MicroRNAs Put a Brake on Metastasis

By Glorianne Lazaro

Breast cancer is the most common cancer in women in the U.S., and subject to intense research. Despite advances in therapy, treating metastasis (the spread of the cancer to distant organs) remains a major challenge. One particularly aggressive type of breast cancer, the triple-negative breast cancer subtype (TNBC), is difficult to treat, largely due to the prevalence with which it metastasizes and the lack of specific therapies against it (1). Metastasis is a multistep process in which tumor cells acquire invasive properties while the tumor microenvironment is remodeled, allowing the tumor cells to break free from the primary tumor. Metastasizing cells then enter circulation and travel to distant locations in the body, where a new colony is established. Although several different biological molecules have been implicated in this process, the precise mechanisms that lead to metastasis remain unclear.

One active area of cancer research is the function of microRNAs (miRNAs), which are gradually stealing the limelight in cancer research. First discovered in 1993 in Caenorhabditis elegans worms (2), miRNAs are small, approximately 22 nucleotide-long RNA molecules that do not encode for a protein. Instead they function by binding to messenger RNA (mRNA) sequences that are transcribed from other genes, thus "silencing" gene expression by inhibiting protein production and/or degradation of the mRNA. One miRNA can potentially regulate the expression of thousands of genes, and thus, it is unsurprising that deregulation in certain miRNAs could regulate several cancer-related genes.

In 2002, Calin et al. first reported an association between cancer and miRNAs when they found that the miRNAs miR-15 and miR-16 were suppressed in chronic lymphocytic leukemia (3). Since then, several studies have used genome-wide techniques to demonstrate global changes in miRNA in tumor tissue relative to normal tissues. Of particular interest, some of those miRNAs, miR-10b, miR-21, and let-7 family members, were most altered in breast cancers, opening a new avenue for potential therapeutic targets (4,5,6). Additionally, there is accumulating evidence that miRNAs also regulate metastasis. Recent studies have shown that suppression of miR-335 and miR-126, as well as increases in miR-10b may be involved in initiating metastasis (7,8). Identifying these associations may lead to new "tailored" therapeutic targets, especially for cases of TNBC, which currently have limited therapeutic options. And as evidenced by one recent study, miRNAs may also serve as useful markers that could predict likely recurrence and lead to more effective disease control (9).

In one recent study, Ryu S. et al. (10) initially performed a powerful miRNA sequencing (miRNA-seq) analysis of a cell line derived from metastatic breast cancer cells and found several miRNAs that had altered expression when compared with non-metastatic mammary cells. The authors further analyzed one of them, miR-708, and found it to be suppressed in cultured metastatic cells in vitro as well as in lymph node and metastatic lesions from breast cancer patients. Re-introducing miR-708 into cultured cells before implanting them into mice resulted in a significant reduction in lung metastases. Interestingly, this reintroduction of miR-708 did not affect growth of the primary tumour, indicating that miR-708 functions specifically in metastasis.

Further studies revealed that reduced expression of miR-708 consequently led to increased levels of a protein called neuronatin, found on the surface of the cell's endoplasmic reticulum (a network of membranes in the cell that is involved in protein synthesis and regulation of ion levels, among other functions). Neuronatin carefully regulates calcium release, which is critical for cell migration (11). In the absence of miR-708, the resulting abnormal release of calcium from the endoplasmic reticulum alters the activity of proteins that typically drive cell migration. The authors also examined the underlying mechanism for miR-708 suppression and found that this suppression was mediated by polycomb group complexes (protein complexes that repress expression of many genes by altering the structure of packed DNA).

Through their work, Ryu et al. have identified, rigorously characterized, and exemplified the strong potential of miR-708 as a therapeutic target in metastatic triple-negative breast cancer. Restoring expression of miR-708 could significantly limit metastatic spread and potentially

drive a considerable advance in breast cancer prognosis and management. The potential of microRNA-based cancer therapies has yet to be realized in clinical trials as these therapies are challenged by inefficient tissue delivery systems and off-target effects. However, a few trials are now gaining traction, as exemplified by a trial for liver cancer, NCT01829971, and another demonstrating the efficacy of inhibiting miR-122 for chronic hepatitis C (HCV) infection (12). These trials highlight the feasibility of this approach and will hopefully be the first of several trials assessing this new class of promising therapies.

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