Editorial

Is microRNA-31 a key regulator of breast tumorigenesis?

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To date, investigation of microRNA (miRNA) is still attractive trend in molecular oncology due to a large number of known miRNA sequences, hence their function in tumorigenesis is unexplored for majority. Involvement of miRNA in various cell pathways and alteration of their expression observed in cancer emphasizes key role of miRNA in cell cycle regulation and in tumor development. For the few years alteration of those small non-coding RNA is carefully tested in various human neoplasms as potential tumor drivers and missing piece in triggering process of malignant transformation (1,2). Exploring role of selected miRNA can contribute to understanding their function in malignant transformation including regulation of breast tumorigenesis. Unfortunately, breast cancer is still leading women malignancy despite the progress in cancer detection and achievements of novel therapy methods. Similarly like in other cancers, tumor development is frequently latent and insidious, thus disease is often detected in advanced stage of the differentiation with occasional manifestation of clinical symptoms. Recent findings emphasize emerging role of miRNA in malignant transformation of the breast.

Among most promising miRNA molecules which could serve as breast cancer biomarker, miRNA-31 seems to be most attractive due to acting as tumor-suppressor miRNA of mammary gland stem cells. Moreover, under physiological conditions miRNA-31 was identified as a significant regulator of adult muscle and mesenchymal mammary progenitor stem cells and also is involved in diverse biological processes including fertility, embryonic development and bone formation (3-5). Interestingly, in neoplastic diseases miRNA-31 is either considered as a tumor-suppressor miRNA or oncogenic miRNA. Regarding its role as suppressor molecule miRNA-31 was found significantly downregulated in liver cancer (target genes—*HDAC2*, *HDK*), ovarian cancer (target genes—*STMN1*, *MET*, *VMN*) and brain tumors (target genes—*DOCK1*, *FIH1*) what promoted overexpression of mentioned genes involved in molecular pathways leading to uncontrolled cell proliferation. As for oncogenic role of miRNA-31 was found upregulated in lung cancer (target genes—*MET*, *BAP1*, *RASA1*), colon cancer (target genes—*CDKN2B*, *FIH1*, *SATB2*) and pancreatic cancer (target gene—*RASA1*), what led to inhibition of genes involved in proper cell function (5). Interestingly, some papers believed that miRNA-31 is also a key regulator of breast cancer invasiveness, therefore is carefully investigated as potential regulator of breast cancer metastasis (5,6). The available literature data indicate this molecule as a leading initiator or regulator of breast cancer development. The loss of miRNA-31 expression was found in many breast cancers, hence activation of its targets including *FZD3*, *ITGA5*, *M-RIP*, *MMP16*, *RDX*, *RHOA* is promoted and could cause metastasis formation (7,8). Truly, this fact was confirmed in other studies, therefore miRNA-31 is estimated as a key regulator of breast cancer metastasis formation through activation of cell invasiveness. Interestingly, in case of aggressive breast cancer presence, the high miRNA expression protected against cells invasiveness and metastasis, from the other hand even non-aggressive tumor developing, the down-expression of miRNA-31 promoted

cancer cells to metastasize (9). Available data indicate also other mechanisms mediated by this miRNA. There is strong evidence that *GNA13* (α subunit of a heterotrimeric G protein) expression is involved in breast tumorigenesis through enhancement of cell invasion, while partially regulated post-transcriptionally by miRNA-31 in breast cancer cell lines. Down-expression of miRNA-31 and hence increased *GNA13* level leads to cancer progression (10). Based on previous findings provided by several studies miRNA-31 seems to be considered especially as a major regulator of metastasis formation in breast cancer patients as well as a crucial suppressor of mammary stem cells (MSC) neoplastic transformation. Down-expression or knock-down of this molecule is a trigger mechanism for uncontrolled cell proliferation and migration through activation of numerous molecular pathways.

Most recently, Lv *et al.* (11) investigated role of miRNA-31 in controlling MSC activity and breast cancer development. MSC are controlled by multiple and complex molecular pathways including hormone, Notch and Wnt signaling. Among these Wnt/β-catenin signaling with its ligands Wnt4 and Rspo1 seems to be most significant for promoting MSC activity and determining a basal cell fate and MSC self-renewal. Moreover, Wnt/β-catenin signaling is widely demonstrated by breast tumors, especially in basal-like type with higher grade and aggressive behavior. Based on *in vitro* and *in vivo* experiments authors formed important conclusions regarding miRNA-31 function in breast cancer initiation and formation. The first authors found that miRNA-31 is enriched in MSC and breast cancer and its level positively correlated with NF-κB activators RANKL, TNF-α and Akt-IKKα pathway. In a *in vivo* mice model, overexpression of miRNA-31 lead to mammary hyperplasia by induction of cell proliferation, while differentiation of mammary cells was inhibited. Secondly, *in vitro* BT549 cell line treated with miRNA-31 demonstrated morphological epithelial-mesenchymal like transformation. Then, miRNA-31 demonstrated differences in action depending on the signaling pathway that regulates. Interestingly, miRNA promotes Wnt signaling pathway in mammary epithelium directly and indirectly by inhibition of Wnt-antagonists including *Axin1*, *Gsk3*β and *Dkk1* reducing their protein level, however, simultaneously inhibits also TGF-β pathway. All mentioned findings suggest important role of miRNA-31 in MSC self-renewal and induction of breast tumorigenesis through activation of Wnt signaling pathway. In conclusion, this study provided numerous precious findings regarding role of miRNA-31 in breast cancer and the first time its complex function was confirmed in *in vivo* model.

Based on mentioned and previous studies findings miRNA-31 may be considered as a potential attractive therapy target. As discussed above this miRNA-31 is especially interesting molecular target due to its double nature depending on the tumor type. Some papers analyzed its role in tumor development assigned miRNA-31 as tumor-suppressor molecule, whereas in other cancers it was found as a pro-oncogenic miRNA. Perhaps, future therapeutic procedures should be based on a tumor type, however, these findings were provided by *in vitro* models. In a study of Lv *et al.*, the miRNA-31 function was investigated *in vivo* and demonstrated the pro-oncogenic role. Therefore, firstly we should develop knowledge *in vivo* function of miRNA-31 in other cancer types to clearly define its function. Despite this based on current data we have two potential therapeutic ways. In case of loss of tumor-suppressing function of miRNA-31, the miRNA mimic should be applied to recover its function and to maintain proper cell cycle by suppression of uncontrolled expression of genes targeted by miRNA-31. On the other hand, in case of oncogenic activation of miRNA-31, the miRNA inhibitors should be applied to block uncontrolled cell proliferation or migration. This therapeutic option should be especially attractive to breast cancer patients to reduce tumor prevalence or to treat it on an early stage of development. Finally, there worth nothing that similarly like in other cancers, the major concern regarding miRNA is lack of their tissue specificity. Unfortunately, to date none miRNA has been assigned as tissue specific and expressed in an only one type of cancer tissue. The same concerns regard miRNA-31 which also was found altered in colon and lung cancer (12,13). Therefore, regarding miRNA-31 as a significant and master regulator of breast cancer initiation should be treated carefully and need to be further investigated.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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