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Review Article

Small non-coding RNAs as regulators of structural evolution and carcinogenesis

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ABSTRACT

Small non-coding RNAs (sncRNAs) are part of non-coding oligonucleotide regulators with wide physiologic and morphologic functions. They control genetic programing of cells, and may modulate processes of differentiation and death. Biogenesis of sncRNAs is now known, and some sncRNAs have been proposed as markers of malignization. Epigenetic therapy is based on the use of newly discovered genetic modifiers, such as sncRNAs, micro-RNAs, and theirs mimics. However, role of sncRNAs in structural evolution and mechanisms of adaptation is not clearly understood. Certainly, non-coding RNAs participate in processes of cellular and organismal adaptation as well as cellular and tissue structural transformation as response to changing of environmental neighbouring. Investigations into these functions of sncRNAs may be the basis of future epigenetic environmental medicine.

1. Introduction

Every second, multiple internal and/or external stressors act on human organism resulting in adaptation or injury. The strength and duration are the main factors that determine damage or adaptation. A set of internal and external effects may be partly or completely caused by the homeostatic misbalance of cells, leading to its changes. Sufficiently strong influencing factors will may lead to cell death. Influencing factors that are relatively weak and long lasting may induce changes in cellular metabolism, energetics or respiration due to changes in cellular functionality and extracellular communication. Finally, all of the adaptations involving extensive morphologic and genetic rearrangements are aimed at facilitating cell survival. The first signs of cellular structural change are disturbances in the levels of intra- and extra-cellular regulators, which stimulates and supports changes in the cellular genetic program. Small non-coding RNAs (sncRNAs) are primary mediators of the gene regulation at the transcriptional and post-transcriptional levels [1]. These molecules cause adaptive reversible or irreversible changes in cellular genetics and protein synthesis. Primary changes in the system are not stable, but if environmental stressors are repeated or constant, the system will adapt to these stimuli at the molecular, cellular and organismal levels. With time and many rounds of cellular division, the initially reversible changes could become irreversible, and the system will be relatively stable and more adapted to the stressor. In general, the processes of adaptive cellular transformation or structural evolution are similar to the mechanisms of carcinogenesis, in which primary cells that experience a stressful stimulus try to adapt and survive [2–4].

1.1. Carcinogenesis is a maladaptive form of evolution

Carcinogenesis, maybe considered as a maladaptive form of structural evolution, leading to full or partial destruction of the host organism. Carcinogenesis is a complex multistep process of cell transformation that is influenced by many factors. Changes in the cellular microenvironment are the main trigger for the cell to become malignant. This adaptation, as well as structural evolution, is caused by fundamental changes in cell morphology and physiology. Consequently, the long-lasting adaptive processes may cause full reconstruction of the cell and cause changes, including sustaining proliferative potential, evading growth suppressors, resisting apoptosis, supporting replicative immortality, activating metastasis and invasion and stimulating of angiogenesis. These cellular changes are common characteristics of malignant cells [5,6]. Finally, malignant cells have some properties of immortal “warriors”, which captures new tissue territories and kill or build molecular “fortifications” immune antagonists. The main causes of

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malignant transformation are genetic mutations and damage to the epigenetic control of the cellular genetic program.

1.2. Gene therapy of cancer with sncRNAs

Many methods of treating cancer cells have been proposed, but most methods, such as chemotherapy, radiotherapy, and surgery, result in a direct attack on the malignant cells. These approaches for local destruction of tumors do not address generalized pathological processes, such as metastases. Genetic changes in cells will not disappear after tumors are destroyed locally. Gene therapy may be a key to the therapeutic strategy against malignantly transformed cells.

Recently, many new drugs have been proposed for the gene therapy of tumors [7–10]. Despite the large number of potential applications, many challenges need to be addressed, such as finding the direct regulatory sequences for cancer targets, the low transfection efficiency properties of carriers, the fast biodegradation and bio-destruction, toxicity, septicemia, and others [11,12]. In the recent studies, were used polymer carriers for genetic and epigenetic regulators, such as sncRNAs. The used carriers had high transfection efficiency, slow biodegradation, and low toxicity and were inexpensive to produce. In these experiments, cancer cells were successfully reprogramed into other types of cells after transfection using combinations of different sncRNAs with polymer carriers. As a result, CaCo2 cells were transformed into $CD4^+$ cells and Paneth cells, A-549 lung adenocarcinoma cells were transformed into $CD4^+$ cells, Girardi cells were reprogrammed into CD117 + cells, and leukemia cancer cells were transformed into platelet-like cells [13–15]. In these experiments, cancer cells were initially transformed into stem or stem-like cell and then re-reprogrammed these cells into other type of cell (e.g. $CD4^+$, Paneth cells, and platelet-like cells) with selected miRNAs (Fig. 1).

1.3. SncRNAs

The non-coding genome constitutes approximately 98% of DNA, and only 2% of the genome codes for proteins. For a long time, researches did not understand the function of the non-coding parts of the genome. Non-coding molecules and sequences were referred to as “junk”. Recently, investigation of the non-coding genome has increased, and now, non-coding oligonucleotides are known to play key roles in the epigenetic and genetic regulation of cellular functions. Additionally, these molecules often participate in intercellular communication as passengers in exosomes. sncRNAs are small non-coding regulatory molecules. These molecules have a variety of family members, among which the most investigated are small-interfering RNAs, small nuclear RNAs, small nucleolar RNAs, micro-RNAs (miRNAs), and PIWI-interacting RNAs (piRNAs). This class of non-coding RNAs has widespread effects on the genetic and epigenetic functionality of cells. Non-coding RNAs in embryos regulate the differentiation and development. sncRNAs regulate gene expression and affect the organization and modification of chromatin. sncRNAs also control centromere function. The centromere is of vital importance to genetic stability; this region of DNA enables the separation of chromosomes during mitosis and meiosis. ncRNAs derived from centromere repeats participate in the formation of peri-centromeric and centromeric heterochromatin, which is important for proper centromere function. sncRNAs play key roles in the control of metabolism, immunity, cell proliferation and differentiation, organ and tissue development, and apoptosis. sncRNAs participate in processes of carcinogenesis (Table 1.).

The diverse roles of sncRNAs in gene expression suggests that these molecules are indeed the architects of eukaryotic complexity from an evolutionary point of view. A large number of sncRNAs are highly conserved sequences within the animal and plant kingdoms. However, there are phenotypic differences between the two kingdoms. The complexity of higher organisms depends on the activity and regulation of protein-coding genes. SncRNA-associated gene regulation occurs more frequently in higher eukaryotes than in prokaryotes. Processes such as RNA interference, gene silencing, imprinting, co-suppression, methylation, acetylation, position-effect related variegation, and paramutation are cyclically related pathways through which sncRNA signaling is affected [16]. Paramutation is a genetic term for a type of epimutation corresponding to atypical inheritance patterns of traits. A paramutation is induced by a mutant allele in the other allele of the same gene. The allele that induces the changes is the paramutagenic allele, whereas the

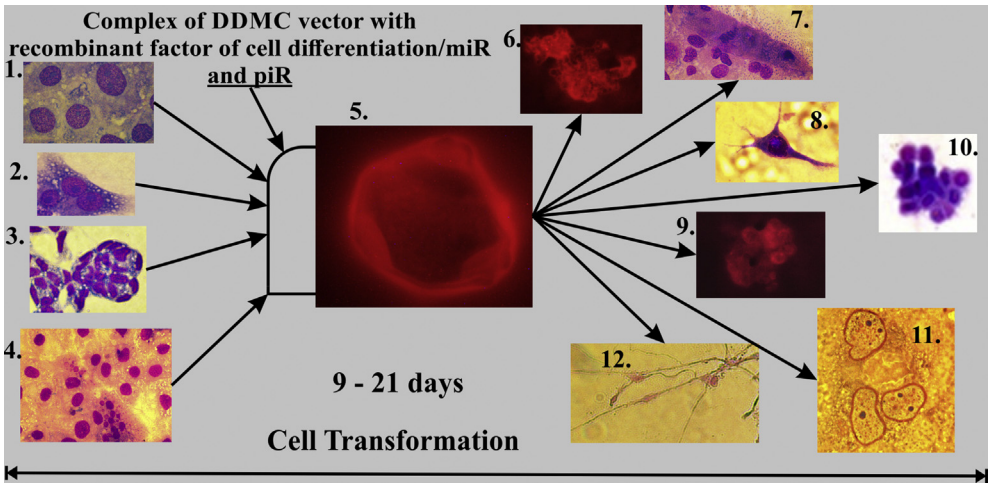

Fig. 1. Scheme of method of cancer cells transformation into other types of cells. Treatment of different cancer cell lines with complex of the DDMC vector with mix of separated sncRNAs with or without cell differentiation factor due to transformation of cancer cells in different types of cells. Cells and cell lines: 1. A-431 (ATCC® CRL-1555™) is human epidermoid carcinoma; 2. A-172 (ATCC® CRL-1620™) is human glioblastoma cell line; 3. IMR-32 (ATCC® CCL-127™) is human neuroblastoma cell line; 4. CaCo2 (ATCC HTB-37 TM) is human colorectal adenocarcinoma cell line; 5. Stem-cell-like cell is intermediate form of cells, which was obtained before full cancer cell transformation; 6. CD117 positive cells [15]; 7. Epithelization-like process (not published); 8. Dendritic-like cell (not published); 9. CD4 positive cells [14,15]; 10. Platelet-like cells [13]; 11. Paneth-like cells (not published); 12. Neuron-like cells (not published). (Author made all microscopic photos. Magnification of fluorescent and light microscopy was ×600).

Table 1
Dysregulated small non-coding RNAs in the four most common cancers [1].

Type of cancer		Biomarker sncRNAs	Elevated levels	Down-regulated
Lung cancer	miR-29c, miR-93, miR-429, miR-19a, miR-17-5p, miR-210, miR-21, miR-486, miR-145, miR-155, miR-146b, miR-221, miR-let-7a, miR-27a, miR-106a, miR-29c, miR-20a-5p, miR-25-3p, miR-191-5p, miR-223-3p, miR-296-5p, miR-320-3p, miR-let-7f-5p, miR-24-3p, miR-126-3p, miR-145-5p, miR-152-3p, miR-199a-5p, miR-197, miR-182 [2].	miR-21, miR-17, miR-155, miR-150, miR-3940-5p, miR-183, miR-30e-5p, miR-125a-5p, miR-let-7e, miR-19a [2]; piR-651 [3].	miR-31, miR-10a, 16 [2]; piR-L-163 [3].	
Breast cancer	let-7a, let-7b, let-7c, miR-1308, miR-21, miR-494, miR-923 [5]; miR-15a, miR-18a, miR-107, miR-425, miR-133a, miR-133b, miR-139-5p, miR-143, miR-145, miR-365, miR-155, miR-1, miR-92a, miR-148b, miR-376c, miR-409-3p, miR-801, miR-16, miR-21, miR-451, miR-145 [6].	miR-21, miR-155, miR-10b, miR-373/520c, miR-27a, miR-221/222 [4]; miR-183 [5]; miR-10b, miR-155, miR-373, miR-520c [6]; miR-30b-5p, miR-182-5p, miR-374b-5p, miR-942b-5p [7]; piR-4987, piR-20365, piR-20485, piR-20582, piR-36743, piR-36026, piR-31106 [3, 8].	MiR-206, miR-17-5p, miR-125a,b, miR-200c, let-7, miR-34a, miR-31, miR-335, miR-27b, miR-126, miR-101, miR-145, miR-146a/b, miR-205 [4]; miR-125b, miR-205, miR-17-92, miR-206, miR-200, miR-146b, miR-126, miR-335, miR-31 [6]; piR-34736, piR-36249, piR-35407, piR-36318, piR-34377 [3, 8].	
Colorectal cancer	miR-92a [9].	Let-7, miR-17-5p, miR-20a, miR-29a, miR-21, miR-31, miR-92a, miR-181b, miR-203 [9]; let-7g, miR-15b, miR-192, miR-215, miR-21, miR-200 [10].	miR-106a, miR-126, miR-143, miR-145 [9]; miR-145, miR-15a, miR-181b [10].	
Prostate cancer				

Table 1 (*continued*)

Type of cancer		Biomarker sncRNAs	Elevated levels	Down-regulated
	miR-222-3p, miR-24-3p, miR-30c-5p, miR-125b-5p, let-7a-5p, miR-151-5p [13].	miR-30c, miR-122, miR-125a, miR-181a, miR-181c, miR-146b-5p, miR-184, miR-193a, miR-193b, miR-214, let-7f, miR-1, miR-17, miR-98, miR-122, miR-125b, miR-125a-5p, miR-144, miR-142-5p, miR-146b-5p, miR-181a, miR-210, miR-32, miR-98, miR-138, miR-142p, miR-144, miR-181c, miR-183, miR-184, miR-205, miR-206, miR-215, miR-272, miR-301 [11]; miR-125b, miR-21, miR-17-92, miR-25, miR-205, miR-24, miR-629, miR-660, miR-20a, miR-107, miR-143, miR-141, miR-221, miR-375 [12]; miR-30a/b/c-5p, miR-125b-5p [13].	miR-15-16, miR-145, miR-107, miR-205, miR-29b, miR-331-3p [12]; miR-31-5p, miR-141-3p, miR-146a-5p, miR-24-3p, miR-222-3p [13].	

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epigenetically altered homologous allele is termed the paramutant allele. A paramutant allele leads to altered gene expression profiles, which are often associated with a phenotype [17]. Paramutable alleles can provide a continuous spectrum of phenotypic variation, thus driving allele frequencies toward non-Mendelian patterns, and they can facilitate the inheritance of acquired characteristics. Paramutations occur as a response of the nucleus to the actions of environmental stimuli. Maternal miRNAs and piRNAs appeared to inhibit the efficiency of the germline transmission of the paramutations. In maize, the induction of paramutations appears to be mediated by small RNAs [17]. sncRNAs are intermediaries step between environmental and nuclear systems that accommodate the competing interests of transposons and genome integrity for evolutionary success [18].

1.4. piRs and mobile transposable elements

The sncRNAs family includes piRNAs, which are less studied because of their greater amount to compare with miRNAs. piRNAs play a main role in the regulation of transposable elements (TEs). The TE activity induced by external stimuli should thus be considered an evolutionary adaptive mechanism. TEs play a main role in the selection process and have been referred to as a “moving force of mammalian transcriptome evolution”. Newly inserted TEs may lead to large changes in nearby gene expression, thereby supporting the development of new phenotypes that will be subjected to evolutionary selection [19,20]. However, TEs, particularly L1 long interspersed nuclear element (LINE) and Alu and SVA short interspersed nuclear elements (SINE), may induce irreversible changes in the genome due to malignant transformation [21]. TE activity in cancer cells is associated with a breakdown in cellular TE repression mechanisms, and increased TE activity is connected to non-adaptive responses in cancer cells. piRNAs may directly inhibit TEs. On the one hand, piRNAs may act as genetic immune guardians to control the silencing of TEs, which are cause genetic instability in cancer cells [22–24]. On the other hand, piRNAs bind transposons and block adaptive transformations in cells [25]. Therefore, TEs and theirs silencer piRNAs can be considered a byproduct of genome flexibility that is meant to optimize cellular adaptation [26].

Complex therapy with miRNAs and piRNAs can correct transcriptional and post-transcriptional non-adaptive cellular program.

2. Conclusion

These findings indicate that sncRNAs are key regulators in both structural evolution and carcinogenesis. Certainly, sncRNAs that regulate these two processes will be promising tools to treat cancer and regulate adaptive responses.

3. Key points

- Mobile transposable elements are inducers and promoters of malignization.
- SncRNAs can modify functions of epigenetic regulators and can directly inhibit mobile transposable elements.
- Small non-coding RNAs can modify cellular functions and morphology, which result in structural adaptation of cells.
- Gene therapy with sncRNAs may be a key tool in the target therapy of cancer and new tool in adaptive epigenetic medicine.

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