Non-Coding RNAs and CSCs

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Cancer stem cells (CSCs) are important factors for the initiation and progression of carcinogenesis. CSCs distinct features can be either promoted or suppressed by the function of non-coding RNAs (ncRNAs), mainly miRNAs, lncRNAs and circRNAs, primarily through the targeting of crucial signaling pathways, such as Wnt, Notch and Hedgehog pathways.

Keywords: Cancer stem cells, non-coding RNAs, carcinogenesis

Introduction

The identification of cancer stem cells (CSCs) as initiators of carcinogenesis has revolutionized the era of cancer research and our perception for the disease treatment options. Additional CSC features, including self-renewal and migratory and invasive capabilities, have further justified these cells as putative diagnostic, prognostic, and therapeutic targets. Given the CSC plasticity, the identification of CSC-related biomarkers has been a serious burden in CSC characterization and therapeutic targeting. Over the past decades, a compelling amount of evidence has demonstrated critical regulatory functions of non-coding RNAs (ncRNAs) on the exclusive features of CSCs. We now know that ncRNAs may interfere with signaling pathways, vital for CSC phenotype maintenance, such as Notch, Wnt, and Hedgehog.

Major Types of ncRNAs Involved in Cancer Biology

There are three major classes of ncRNAs reported to play a critical role in cancer pathogenesis. The classification has been based on their size and conformation.

MiRNAs: As their name declares, microRNAs (miRNAs) are small, linear, and single-stranded ncRNA molecules, with an average length of 22 nucleotides [1][2]. miRNAs contribute to a wide range of normal and abnormal biological processes by functioning in RNA silencing and post-transcriptional regulation of gene expression. miRNAs bind via base pairing to 3′ UTRs of mRNAs, causing their cleavage or translational repression [3][4]. In animal cells, the miRNA-coding genes are usually transcribed as long primary transcripts (pri-miRNAs), which are processed by the Drosha microprocessor complex into precursor hairpin stem-loop sequences (pre-miRNAs). These hairpins are exported from the nucleus to the cytoplasm, where the stem-loop is cleaved by the Dicer enzyme to produce a ~22 nt duplex. One strand of the duplex associates with an Argonaute (AGO) protein and this microRNA-ribonucleoprotein complex (miRNP) binds to 3′ UTRs of mRNAs. The Ago-miRNP complex then recruits other proteins, which typically mediate either the degradation or the translational repression of the mRNA [1]. The human protein-coding genes are under selective evolutionary pressure to maintain miRNA binding sites, also called miRNA response elements (MREs) [5].

Accumulating data demonstrate that miRNAs are further embraced in cancer biology [6]. Deregulated patterns of miRNA expression are a common feature among several cancer models affecting, either positively or negatively, cancer hallmarks, including malignant transformation, uncontrolled cell proliferation, resistance to endogenous and exogenous apoptotic stimuli, as well as induction of the epithelial to mesenchymal transition (EMT) and metastasis [6][7][8]. MiRNAs exert their suppressing actions in gene transcripts critical for the smooth operation of signaling molecular networks involved in the control of the above processes [9]. The major underlying mechanisms of miRNA dysregulation includes, but is not limited to, abnormal transcriptional regulation of miRNA-coding genes, loss or amplification of miRNA loci, and epigenetic changes in the miRNA biogenesis machinery [6]. The role of miRNAs has been further evaluated in CSC models [10]. A plethora of miRNAs have now been identified as typical molecular signatures of certain CSC stemness features and may therefore serve as novel biomarkers for CSC targeting [10][11].

LncRNAs: The long non-coding RNAs (lncRNAs) are one of the most abundant ncRNA families in humans, counting for more than 60,000 identified members [12][13]. LncRNA transcripts have a length greater than 200 nucleotides, show little to no evidence of protein-coding potential, while they display significant tissue specificity [14][15][16]. Most lncRNAs are located and transcribed as complex within the intergenic stretches of the genome, interwiring networks of overlapping

sense and antisense transcripts that often include protein coding genes [17]. Transcriptomic sequencing using Next Generation Sequencing (NGS) has suggested that only a small proportion of the identified lncRNAs in humans may be actually biologically relevant [18]. Compelling evidence has demonstrated that lncRNAs play a critical role in regulating gene expression, mainly through cis-regulation or trans-regulation [19]. Although their function has been reported at all levels of gene regulation, including epigenetic, transcriptional, translational, and post-translational actions, the exact underlying mechanisms of lncRNA-mediated effects on gene regulation are still largely unknown [19][20].

The involvement of lncRNAs in the onset and pathophysiology of cancer has been recently demonstrated. Deregulated lncRNA expression patterns have been proved to significantly interfere with cancer hallmarks, including aberrant tumor cell proliferation and tumor aggressiveness, reflected by increased metastatic potential [21][22]. Therefore, lncRNAs may be considered putative therapeutic targets for cancer management.

CircRNAs: Forty years ago, a new class of ncRNA was described, now known as circular RNA (circRNA) [23]. The circRNAs have covalently closed-loop structures that are highly stable and conserved among species [24]. These RNAs are single-stranded RNAs, which are commonly generated by the pre-mRNA splicing machinery, via back-splicing reaction, in which an upstream acceptor site is joined with a donor by intronic repeat sequences that base-pair to one another and bring the intervening splice sites into close proximity [25][26]. The majority of the circRNAs are rarely produced and accumulate to low levels, although some are expressed at levels 10 fold higher than their associated linear mRNAs [27][28]. Although a large number of circRNA functions are still unknown, within the last decade, there have been compelling evidence demonstrated that circRNAs may interact with other ncRNAs such as acting as miRNA sponges or competing with pre-mRNA splicing. They can further interact with RNA-binding proteins and participate in protein translation, nuclear translocation, and scaffolding, while they can serve as autophagy regulators [24][29]. Recently, an important role of circRNAs has been identified in the pathophysiology of several diseases including cancer. A growing number of reports has demonstrated the involvement of circRNAs in oncogenesis and cancer progression by regulating tumor growth, invasion, metastasis, vascularization, and resistance to apoptosis [23]. Therefore, circRNAs have been suggested as a novel class of biomarkers and therapeutic targets in oncology, probably exerting dual roles in the functions and properties of CSCs.

Conclusion

Overall, the regulatory role of a plethora of different ncRNAs in critical cancer-related processes, including CSC-dependent oncogenesis and tumor aggressiveness, is an indisputable fact. An efficient identification and characterization of ncRNAs with CSC-related or, even better, CSC-specific deregulated expression motifs, along with a deep understanding of their action in CSC properties, might be the golden key for designing revolutionary therapeutic protocols against CSCs.

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