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Review Article

Non-coding RNAs are promising targets for stem cell-based cancer therapy

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ABSTRACT

The term "non-coding RNA" (ncRNA) is generally used to indicate RNA that does not encode a protein and includes several classes of RNAs, such as microRNA and long non-coding RNA. Several lines of evidence suggest that ncRNAs appear to be involved in a hidden layer of biological procedures that control various levels of gene expression in physiology and development including stem cell biology. Stem cells have recently constituted a revolution in regenerative medicine by providing the possibility of generating suitable cell types for therapeutic use. Here, we review the recent progress that has been made in elaborating the interaction between ncRNAs and tissue/cancer stem cells, discuss related technical and biological challenges, and highlight plausible solutions to surmount these difficulties. This review particularly emphasises the involvement of ncRNAs in stem cell biology and *in vivo* modulation to treat and cure specific pathological disorders especially in cancer. We believe that a better understanding of the molecular machinery of ncRNAs as related to pluripotency, cellular reprogramming, and lineage-specific differentiation is essential for progress of cancer therapy.

1. Introduction

Huge efforts undertaken to understand how tissues are formed during development and are sustained by stem cells throughout life have mainly concentrated on the genomes that can code proteins. In the past decade, however, our comprehension of the non-coding genome and its importance in cell biology has dramatically shifted. Although most non-coding RNAs (ncRNAs) used to be regarded as "junk", the identification of thousands of long and short ncRNAs has revealed that much of the genome, including ncRNAs, most likely has functional roles [1] [2].

Although there are several classes of ncRNAs, they can basically be classified into small ncRNAs and long ncRNAs (lncRNA) [3]. Among them, microRNAs (miRNAs) in small ncRNAs and lncRNAs especially have peaked the interest of many researchers. Various aspects of both types have been scrutinised in terms of cellular biology and have been implicated as key regulators in a variety of cellular processes including stem cell biology [4] [5] [6]. One of the features of miRNAs and lncRNAs that make them promising candidates for essential roles in stem cells is that their unique expression patterns in stem cells have proved their involvement in the maintenance of stemness [7] [8]. In addition, both miRNAs and lncRNAs exhibit specific temporal and spatial patterns indicating that they should play an important role in the developmental stage [9] [10] [11].

In the last decade, the term "cancer stem cell" (CSC) was defined as a cell within a tumour that possesses the capacity to self-renew and to form heterogeneous lineages of cancer cells that consist of the tumour [12]. Although there are numerous difficulties in accurately characterising CSCs, several markers, such as LGR5 for colorectal cancer and CD133 for several solid cancers, have been widely validated and accepted [13] [14]. In accordance with dissecting the CSC markers out, it was proved that ncRNAs could also

Abbreviations: CD, cytosine deaminase; CSC, cancer stem cell; EMT, epithelial to mesenchymal transition; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; lincRNA, long inverting non-coding RNA; lncRNA, long ncRNA; MSCs, mesenchymal stem cells; MET, mesenchymal to epithelial transition; miRNAs, microRNAs; ncRNAs, non-coding RNAs; T-UCR, transcribed ultraconserved region.

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contribute to CSC maintenance. Indeed, the lists of CSC markers and ncRNAs in non-cancerous stem cells and CSCs are rapidly growing. It is a daunting task to keep up with new insights into how these complicated machineries are organised and their functions are carried out.

In this review, we present an overview of the interaction between ncRNAs and non-cancerous stem cells/CSCs. We then survey the present status of regenerative medicine in cancer treatment. Finally, we detail ways to overcome the problem of the practical use of ncRNAs in regenerative medicine for cancer treatment.

2. miRNAs in non-cancerous stem cells

Due to the difficulty in isolating adequate amounts of tissue stem cells for RNA study, most studies have focused on miRNA expression in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). After the establishment of iPSCs with the delivery of a few pluripotency factors, in-depth analyses of miRNA expression patterns revealed that the miRNA expression profile in iPSCs is quite similar to that in ESCs [15] [16]. Specifically, miRNAs involved in pluripotency, such as the miR-290-295 cluster, miR-302-367 cluster, and miR-17 family, are upregulated, and those concerning cell differentiation, such as the let-7 family and miR-34 family, are downregulated while reprogramming is under way [17] [18] [19] [20] [21]. Although this data seems to imply that some miRNAs are deregulated in accordance with cell conversion, miRNAs genuinely play an essential role in the maintenance of iPSCs/ESCs as the maintenance is disturbed by the loss of Dicer expression [7].

One straightforward scheme to identify miRNAs effecting cell pluripotency is simply to search for those miRNAs that are most likely to interact with representative pluripotency-related genes, including SOX2, OCT4, KLF4, and c-Myc. The miR-34 family is well known to induce and maintain cell pluripotency by regulating SOX2, n-Myc, and Nanog, and the let-7 family oppositely hinders the induction of pluripotency through targeting of c-/n-Myc and Lin28 [20] [22]. Prior studies have also emphasised that the conversion of terminally differentiated cells to iPSCs requires mesenchymal to epithelial transition (MET), and ESCs can inversely proceed with the reverse process, so-called epithelial to mesenchymal transition (EMT) [23]. Several lines of research have actually determined that miRNAs concerned with the transition from epithelial into mesenchymal cells, and vice-versa, are involved in pluripotency or can potentially be promising markers for the identification of stem cell populations. Indeed, miRNAs that play an essential role in EMT/MET, such as the miR-370-373 cluster, miR-302-367 cluster, miR-200, and miR-17 family, are well known as modulators of pluripotency [24] [25] [26] [27]. Especially, exogenous induction of the miR-302-367 cluster has been reported to efficiently promote the reprogramming of somatic cells [28]. These data have further shown that the generation and/or maintenance of iPSCs/ESCs cannot be completed without miRNAs. Table 1 shows a summary of miRNA clusters/families that are related to maintenance of ESCs/iPSCs.

3. lncRNA in non-cancerous stem cells

Most of the previous studies focused on the expression of lincRNAs in ESCs and iPSCs due to the limitation on the amount of tissue stem cells available for RNA study. Microarray-based analysis revealed that 174 lncRNAs were significantly upregulated in ESCs in comparison with those of somatic cells [29]. Further extensive studies found that key factors for the induction of iPSCs, such as OCT4, SOX2, c-Myc, and Nanog, were thought to regulate 10–12% of ESC-enriched lncRNAs, which were further validated by functional screenings based on short-hairpin RNA and reporter gene assays [30] [31]. These findings showed that lncRNAs are quite essential in the regulatory network of pluripotency. However, some lncRNAs were found to take part in the opposite machinery: enhancing the differentiation of stem cells. Indeed, Gomafu (AK028326) and lincRNA-RoR were directly upregulated by Oct4 and appeared to control Oct4 expression in a regulatory feedback loop [32] [33]. Conversely, Xist was found to interfere with the transcription of Sox2, Oct4, and Nanog in ESCs, and lncRNA_N1/2/3 were identified as a key regulator of neuronal differentiation that can directly interact with nuclear factors such as REST and SUZ12 [34] [35]. Table 1 shows a summary of lncRNAs that are related to maintenance of ESCs/iPSCs.

4. Possible involvement of the transcribed ultraconserved region (T-UCR) in stem cell biology

The T-UCR is one of the novel classes of lncRNAs transcribed from the genomic regions that are completely conserved in most vertebrates including human, rat, and mouse [36]. The 481 coding region of T-UCRs has been identified, and two transcripts are generated from the sense/anti-sense strand of each region, which means that 962 T-UCRs have been found thus far. Two major machineries are involved in the regulation of T-UCR expression: DNA hypermethylation and interaction with miRNAs [37]. As miRNAs have a crucial role in stem cell biology, an interaction between miRNAs and T-UCRs presumably contributes to at least a part of the regulatory mechanism of stem cells. However, no reports have mentioned the involvement of T-UCRs in stem cell biology. Further in-depth studies focusing on T-UCRs could have great potential to lead to a better understanding of the bigger picture of stem cell biology.

5. Non-coding RNAs in CSCs

Several lines of evidence have shown the critical roles of ncRNAs in CSC biology. A comparative study of the miRNA expression profile between ESCs and breast CSCs revealed that 37 miRNAs were differentially expressed in breast CSCs, and 3 clusters of the miR-200 family were significantly downregulated among them, suggesting the induction of EMT and stemness in breast CSCs [38] [39]. A comprehensive miRNA expression analysis using pancreatic CSCs exhibited a distinct signature; 210 miRNAs that are involved in self-renewal and differentiation were deregulated [40]. miR-34 was found to be downregulated in pancreatic CSCs, and the restoration of miR-34 inhibited self-renewal in these CSCs by disturbing BCL2 expression and NOTCH signal transduction [41].

Accumulating evidence has provided insights into the importance of other ncRNAs as regulators in several critical steps of cancer development, such as carcinogenesis, cancer invasion, and metastasis. HOTAIR, one of the well-characterised lncRNAs, affects cancer cell invasiveness by altering the methylation pattern of H3K27 and is also a useful marker for predicting the clinical outcome of patients with breast cancer [42]. In gastric cancer, piRNA-651 is upregulated and piRNA-823 is downregulated, and both are involved in tumour growth [43,44]. Based on these findings, both the dysfunction and deregulation of ncRNAs could potentially be involved in cancer progression. However, the practical contributions of these ncRNAs to CSC biology remain unclear. Hence, extensive analyses are needed to attain a deeper grasp of the detailed biological machinery behind how ncRNAs are directly

Table 1
A summary of non-coding RNAs related to generation and/or maintenance of ESCs/iPSCs.

Non-coding RNA	Expression status in ESCs/iPSCs	Validated target genes	Functional roles
miRNA cluster/family			
miR-290-295 cluster	Upregulated	Wee1, Fbxl5	cell cycle regulate
miR-302-367 cluster	Upregulated	p16, CDK2/4/6, AKT1, TGFBR2, EGFR	cell cycle regulate regulator of signal transduction
miR-370-373 cluster	Upregulated	p21, PTEN, SOS1	cell cycle regulate cell death & apoptosis
miR-17 family	Upregulated	p21, Bim, CTGF, Tsp1	cell proliferation, apoptosis angiogenesis
let-7 family	Downregulated	RAS, MYC, HMGA2, CyclinD, CDC25A	cell proliferation/differentiation
miR-34 family	Downregulated	Bcl-2, CyclinD1/E2, CDK4/6 c-/N-Myc, SIRT1	apoptosis, cell cycle regulate cell senescence
long non-coding RNA			
Gomafu	Up/Downregulated	SF1, Oct4	regulate Oct4 expression
linc-RNA RoR	Up/Downregulated	Oct4	regulate Oct4 expression
Xist	Downregulated	PRC2	Silencing H3K27Me3
lncRNA_N1/2/3	Up-regulated	REST,SUZ12	neural differentiation

involved in the development and progression of cancer.

6. Technologies to induce expression of ncRNAs for regenerative medicine

As we have shown accumulating evidence of how ncRNAs contribute to cancer and CSC biology, they could potentially be hopeful targets for stem cell-based cancer therapy. One useful way to modify the expression of any particular ncRNA could be through synthetic nucleic acids. One challenge in the modulation of ncRNA expression is the selection of the right candidate and the proper evaluation of how the designed oligonucleotides affect a specific biological pathway [45]. To reduce the possibility of enhancing cancer development as a potential side effect, the optimal modulation of key ncRNAs must be well monitored when researchers try to use stem cells for therapeutic purpose. There are several techniques to deliver ncRNAs to live cells, such as direct injection, viral delivery, and non-virus based methods (Fig. 1).

6.1. Direct injection

The simplest ways for delivery of ncRNAs is by direct injection. The effect is typically believed to be quite short because the oligonucleotides are usually degraded by nucleases in most of the body fluids. However, a single bolus injection of nucleic acid, an antagonist of ncRNAs, is more likely to be active for several weeks [46].

6.2. Viral delivery

Virus-based ncRNA delivery to cells using adenovirus, lentivirus, or retrovirus vectors is one of the most widely accepted techniques especially *in vitro* [47]. Although the viral vectors enable long-term stable expression of ncRNAs, this approach does not seem to be appropriate for *in vivo* study due to issues of toxicity and immunity [48].

6.3. Lipid nanoparticles

In the field of regenerative medicine, precisely controlled release of the designed reagents is quite important to regulate cell differentiation. One upside of nanoparticles is that they can provide more flexibility in formulation and design for improved uptake by the cell [49]. However, one of the main limitations of this technique is the lack of a proper mechanical support compound that is essential to enhance the efficiency of the designed reagents [50].

These highly sophisticated miRNA delivery techniques cannot only induce the expression of ncRNAs but can also be useful for preparing the desired payload of ncRNAs for efficient stem cell-based therapy.

7. State-of-the-art approach to stem cell-based cancer therapy

One cutting-edge strategy for stem cell-based cancer therapy is

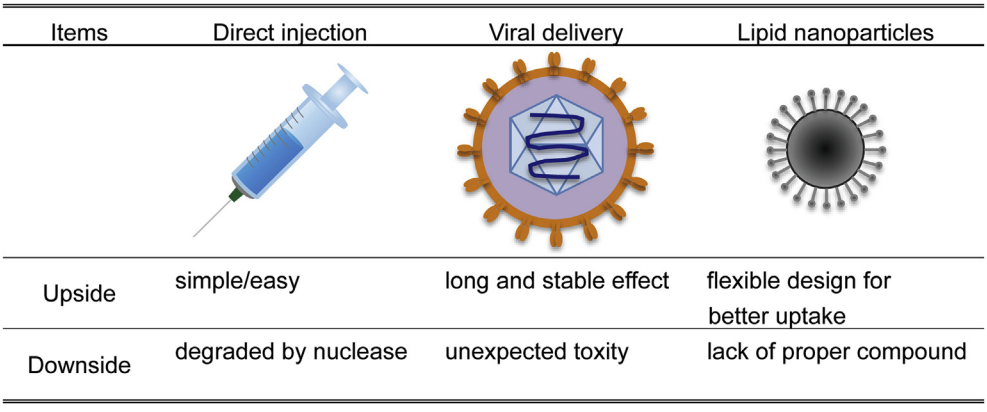

Fig. 1. A brief summary of current approaches for ncRNA delivery.

to generate stem cells that can concurrently express and secrete multiple therapeutic reagents to potentially repress several lines of cancer-related pathways [51]. Two examples of bimodal stem cells are the combinations of herpes simplex virus thymidine kinase therapy with TRAIL in glioblastoma models and cytosine deaminase (CD) with interferon-β in glioblastoma and breast cancer models in mice [52] [53] [54]. A similar strategy was applied for use in creating human umbilical cord mesenchymal stem cells (MSCs) to secrete a CD20-specific single-chain Fv antibody fragment combined with TRAIL [55]. Delivery of this fused immunoconjugate with MSCs was much more efficient than with TRAIL alone in a mouse model of non-Hodgkin's lymphoma as it simultaneously repressed tumour cell growth and specifically led to apoptosis in tumour cells. This strategy could potentially be useful for cancer therapy via generation of MSCs that can secrete several suppresive ncRNAs against cancer progression (Fig. 2). These results strongly support the utility of MSCs for cancer therapy, and in-depth studies will be required for further validation of the best combinations of ncRNA target therapy for a given cancer.

8. Conclusion

With cues taken from the processes of tissue generation and development, there is a significant potential to modulate the expression of ncRNAs in cancer cells and CSCs by both endogenous and exogenous methods to direct the activity of implanted stem cells in cancer therapy. Although the spatial and temporal signaling networks of ncRNAs need to be further elucidated, pursuit of the best ncRNA-based therapy has immense potential to establish a new scheme of cancer therapy.

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Conflict of interest

The authors have no relationships or conflicts of interest to declare.

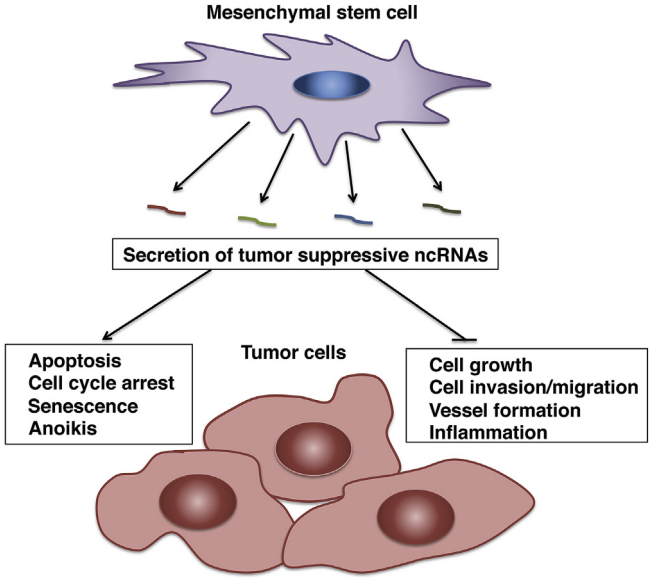

Fig. 2. Utility of mesenchymal stem cells to cancer therapy.

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