MedicalXpress

New research identifies a microRNA that drives both cancer onset and metastasis

July 3 2013

A mere 25 years ago, noncoding RNAs were considered nothing more than "background noise" in the overall genomic landscape. Now, two new studies reveal that one of these tiny noncoding molecules – microRNA-22 – plays an outsized role in two types of cancer.

Reported online today in the journals *Cell* and *Cell Stem Cell*, the two papers demonstrate in mouse models that miR-22 drives both the onset and spread of breast cancer, as well as the onset of blood cancer. The findings, led by investigators at Beth Israel Deaconess Medical Center (BIDMC), further suggest that inhibition of miR-22 through a "decoy" method offers a novel therapeutic option for treating hematological malignancies.

"This is the first time that a microRNA has been shown to drive both cancer initiation and metastasis in a mouse model," explains senior author Pier Paolo Pandolfi, MD, PhD, Scientific Director of the Cancer Center at BIDMC and the George Reisman Professor of Medicine at Harvard Medical School. "It's amazing that, by itself, this one little microRNA can trigger cancer in two different organs, perhaps in many more, and in the case of breast cancer, can also promote metastasis."

Although many advances have been made in identifying the genetic causes of some cancers, it has become apparent that changes in the primary DNA sequence alone cannot explain the many steps that are necessary to turn a normal cell into a cancer cell. As these new papers confirm, epigenetic modifications – which occur apart from changes in

the underlying DNA sequences and include DNA methylation and histone modification – have now been recognized as playing integral roles in cancer.

"Our discovery is exciting for several reasons," says Pandolfi. "Mechanistically, we have revealed one way in which microRNAs can fundamentally reconfigure the way that DNA is read. Our findings show that miR-22 triggers an epigenetic 're-wiring,' if you will, which represses the expression of certain genes as well as other selected microRNAs. Based on these studies, we now know that one miRNA can communicate and repress other miRNAs epigenetically. In this particular case, we have also learned that miR-22 does so by silencing a family of enzymes called TET proteins, which act as tumor suppressors."

In addition, the scientific team, led by first author Su Jung Song, PhD, a postdoctoral fellow in the Pandolfi laboratory, discovered that overexpression of miR-22 also triggers metastasis – the spread of cancer from a primary site to other organs, in this case, from breast tissue to the lungs.

Metastasis remains one of the most complex and challenging problems of oncology. Recent studies have demonstrated that as tumors progress, genetic and epigenetic mechanisms may lead to the emergence of a self-renewing metastatic cancer stem cell or cancer-initiating cell, which can enter the blood stream and seed a secondary tumor in a distinct organ.

"We showed that by promoting epithelial to mesenchymal transition [EMT], a process by which cancer cells gain properties that enable them to become both more motile and more invasive, miR-22 promotes aggressive metastatic disease in breast cancer," explains Song, who describes this course of events in the paper published in *Cell*. Specifically, she adds, miR-22 silences the anti-metastatic miR-200 through direct targeting of TET proteins, as shown in a mouse model.

But, notes Pandolfi, "While these findings are extremely novel, what makes this work even more exciting is its therapeutic implications."

As described in the team's second paper, in *Cell Stem Cell*, the new findings further identify miR-22 as an epigenetic modifier and key oncogenic determinant for the pathogenesis of myeolodysplastic syndrome (MDS) and leukemia in a mouse model of disease – thus identifying a novel therapeutic target for blood and breast malignancies.

"We already have ways to shut down microRNAs," explains Pandolfi. "We can go in with very tiny decoy molecules that block the function of miR-22, and thereby reverse its oncogenic function. " As he further explains, these new papers demonstrate that a locked nucleic acid (LNA)-based therapeutic targeting of miR-22 may represent an effective strategy for TET2 reactivation as a treatment option for a number of diseases, including MDS, leukemia and other metastatic cancers.

"This is not wishful thinking," adds Pandolfi. "The identification of this new oncogenic miRNA provides straightforward therapeutic opportunities because we can test the effects of its inhibitors right away."

Provided by Beth Israel Deaconess Medical Center

Citation: New research identifies a microRNA that drives both cancer onset and metastasis (2013, July 3) retrieved 2 May 2024 from https://medicalxpress.com/news/2013-07-microrna-cancer-onset-metastasis.html