Metastatic RNA

A new study shows the role of a special type of ribonucleic acid in spreading cancer

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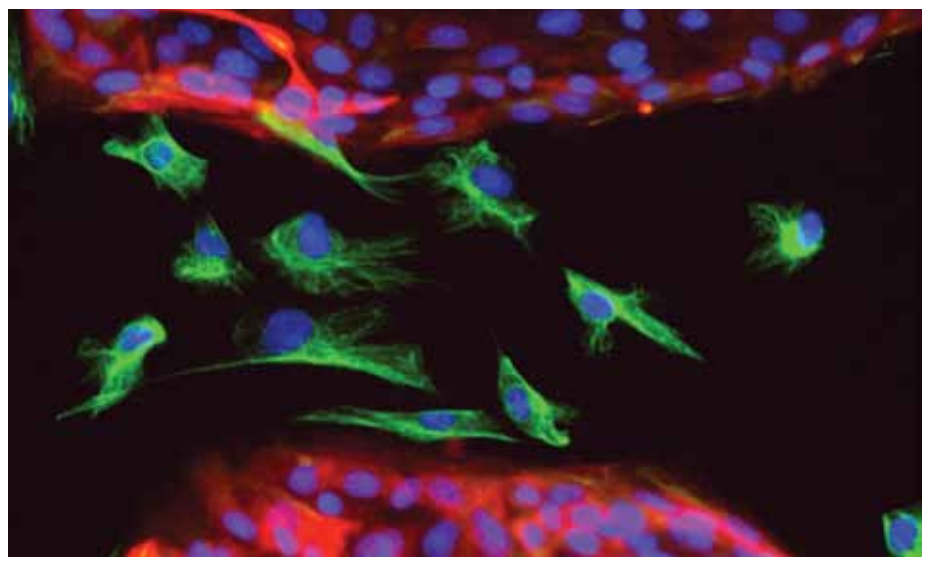
The sequences of the human genome that do not encode proteins, which a decade ago were considered to be junk DNA, have been shown to be important in understanding the cellular machinery involved in certain biological processes and diseases. HOTAIR, a gene located on human chromosome 12, generates a very long RNA comprising 2,200 nucleotides. However, it does not encode a protein. Recent studies indicate that this portion of the genetic sequence appears to play an important role in regulating metastasis, the cellular mechanism that allows cancer cells to spread from one organ to another, thus leading to tumors in other parts of the body. A new study by researchers at the Center for Cell-Based Therapy (CTC) at the Ribeirão Preto School of Medicine of the University of São Paulo (FMRP-USP) details the important role of HOTAIR RNA in the metastatic process.

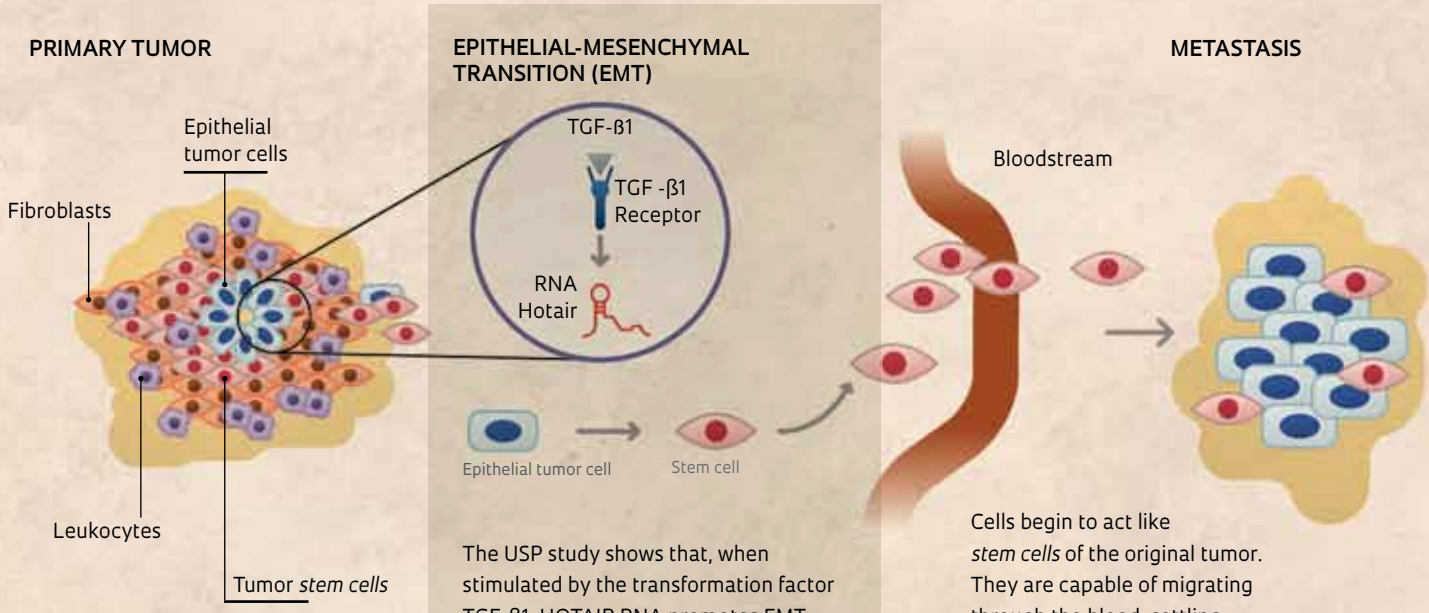
This study indicates that HOTAIR is responsible for activating the epithelial-mesenchymal transition (EMT) in tumors. EMT is a process that alters the morphology and functionality of a subset of cancer cells. "Thus, the tumor's epithelial cells are transformed into mesenchymal cells and start to behave as if they were cancer *stem cells*," says Wilson Araújo da Silva Junior, a CTC geneticist and one of the authors of the study that was published in the September 2013 issue of *Stem Cells*. "Cancer cells gain the ability to detach from the original tumor, migrate



Epithelial cells (*in red*) and mesenchymal cells (*in green*): the green are capable of migration, while the red are not

The role of HOTAIR in tumor migration

RNA stimulates some cancer cells to gain the ability to spread to other organs



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through the bloodstream and adhere to other organs and generate new cancers." In addition to promoting the spread of the disease throughout the body via metastasis, EMT also helps to perpetuate the cells of the original tumor.

EMT is a transformation that typically occurs in the early stages of embryonic development and is involved in generating various types of body tissue. It is also associated with healing processes such as fibrosis and wound regeneration. In these normal processes, EMT is beneficial to the preservation of life. However, EMT also contributes to the development of tumors. Epithelial cells form the both the skin and the internal lining (mucosa) of its cavities. They are unable to break away from other cells and cannot spread throughout the body or become other cell types. Their appearance and functions differ from those of mesenchymal cells, which are able to spread throughout the body and transform into other cell types. Therefore, without EMT, it would be difficult for a tumor to spread throughout the body.

CELLULAR REPROGRAMMING

Chemotherapy and radiation are able to kill most cancer cells, but not those that are part of the EMT, such as cancer *stem cells*. Cancer *stem cells* are thought to be responsible for the return of the original tumor and its appearance elsewhere in the body. "Tumor cells are heterogeneous," says Marco Antonio Zago, another author of the article and coordinator of the CTC, one of the Research, Innovation and Dissemination Centers (RIDCs) maintained by FAPESP. "In the experiment, when we suppressed the HOTAIR, we saw that EMT did not occur." While the data are only preliminary, evidence suggests that blocking the action of HOTAIR may be a way to combat metastasis.

The USP researchers worked with human tumor cells from the breast and colon. "These forms of cancer are widely used models in this type of study," says Cleidson Pádua Alves, a biologist who did his postdoctoral studies at the USP center and is the primary author of the article. Dr. Alves and colleagues discovered that by administering the transformation factor TGF-ß1 to cancer cells grown in vitro, the HOTAIR RNA was activated. This led to changes in the functions of several genes, and EMT occurred. Increased HOTAIR activation further intensified this process. However, neutralization of the gene that produces the HOTAIR RNA blocked EMT. "This RNA is part of the cellular programming required for metastasis to occur," says Silva. Prior to this study, there was evidence that both HOTAIR, which belongs to a new class of RNAs termed lincRNAs (long intergenic non-coding RNAs), and the EMT mechanism were related to cancer progression. However, it was not known that HOTAIR played an essential role in activating EMT. ■

Project

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ALVES, C.P. *et al.* The lincRNA HOTAIR is required for the epithelial-to-mesenchymal transition and stemness maintenance of cancer cell lines. **Stem Cells**. In press.

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