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Researchers find micro RNA plays a key role in melanoma metastasis

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Scientists have long wondered how melanoma cells travel from primary tumors on the surface of the skin to the brain, liver and lungs, where they become more aggressive, resistant to therapy, and deadly. Now, scientists from NYU Langone Medical Center have identified the possible culprit—a short strand of RNA called microRNA (miRNA) that is over-expressed in metastatic melanoma cell lines and tissues.

The new findings, published online this week and in the February 10, 2009 print edition of the *Proceedings of the National Academy of Sciences* (*PNAS*), suggest that miRNA silencing to counteract or attack this mechanism may be an effective therapeutic strategy for metastatic melanoma, according to Eva Hernando, Ph.D., assistant professor in the Department of Pathology at NYU School of Medicine, and the lead author of the study. Dr. Hernando is also a member of the NYU Cancer Institute at NYU Langone Medical Center.

The highly aggressive character of melanoma, says Dr. Hernando, makes it an excellent model to probe the mechanisms underlying metastasis, the process by which cancer cells travel from the primary tumor to distant sites in the body. Though other researchers have found that altered miRNAs contribute to breast cancer metastasis, this is the first study to examine the role of miRNA in metastatic melanoma.

"Melanoma becomes deadly after the cells leave the primary tumor through the blood and metastasize in other organs where they are resistant to therapy," says Dr. Hernando, who notes that the average

survival for patients after melanoma metastasis occurs is only nine months. "Normal cells are unable to travel and survive in alien locations, so we are very interested in understanding the invasive, adaptive, and resistant traits of the very aggressive melanoma cell."
miRNAs are short pieces of RNA that block the expression of proteins that are encoded by messenger RNAs. They serve as regulators of protein expression, acting like the volume control on a radio. In recent years, miRNAs have been linked to the over- or under-expression of a variety of genes linked to cancer and other diseases.

Dr. Hernando's lab found a miRNA is over-expressed in metastatic melanoma cell lines and tissues. The lab found that the elevated expression of miRNA 182 turns it into an oncogene (a gene involved in cancer tumor initiation or progression), by increasing the invasive capacity of melanoma cells in vitro and stimulating the cell's metastatic potential in a mouse model.

In addition, the NYU scientists found that miRNA 182 also represses the expression of two tumor suppressors called FOXO3 and MITF, which normally prevent cells from becoming malignant. By repressing the suppressors, miRNA 182 permits melanoma cells to migrate and survive independently, two properties necessary for metastasis.

MiRNA 182 also belongs to a cluster located in a genomic region, chromosome 7q, that is frequently amplified in melanoma and contains two other oncogenes; BRAF and C-MET. The study found a correlation between genomic amplification and miRNA over expression, though it is unclear whether other molecular mechanisms play a role in this effect, according to Dr. Hernando.

Finally, the scientists observed that in a significant fraction of metastatic melanomas, high miRNA 182 levels correlate with low levels of FOXO3 and MITF, supporting the relevance of this mechanism in human

melanoma.

The study suggests that miRNA 182 is a novel therapeutic target. When it is inhibited, it impairs the invasive potential of melanoma cells and induces cell death. In theory, the administration of anti-miRNA 182 could block the growth or expansion of the primary melanoma tumor. Several academic laboratories and pharmaceutical companies are working to improve the delivery of anti-miRNAs by using chemical modification and nano particles to increase their stability, specificity, and ability to reach tumors in sufficient doses with low toxicity.

The NYU Cancer Institute is currently studying whether anti-miRNA will work on miRNA 182 to inhibit the growth or spread of primary melanoma in mice. Dr. Hernando says that even if the anti-miRNA cannot do this on its own, it might work in combination with conventional chemotherapy or novel targeted therapies.

This study is the result of an extensive collaboration between members of NYU's Interdisciplinary Melanoma Cooperative Group, led by Iman Osman, M.D. , one of the study's co-authors, which has a large biospecimen bank comprising human tissue, blood and patient clinico-pathological information.

"The existence of this bank permits us to validate our laboratory findings using human tissue," says Dr. Hernando. "In this study, we began looking at cell lines and then at melanoma tissue. Now that the mechanism has been proven using cell lines and mice, the next step will be to perform in-vitro studies with cell lines to assess the effect of anti-miRNA on cell death in both normal and melanoma cells. Once that study is completed, we can use this model for studies in mice to block the growth of the primary melanoma tumor or the metastasis by using anti-miRNA. All these steps will determine if this approach could be eventually applied to humans."

Source: New York University School of Medicine