Published in final edited form as:
Cell Cycle. 2010 September ; 9(17): 3391–3392.

HOTAIR: Flight of noncoding RNAs in cancer metastasis

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Abstract

The genetic makeup of most cells in the body is identical. Hence what makes one cell type different from another cell type in the body is largely determined by epigenetics, via differences in chromatin states. Changes in chromatin modifications can alter cell fate, causing cells to forget their cellular identity and take on different properties that may be detrimental to the overall organization of the body, including cancer. In metastasis, cancer cells proliferate, invade out of their tissue boundaries, enter the blood stream and colonize in a foreign tissue. The long intergenic noncoding RNA HOTAIR has been recently discovered to provide such a link between chromatin state, cell positional identity, and cancer metastasis[1].

The *HOX* family of transcription factors are master regulators of positional identity in bilaterians[2]. In mammals, genes encoding the 39 HOX proteins are clustered in 4 chromosomal loci that are interspersed by numerous long noncoding RNAs and several microRNAs[3]. Gene activation occurs temporally from one end of the cluster, in correlation with the sequential development of the body plan, a concept known as collinearity[4]. Accurate transcription of HOX genes at the right time and dosage is crucial to the normal development of the body and specifies cellular positional identity. Interestingly, this positional identity is retained in adult tissues such as fibroblasts and other cell types, and requires the sustained expression of the right cocktail of *HOX* genes to maintain cell fate[5–8].

The Polycomb group proteins encode histone methylase complexes that regulate chromatin states in normal development and cancer[9]. First identified as regulators of *HOX* gene expression, Polycomb proteins form a complex (PRC2) that include the histone methylase EZH2 to enforce gene silencing by methylating histone H3 on lysine 27 (H3K27me3). Overexpression and amplification of EZH2 is frequently found in human breast and prostate cancers[10]. However how Polycomb proteins are targeted to specific genes is unclear. Long intergenic noncoding RNAs (lincRNAs) are a recently recognized class of pervasively transcribed genes that can serve as the interface between DNA and chromatin modification complexes3, 11, 12. Certain lincRNAs tether Polycomb complex to nearby genes *in cis*, such as in developmental dosage compensation and imprinting[13]. The lincRNA HOTAIR is the first example of a lincRNA that regulates genes at a distance[3]. HOTAIR is transcribed from the *HOXC* locus, binds to Polycomb, and targets Polycomb to *HOXD* genes located on a different chromosome, resulting in cross regulation of *HOX* genes for proper positional identity.

Gupta et al. recently revealed an important role for HOTAIR in breast cancer metastasis[1]. HOTAIR is highly induced (up to 2000-fold) in metastatic breast cancer samples, and high expression of HOTAIR in primary breast tumors is a powerful predictor of eventual metastasis and death, independent of known clinicopathologic risk factors. Over-expression of HOTAIR in breast cancer cell lines results in increased cell invasion *in vitro* and

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metastasis *in vivo*. This increase of metastatic potential in HOTAIR over-expression is accompanied by an altered chromatin state: PRC2 is recruited to 854 genes that normally do not bind to PRC2 in epithelial cells, resulting in the downregulation of multiple metastasis suppressor genes, including *HOXD10* and many others. Intriguingly, this altered PRC2 occupancy profile induced by HOTAIR in breast epithelial cell resembles the PRC2 occupancy profile in distal fibroblasts, where HOTAIR is normally expressed. Importantly, the gene regulatory and metastatic effects of HOTAIR overexpression are largely reversed by concomitant PRC2 depletion, revealing a lincRNA-Polycomb pathway for cancer invasion.

An intriguing parallel pathway also links the actions of a microRNA to breast cancer metastasis. mir10b is a microRNA transcribed from the 3' *HOXD* locus. mir10b is induced by Twist, a key transcription factor for epithelial-mesenchymal transition, and is upregulated in invasive versus non-invasive breast cancer cell lines[14]. Over-expression of mir10b increases the ability of tumor cells to invade *in vitro* and to metastasize to lungs *in vivo*. mir10b binds to the 3'UTR of *HOXD10* to inhibit HOXD10 protein translation. HOXD10 controls a battery of genes involved in cell migration, extracellular matrix remodeling, and play important roles in metastasis.

The integrated pathways through which lincRNAs, chromatin modifications, and microRNAs define gene activity provide a glimpse into the complexity of regulatory networks in normal development and in cancer metastasis (Fig. 1). Different cells in the body express a specific concoction of these genes, at the right dosage, to define their cell fate, and misregulation can result in dire consequences such as metastasis[4, 15]. An attractive but unproven idea is that cancer cells can reprogram their own positional identity (via lincRNAs or miRNAs) to enable their colonization of distant organs. While changes in *HOX* genes and noncoding RNAs may cause aberrant regulation of genes important in cell migration, invasion, and cancer metastasis, it is unclear whether genes in the *HOX* loci are also involved in specifying the cellular address to which the cancer cells colonize. Cancer cells originating from different body parts have been shown to preferentially metastasize to specific tissues[16]. A detailed study of organ-specific metastasis and altered *HOX* code in primary tumors may start to address this question.

Acknowledgments

Y.W. is supported by A*STAR (Agency of Science, Technology and Research) of Singapore. H.Y.C. is supported by NIH (R01-CA , R01-HG), California Institute for Regenerative Medicine, American Cancer Society, and is an Early Career Scientist of the Howard Hughes Medical Institute.

References

1. Gupta RA, et al. Nature. 2010; 464:1071–1076. [PubMed: 20393566]
2. Chang HY. Science. 2009; 326:1206–1207. [PubMed: 19965461]
3. Rinn JL, et al. Cell. 2007; 129:1311–1323. [PubMed: 17604720]
4. Kmita M, et al. Science. 2003; 301:331–333. [PubMed: 12869751]
5. Chang HY, et al. Proc Natl Acad Sci U S A. 2002; 99:12877–12882. [PubMed: 12297622]
6. Gesta S, et al. Proc Natl Acad Sci U S A. 2006; 103:6676–6681. [PubMed: 16617105]
7. Chi JT, et al. Proc Natl Acad Sci U S A. 2003; 100:10623–10628. [PubMed: 12963823]
8. Rinn JL, et al. Genes Dev. 2008; 22:303–307. [PubMed: 18245445]
9. Sparmann A, et al. Nat Rev Cancer. 2006; 6:846–856. [PubMed: 17060944]
10. Kleer CG, et al. Proc Natl Acad Sci U S A. 2003; 100:11606–11611. [PubMed: 14500907]
11. Khalil AM, et al. Proc Natl Acad Sci U S A. 2009; 106:11667–11672. [PubMed: 19571010]
12. Tsai MC, et al. Science.

13. Zhao J, et al. Science. 2008; 322:750–756. [PubMed: 18974356]
14. Ma L, et al. Nature. 2007; 449:682–688. [PubMed: 17898713]
15. Tarchini B, et al. Dev Cell. 2006; 10:93–103. [PubMed: 16399081]
16. Nguyen DX, et al. Nat Rev Cancer. 2009; 9:274–284. [PubMed: 19308067]

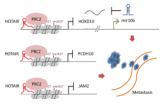

Figure 1.
Integrated pathways of non-coding RNAs in metastasis. mir10b downregulates HOXD10 post-transcriptionally. HOTAIR recruits PRC2 to transcriptionally down-regulate HOXD10 and other tumor suppressors genome-wide, resulting in changes in cell fate and increased metastasis.