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Review

Non-coding RNAs as emerging molecular targets of gallbladder cancer

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ABSTRACT

Gallbladder cancer is one of the most common cancers of biliary tract with aggressive pathophysiology, now emerging as a global health issue. Although minority of gallbladder cancer patients could receive such curative resection due to late diagnosis, this increases the survival rate. Lack of potential target molecule (s) for early diagnosis, better prognosis and effective therapy of gallbladder cancer has triggered investigators to look for novel technological or high throughput approaches to identify potential biomarker for gallbladder cancer. Intervention of non-coding RNAs in gallbladder cancer has been revealed recently. Non-coding RNAs are now widely implicated in cancer. Recent reports have revealed association of non-coding RNAs (microRNAs or miRNAs and long non-coding RNAs or lncRNAs) with gallbladder cancer. Here, we present an updated overview on the biogenesis, mechanism of action, role of non-coding RNAs, the identified cellular functions in gallbladder tumorigenesis, their prognostic & therapeutic potentials (efficacies) and future significance in developing effective biomarker(s), in future, for gallbladder.

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Contents

1. Introduction

The first report of gallbladder cancer came back in 1777 (De Stoll, 1777). It is one of the most common cancers of biliary tract and is now becoming a major global health issue, particularly for middle aged women (Barbhuiya et al., 2009; Randi et al., 2008; Siegel et al., 2015). Late symptomatic onset and diagnosis at advanced stage increases difficulties in prognosis and therapy. Curative resection is the most common practice to treat gallbladder cancer patients. However, only minority of gallbladder cancer patients get the benefits of such curative resection. Increasing the survival rate of gallbladder cancer patients has remained a major challenge at present. This can only be achieved once appropriate and specific diagnostic, prognostic or therapeutic biomarker(s) is/are identified and developed to check the tumorigenic pathophysiology, i.e., inhibition of tumor birth and growth. Recent advancements in high throughput technologies have contributed significantly to these goals.

Non-coding RNAs are a class of RNAs transcribed consistently, covering more than 75% of the genome (Eddy, 2001; Djebali et al., 2012). ncRNAs are a large and heterogeneous class of RNAs, which include small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), piwi interacting RNAs (piRNAs), long non-coding RNAs (lncRNAs), long intergenic

Abbreviations: GBC, gallbladder cancer; lncRNA, long non-coding RNA; miRNA, microRNA; LincRNA, long intergenic non-coding RNAs; MALAT1, metastasis-associated lung adeno carcinoma transcript 1; CCAT1, colon cancer associated transcript 1; ITGB1, integrin beta 1; UCRs, ultraconserved regions; RISC, RNA Induced Silencing Complex; SNP, single nucleotide polymorphism; HMGA2, high mobility group AT hook 2.

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non-coding RNAs (lincRNAs) and ultraconserved regions (UCRs). LncRNAs share the largest portion of the mammalian non-coding transcriptome (Mercer et al., 2009). They are of size longer than 200 nt and are processed from the unprocessed transcripts (Guttman et al., 2009; Ulitsky and Bartel, 2013). LncRNAs and miRNAs are well known for diverse functions. Their implication in cancer is not yet fully elucidated, however, they are being considered as the major target for biomarker discovery. In this review, we have discussed biogenesis, mechanisms of action, disruptions of these non-coding RNAs and the identified cellular functions of gallbladder cancer. A brief account of future prospect of biomarker development for early diagnosis, better prognosis and effective therapy of gallbladder cancer is also given.

2. Biogenesis and functions

2.1. miRNAs

The biogenesis of miRNAs has been widely reviewed (Bartel, 2004; Esteller, 2011). Generally, miRNAs are embedded in the genomic regions or within the exons of protein coding genes (Kim and Kim, 2007). In brief, miRNAs are initially transcribed inside the nucleus by RNA polymerase II as a long, capped (at 5′ end) and polyadenylated (at 3′ end) long primary transcript, with hairpin stem loop structure, known as poly-cistronic miRNA clusters or pri-miRNAs. These miRNAs are recognized and further trimmed by an RNA polymerase III enzyme, Drosha, with DGCR8 as a co-factor, to ~70 nt long sequence, known as pre-miRNAs. These molecules are then exported to cytoplasm by a cargo, Exportin-5/Ran-GTP. Further trimming is done by another RNA pol III enzyme, Dicer, producing ~22 nt long mature miRNA. Helicase separates the strands of the double stranded miRNA, producing single stranded stable miRNA, while, the other strand is processed for autolytic degradation. Dicer-TARBP2 (TARR RNA Binding Protein 2) load the stable mature miRNA strand to RNA Induced Silencing Complex (RISC) to mechanistically target 3′-Untranslated Regions (3′ UTRs) of protein coding mRNAs, consequently acting in post transcriptional regulation via two mechanism: mRNA degradation for the perfect complementarity and inhibition of translational initiation for incomplete complementarity (He and Hannon, 2004). Loading of miRNAs to RISC and regulatory mechanism of RISC are tightly regulated (Krol et al., 2010). Recent reports have claimed 3′-UTRs and 5′ UTRs as emerging targets of miRNAs (Esteller, 2011). Argonaute proteins play crucial role in assembling RISC components, where they act as catalytic endonuclease. *lin-4* is the first miRNA discovered by Ambros lab and is found to have base sequence complementary to 3′-UTR of *lin-14* in *Caenorhabditis elegans*. It triggers the transition of cell division from the first larval stage to the second larval stage (Lee et al., 1993). Recent reports have identified the functional roles of miRNAs in many biological and cellular processes, including cell proliferation, differentiation, apoptosis, senescence and development (Esteller, 2011).

2.2. Long non-coding RNAs

LncRNAs are a class of non-protein coding RNAs. These diverse and heterogeneous class of RNAs are defined by size discrimination of more than 200 nt long transcripts without open reading frame. Generally, lncRNAs are also transcribed by RNA polymerase II. These long lncRNA transcripts are subjected to normal pre-splicing editing, such as 5′ capping and 3′ polyadenylation (Li and Chen, 2013). There are few reports suggesting the role of lncRNAs in transcriptional regulation of genes. LncRNAs function in the epigenetic modification of DNA, specific to chromatin remodeling structures at specific loci (Navarro et al., 2006). Hundreds of lncRNAs have been identified at the human HOX gene loci. They are expressed during transcription and regulate the chromatin structure, which involves histone modification enzymes and RNA polymerase (Rinn et al., 2007). LncRNAs are also involved in X-chromosome inactivation in mammals. During X-chromosome inactivation, polycomb complex is recruited by X-inactivation Specific Transcript (*XIST*), a lncRNA, to silence the X-chromosome *in-cis* (Plath et al., 2003). Interestingly, a recent study reported interacting network of lncRNAs with protein coding genes and even with miRNAs (Ma et al., 2015).

3. Deregulation of miRNAs in gallbladder cancer

3.1. MicroRNAs

With the discovery of miRNAs (Lee et al., 1993) and RNA interference (Fire et al., 1998), the scope of research to identify novel potential biomarker has widened to a great extent. This has provided a novel strategy for investigators to discover specific early diagnostic biomarker of gallbladder cancer. Efforts are still ongoing to elucidate significant association of miRNAs with gallbladder cancer. Disruptions in the nucleotide sequences have also been detected. Variations in the single nucleotide polymorphism (SNP) of pre- & pri-miRNAs may alter the expression level of the respective miRNAs, thereby, suggesting possibility to identify potential biomarkers of gallbladder cancer. Genetic variants of *miR-196a*, *miR-499*, *miR-146a*, *miR-27a*, *miR-570* and *miR-181a* are not associated with gallbladder cancer (Srivastava et al., 2010; Gupta et al., 2015). However, accumulation of these three variants (*miR-27a*, *miR-570* and *miR-181a*) was found to influence the chemotherapy toxicity, i.e., poor prognosis in gallbladder cancer (Gupta et al., 2015). The miRNA profiling in BK5.erbB2 gallbladder cancer mice revealed deregulation of few miRNAs. When treated with histone deacetylase inhibitor, PCI-24781, gallbladder cancer cells showed downregulation of *miR-21*, *miR-142-3p*, *miR-142-5p* and *miR-223*, whereas, *miR-122*, upregulated (Kitamura et al., 2012). The level of *miR-146b-5p* was observed to be very low in tumor tissues of gallbladder (Cai et al., 2015). Restoring *miR-146b-5p* expression in the gallbladder cancer cell line, SGC-996, inhibited tumor growth through enhanced apoptosis and G1 phase arrest. *miR-146b-5p* also regulates the expression of EGFR (Cai et al., 2015) (see Fig. 1 and Table 1). This small sized miRNA has potential to inhibit tumor growth and arrest defective cell cycle steps. Elevated levels of *miR-20a* and TGF-β1 lower the survival rate of gallbladder cancer patients. Exogenous introduction of *miR-20a* *in vivo* and *in vitro* enhanced epithelial to mesenchymal transition (EMT) and metastasis of gallbladder cancer cells via targeting 3′ UTR of Smad7 and nuclear translocation of β-catenin (Chang et al., 2013). Down-regulation of *miR-34a* and long telomere length increased the poor prognosis and survival of gallbladder cancer. Introduction of *miR-34a* in CD44 + CD133 + gallbladder cancer tumor stem-like cells inhibited cell proliferation *in vitro* and xenograft tumor growth *in vivo* (Jin et al., 2014). *MiR-133a*, *miR-133b*, *miR-143-3p*, *miR-145-5p* and *miR-1* are significantly downregulated in gallbladder cancer (Letelier et al., 2014). Ectopic expression of *miR-1* and *miR-145-5p* in gallbladder cancer cell line, NOZ, inhibited cell viability and colony formation, and decreased the expression of VEGF-A and AXL (Letelier et al., 2014). Downregulation of *miR-138* and upregulation of Bag-1 were also observed in gallbladder tumor tissues. Ectopic expression of *miR-138* results in the silencing of Bag-1 and proliferation of gallbladder cancer cells (Ma et al., 2015). The proposal for potential use of *miR-155* as a therapeutic biomarker came from a report in which gallbladder cancer patients with upregulated *miR-155* showed poor prognosis with lymph node metastasis as compared to those with down-regulated *miR-155*. This may also be associated with cell proliferation, aggressive behavior with increased lymph node metastasis and vessel invasion (Kono et al., 2013). It is suggested that xanthogranulomatous cholecystitis can be distinguished from gallbladder cancer based on expression profile of *miR-155*. Consistency of gallbladder cancer specific *miR-155* expression without any other alteration during inflammatory conditions, associated with pancreatobiliary malfunction and possibility of its accurate detection in serum/bile, mark it as a prospective novel diagnostic marker for gallbladder cancer (Kono et al., 2013). A recent study

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