]. According to the study, miRNA-21 regulates autophagy *via* PDCD4 and the autophagy-related gene ATG5.

We believe that the miRNA21 mimic study should also be conducted prior to planning translational research. The mimic-miRNAs are chemically synthesized duplexes that are designed to activate only one miRNA strand. It is often used to overexpress miRNA transiently and to augment endogenous microRNA activity for investigating gain or loss of function. In conjunction with microRNA and gene expression profiles, miRNA mimics and inhibitors may be tested for their role in identifying specific microRNA-gene relationships.

Several genes can be affected by a single microRNA, which is well established. They may, for instance, influence to the expression of proteins that are essential for normal biochemical reactions and physiological functions, or they may contribute to the development of diseases. In order to achieve therapeutic success, mimic-miRNA-based *in vivo* and *in vitro* studies must be performed to explore all possible target sites. Thus, miRNA-mimics-based studies can provide a complete understanding. It is thus may possible to unravel the whole scenario of gene targets just by increasing the targeted oligonucleotides (miRNA mimics).

Autophagy plays a context-dependent role in the development of cancer. CSCs have been found in almost all types of cancers with mildly altered immunophenotype but almost identical functions. Further, recent findings lend support to the hypothesis that the CSCs microenvironment can intriguingly regulate autophagy. Cells of malignant tumors, for example, induce autophagy in the microenvironment to increase the availability of recycled nutrients to support their own growth. Autophagy inhibition within the tumor has moderate effects on tumor progression through modulation of essential signaling pathways or by promoting resistance to chemotherapy, while autophagy inhibition through chloroquine oral administration reduces tumor growth and invasion more noticeably. Cancer (CSCs) regulates autophagy in vivo, but its exact role in tumor growth remains unclear. Recently, a study in the animal model of *Drosophila melanogaster* malignant tumors confirmed that autophagy is induced within the tumor microenvironment and distant tissues. It also reported that metabolically stressed tumor cells trigger autophagy through *Drosophila* tumor necrosis factor and interleukin-6-like signals[9].

We thus agree with the authors that modulating epigenetic factors (methylation, non-coding RNAs) and CSCs can modulate autophagy, and lead to better cancer treatment. Thus, translational cancer research must be planned in order to facilitate a paradigm shift from laboratory to bedside sites in the future and to pave the way for better cancer management.

FOOTNOTES

Author contributions: Dwivedi S conducted the experiment; Pareek P, Vishnoi JR, and Misra S provided clinical guidance; and Sharma P interpreted and analyzed the results.

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