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PERSPECTIVE ARTICLE

RNA-Directed Epigenomic Reprogramming—An Emerging Principle of a More Targeted Cancer Therapy?

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Epigenetic aberrations are recognized as an early and common event during carcinogenesis. This provides a strong rationale for a therapeutic intervention at the epigenetic level. Current epigenetically active drugs, however, lack specificity for particular genomic loci. Better processes for a more targeted manipulation of the cancer epigenome are needed. One option could be the ability of long noncoding RNAs (lncRNAs) to recruit the chromatin modification complexes to particular genomic loci. In consequence, epigenetic variations would not be stochastic but controlled by a directed programme, through which specific groups of genes are regulated by promoter methylation and(or) histone marks, even if located on different chromosomes. lncRNAs are known to be functionally involved in cell fate specification and carcinogenesis. Depleting lncRNAs with oncogenic potential or replacing scarce molecules with tumor suppressor activity could therefore be employed for a specific reprogramming of the epigenome of cancer cells. Apart from the targeted manner and thus specificity, the mode of action by itself could be an advantage of lncRNA-associated therapy. Similar to what happens naturally during cell fate decisions, the whole developmental programme of a cell or particular parts of it could be reset. In consideration of the early onset of epigenetic aberrations, such an approach could even be useful for cancer prevention.

INTRODUCTION

Development of specific strategies for an effective prevention and treatment of cancer is the ultimate goal of molecular cancer research. The substantially improved understanding of the role of genetic aberrations that are intrinsic to cancer cells has already lead to a conceptual shift in drug discovery. The concept of targeted cancer therapy (Sawyers, 2004) is meant to suppress tumor growth by interfering with aberrantly operating molecules and signalling pathways that favor carcinogenesis. Some new, target-specific drugs have exhibited promising results and have been approved for clinical applications (e.g., Hudis, 2007; Sequist et al., 2008). Still, the overall efficacy is not as good as anticipated. This raises the question if alternative therapeutic principles might exist that lead to better results. To target cancer at its root, a solid understanding of the biological nature of carcinogenesis is required (Huang et al., 2009) to bring about high specificity of any treatment option for malignant cells. While the current targeted drugs meet the criterion of specificity, they are rather based on a mechanistic view of targeting known molecular aberrations, which may be secondary, however, in the context of tumor development (Huang et al., 2011).

The biological starting point of carcinogenesis could be an aberrant launch of developmental or regenerative programmes in stem cells (Beachy et al., 2004; Widschwendter et al., 2007). The facts that epigenetic programming is involved in cell fate specification (Bröske et al., 2009) and that ubiquitous and concurrent epigenetic alterations are detectable already during very early stages of tumor development (Crawford et al., 2004; Issa, 2004; Suzuki et al., 2004) strongly suggest that epigenetic disruption in stem cells may be a unifying theme in cancer etiology (Feinberg et al., 2006). Moreover, the capability of reprogramming most properties of tumor cell genomes—for example, by their injection into a blastocyst (Illmensee and Mintz, 1976); by transplantation of nuclei into normal oocytes (Hochedlinger et al., 2004); by induction of differentiation

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(Lotem and Sachs, 2002); or through generation and differentiation of induced pluripotent stem cells (Carette et al., 2010)—provides a clear indication for the decisive role of the epigenetic architecture in the establishment and maintenance of malignant phenotypes. Collectively, this growing line of evidence provides a strong rationale for considering the therapeutic modulation of neoplastic epigenomes as a promising approach for the prevention and treatment of cancer.

Several epigenetics-based therapeutic approaches have been suggested (Yoo and Jones, 2006), and promising preclinical and clinical trials have been conducted for the treatment of patients with malignant diseases such as myelodysplastic syndrome, myelofibrosis, or chronic myeloid leukemia, for example (Rogers et al., 2010; Shen et al., 2010; Park et al., 2011). The compounds used include inhibitors of DNA methyltrasferases (DNMT) (Kaminskas et al., 2005) and histone deacetylases (HDAC) (Marks et al., 2000), with some drugs already being approved for clinical application. However, the current strategies of epigenetic therapy are not capable of specific modifications of cancer epigenomes (Mund and Lyko, 2010). For example, application of DNA demethylating agents such as 5-aza-2′-deoxycytidine (decitabine) leads to global hypomethylation (Fig. 1A) and has both positive and negative consequences, such as the clinically favorable temporal reactivation of aberrantly silenced tumor suppressor genes and the adverse effect of inducing proto-oncogenes, pro-metastatic genes, and transposable elements (Gaudet et al., 2003; Howard et al., 2008; Chik and Szyf, 2011). A targeted epigenetic reprogramming of cancer cells would be superior, and the question arises, which biological processes could be employed to this end.

The existence of natural instructive mechanisms for epigenetic programming has long been suggested by the careful orchestration of chromatin modifications throughout development, although only a small repertoire of chromatin remodelling complexes exists and they exhibit only little specificity for particular DNA motives (Mercer et al., 2009). Concordant epigenetic silencing of numerous cancer-related genes was observed in different tumors (Issa, 2004), adding further evidence for an epigenetic programming process. Once the underlying principles are fully understood, they might be employed for the therapeutic reprogramming of cancer epigenomes. Long noncoding RNAs (lncRNAs) are increasingly recognized to be responsible for target specificity of the chromatin-modification complexes (Rinn et al., 2007; Mattick et al., 2009). lncRNAs are transcripts of more than about 200 nucleotides in length that have little or no protein-encoding capacity (Mercer et al., 2009). They belong to the noncoding RNAs (ncRNAs), which are a structurally and functionally highly diverse group of regulatory transcripts (Costa, 2010; Taft et al., 2010; Pauli et al., 2011). The current classification scheme is largely artificial and based on molecule length (short or long), genomic localization relative to gene regulatory elements (promoter, transcription start site, enhancer) and their biogenesis and functionality (Pauli et al., 2011). Long ncRNAs with epigenetic-related function—the focus of this study—belong primarily to the subgroup of long intergenic ncRNAs (lincRNAs), which are marked by distinctive chromatin signatures of actively transcribed genes (Guttman et al., 2009) and affect expression of targets largely in trans (Guttman et al., 2011). Table 1 provides a short overview of the regulatory noncoding transcriptome in mammals.

Recent findings clearly demonstrate that some lncRNAs can serve as an interface between DNA and histone-modification enzymes and thereby recruit the enzymes to particular genomic loci (Rinn et al., 2007; Khalil et al., 2009). Indeed, about 20% of lncRNAs expressed in various cell types were shown to bind the Polycomb Repressive Complex 2 (PRC2) (Khalil et al., 2009), which induces repressive (H3K27me3) chromatin states and has an important role in stem cell differentiation and early embryonic development (Ringrose and Paro, 2004). Other chromatin-modification complexes also bind to lncRNAs, such as the G9a methyltransferase (Nagano et al., 2008) or the Trithorax group (TrxG) proteins, the latter endowing chromatin with activating (H3K4me2) marks (Rinn et al., 2007). Also, many lncRNA transcripts have been identified by transcriptional profiling of the four human homeotic (*HOX*) loci that are spatially expressed along developmental axes and demarcate differential histone methylation patterns (Rinn et al., 2007). One of these lncRNAs, *HOTAIR*, is transcribed from the *HOXC* locus, binds PRC2 and directs it to the *HOXD* locus, inducing repressive chromatin states. Furthermore, *HOTAIR* functions as a scaffold for assembling different repressive chromatin-modification complexes, for example LSD1-CoREST (a H3K4me2 demethylase), and directs them to particular genomic sites (Tsai et al.,

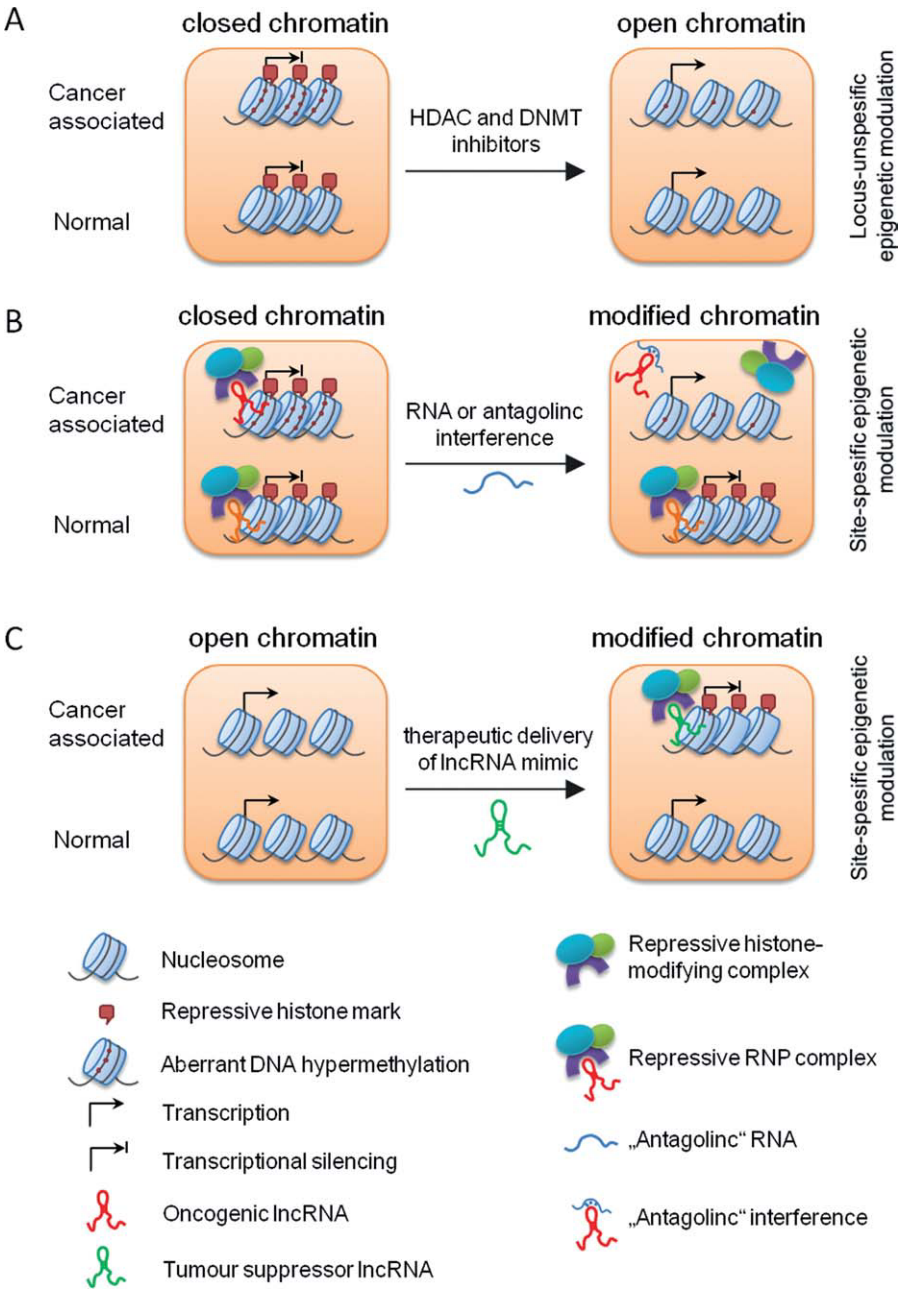

Figure 1. Schematic comparison of the effects of currently employed epigenetic cancer therapy (A) with that of potential lncRNA-based approaches (B,C). "Cancer associated" refers to genomic loci with cancer-specific epigenetic alterations. "Normal" denotes loci that are epigenetically identical in normal and cancer cells. (A) HDAC and DNMT inhibitors induce a genome-wide, unspecific modification of the histone code and the DNA methylation pattern. (B) RNAi- or "antagolinc"-molecules mediate a reduced functionality of oncogenic lncRNAs that are responsible for epigenetic changes associated with cancer. The specificity of lncRNA targeting avoids interference with other epigenetically silenced loci. (C) Expressional restoration of down-regulated lncRNAs that function as tumor suppressors by the therapeutic delivery of an lncRNA mimic, which results in an epigenetic reprogramming of particular (cancer-associated) genomic sites.

2011). The list of functionally characterized lncRNAs is growing continuously (Guttman et al., 2011), with many candidates known or presumed to be involved in scaffolding and recruiting chromatin-modification activities (Loewer et al., 2010; Spitale et al., 2011).

The genomic occupation sites of PRC2 are prone for cancer-specific promoter DNA hypermethylation (Widschwendter et al., 2007), linking numerous lncRNAs to carcinogenesis. Also, cancer-specific lncRNA expression signatures have been reported and potential oncogenic and tumor

TABLE 1. Diversity of Regulatory Noncoding RNAs in Mammals

Class	Subclass	Abbreviation	References
Long ncRNAs	Long (or large) intergenic ncRNA	lincRNAs	Guttman et al., 2009
	Antisense ncRNAs	aRNAs	Morris et al., 2008; Yu et al., 2008
	Promoter-associated long RNAs	PALRs	Kapranov et al., 2007
	Promoter upstream transcripts	PROMTs	Preker et al., 2008
	Other groups: e.g., GAA repeat-containing RNAs, long stress-induced noncoding transcripts, stable excised intron RNAs etc.	GRC-RNAs, LSINCTs	Silva et al., 2010; Zheng et al., 2010; Gibb et al., 2011
Short ncRNAs	MicroRNAs	miRNAs	He and Hannon, 2004
	Piwi interacting RNAs	piRNAs	Siomi et al., 2011
	Endogenous small interfering RNAs	endo-siRNAs	Okamura and Lai, 2008
	Transcription start site-associated RNAs	TSSa-RNAs	Seila et al., 2008
	Promoter-associated short RNAs	PASRs	Affymetrix/Cold Spring Harbor Laboratory ENCODE Transcriptome Project, 2009
	Splicing-dependent intronic microRNAs	miRtrons	Berezikov et al., 2007
	Other groups: e.g., transcription initiation RNAs, unusually small RNAs etc.	tiRNAs, usRNAs	Gibb et al., 2011

suppressor candidates have been described (Huarte and Rinn, 2010). Many lncRNAs seem to have immediate roles in cancer development by inducing altered chromatin states that favor tumoral growth. For example, the lncRNA *HOTAIR* is causally involved in tumor progression. It is significantly overexpressed in metastatic breast cancer. Also, it induces epigenetic reprogramming of almost 900 promoters of cancer-related genes genome-wide, thereby promoting matrix invasion of carcinoma cells and enhancing lung colonisation in a xenograft model (Gupta et al., 2010). A significant reduction of matrix invasion has been detected upon RNAi depletion of *HOTAIR* in breast cancer cells. In combination, these studies suggest that epigenetic perturbations in cancer could at least partially be based on abnormalities of lncRNA expression. Consequently, modulation of lncRNA expression or disruption of their interactions with the chromatin-modification complexes in cancer cells might result in clinically favorable epigenetic signatures.

The strongest rationale for exploring the therapeutic potential of lncRNAs in cancer is their potential to direct chromatin modifications to multiple genomic sites, thereby affecting whole developmental programmes (Huang et al., 2009). For example, expression variations of lincRNA-RoR—a lncRNA that is presumed to function through chromatin remodelling—in induced pluripotent stem cells modulated the expression of 449 genes that are associated with stress pathways, suggesting a crucial role of this lncRNA for the establishment and maintenance of pluripotency (Loewer et al., 2010). Since patterns of epigenetic modifications may dictate cellular identity, their modulation could in principle be employed for a therapeutic reprogramming of the malignant properties of cancer cells, as already discussed for *HOTAIR*. Given the fact that a recruitment of DNA methyltransferases by the PRC2 component EZH2 has been reported (Viré et al., 2006), it is plausible to assume that the result of such interventions could not only be limited to a reimposition of chromatin states, but might also affect the aberrant hypermethylation of relevant promoters.

Two potential, nonexclusive approaches for lncRNA-based epigenetic therapy could be envisaged. lncRNA candidates with an oncogenic activity could be targeted by RNAi or RNAi-like molecules for a reduction of their abundance and thus a diminution of their functional activity (Fig. 1B). The same effect could be achieved by the binding of short RNA sequences (antagolincs) (Tsai et al., 2011) to the lncRNA-protein interfaces, disrupting the interaction. Alternatively, downregulated lncRNAs with a tumor-suppressor potential could be subjected to a replacement therapy (Fig. 1C), which is based on the premise that an aberrant alteration of the epigenetic status in multiple genomic sites could be reversed by a therapeutic delivery of an appropriate lncRNA mimic.

It is stimulating to speculate about characteristic features of a potential cancer therapy that would be based on the above concept. First, it is a targeted therapy because it interferes specifically with RNA molecules that are aberrantly

expressed in cancer cells only. Thus, fewer side effects could be expected. Secondly, it is an epigenetic therapy aiming ultimately at chromatin remodelling. Third, high specificity of the induced epigenetic alterations could be achievable owing to the specific; however, yet to be defined functional principle of RNA-mediated recognition of the genomic target sites (Hung and Chang, 2010). In combination, the last two features would provide a means for specific epigenetic manipulation, a missing option of current epigenetic therapy approaches. Fourth, low toxicity is expected, since physiologic RNA molecules would be delivered as therapeutic agents. Finally, a key feature of lncRNA-based therapeutic intervention might be its biological orientation since modulation of only a single or few lncRNAs would induce epigenetic reprogramming of multiple genomic sites presumably in a manner similar to that occurring naturally during cell fate decisions.

We recognize that the above concept is still speculative, and much additional effort will be required to understand the lncRNA control of complex developmental programmes. Genome-wide analysis of lncRNA expression with a concomitant monitoring of epigenetic alterations could be performed through differentiation of stem cells into terminally differentiated cells in order to find prominent RNA candidates, which may be employed to partially or completely reverting malignant phenotypes of neoplastic cells. The feasibility of performing this task has already been proven in principle, although by other approaches (Illmensee and Mintz, 1976; Hochedlinger et al., 2004; Carette et al., 2010; Teng et al., 2011). Additionally, technical issues still need to be addressed, such as the development of optimal methods for lncRNA delivery, which are required for a replacement therapy or silencing of over-expressed targets. However, sequencing technologies for the analysis of really the entire transcriptome are rapidly getting more accurate and comprehensive. Since also reliable delivery systems exist in principle, current deficiencies in knowledge and technical ability should not be limiting factors in the long run.

In conclusion, an exciting and conceptually novel approach to rational cancer therapy is emerging, which takes advantage of lncRNA-mediated targeting of chromatin-modification complexes and aims at a reprogramming of aberrant epigenomes that determine many malignant properties of cancer cells. As such, it fits to a model of carcinogenesis (Feinberg et al., 2006) that considers epigenetic disruption of stem or progenitor cells as the first step and a unifying principle of cancer development. Because epigenetic alterations are in any case among the earliest if not the initial events during carcinogenesis, the approach has substantial preventive potential. One might expect that lncRNA-based reprogramming of aberrant cancer epigenomes may result in partial or complete reversion of a tumor phenotype. Although intensive research into the biological roles of lncRNAs is still necessary, this recently discovered class of molecules may hold substantial potential and benefit for the treatment of cancer in future.

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