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Editorial

Functions and Therapeutic Applications of Antisense RNAs in Cancer

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Introduction

Non-coding RNAs transcribed from opposite strand of the protein coding sense strand are collectively termed as antisense RNAs (asRNAs). Effective in binding to both DNA and RNA, asRNAs are reported to have a putative role in transcriptional interference and mRNA instability [1]. Also known as Natural Antisense Transcripts (NATs), these are classified under long non-coding RNAs (lncRNAs) and found to occur with 50-70% of all protein coding genes [2]. Despite most of lncRNAs are confined to the nucleus, a relevant and critical observation was that about 73% of the transcribed antisense RNAs were localized and stable in the cytoplasm as other coding mRNAs [3]. This intrigues whether these antisense RNAs are directed for mRNA interaction or if they are being decoyed to avert a nuclear trivial. Antisense RNAs have diversified function of gene silencing and activation ascertaining its importance in tumorigenesis. An antisense to a tumor suppressor or oncogene will be of special interest bearing a cis- effect on parental gene or trans- effect on the downstream target genes. Interestingly, most of asRNAs are transcribed with a positive correlation to sense partners as observed in multiple tumor tissues and cancer cell lines [4]. However, whether the deregulation of antisense RNAs is a more consequence of sense transcript regulation is debatable. Understanding different class of antisense RNAs is persuasive in revealing its mode of transcriptional regulation in relevance to sense mRNAs. Typical classification of antisense transcripts is (i) Head to head: divergently oriented transcripts with overlapping 5' ends of both sense and antisense (ii) tail to tail: Convergent transcribed sense and antisense pairs with their 3' ends overlapping and (iii) Internal: with a fully overlapping sense transcript [5,6]. In addition to these, based on positional effect antisense transcripts are divided into cis and trans that precisely define their functional characteristics.

Functional Role in Cancer

The cis effects of asRNAs (at the region of its transcription) are more frequently encountered than trans (affecting distantly located DNA/transcripts). The cis-acting asRNAs organize the regulatory event like chromatin remodeling of parental or proximal genes, whereas the trans-function of asRNAs include enhancing or repressing the distally located genes. The major functional roles of antisense RNAs are chromatin remodeling, RNA masking, RNAi (RNA interference) and TI (transcriptional interference) [7]. Chromatin reprogramming by as RNATARID (TCF21 antisense RNA inducing demethylation) has been reported to aid in demethylation elucidating a novel epigenetic modulation. TARID physically interacts with TCF21 promoter and localizes GADD45A (growth arrest and DNA-damage inducible, alpha) which in turn recruits TDG (thymine-DNA glycosylase) for TET (Ten Eleven Translocation) mediated conversion of 5-methylcytosine to 5-hydroxymethylation and this demethylation eventually increases the expression of the tumor suppressor TCF21 [8]. Antisense RNAs might form sense/antisense (SAS) duplex masking the sense transcript from processes like splicing, localization and stabilization by deliberately preventing protein-RNA interaction. EMT (Epithelial mesenchymal transition) induction by Zeb2 over expression is an example of RNA masking exerted by as RNA of Zeb2 which prevents the splicing of 5'UTR of Zeb2 retaining the intra-ribosomal entry site for an efficient expression. Yet another interesting functional mechanism of asRNAs is linked to RNAi, where the sense-antisense transcript pair is thought to be processed by DICER resulting in an endo-siRNA. The guide RNA of the endo-siRNA targets the mRNA resulting in RISC mediated translational repression. However, RNAi mechanism involving NATs is frequently argued upon [9]. Transcriptional interference is a retarding effect exerted by the transcriptional complex initiated by antisense promoter over the transcriptional unit of the protein coding strand, besides is a rare event to occur as most of the antisense are co-expressed with sense partner. The classification of asRNAs based on functional mechanism and identifying the binding partners will facilitate their clinical application (Figure 1).

Use of Antisense RNAs in Cancer Therapeutics

The huge class of asRNAs in transcriptional landscape of tumors not only indicates their significant role in carcinogenesis but also propose potential therapeutic targets. At present, the exact functional mechanism of only a very few antisense lncRNAs has been understood, however, certain manipulative asRNAs assure high scope of cancer therapeutics. Two basic modalities of using asRNAs in therapy are by increasing or stabilizing bioavailability of the under expressed antisense and the other is by knocking down oncogenic antisense RNAs. The less expressed antisense RNAs are largely found to be hyper methylated and methylation inhibitor drugs would increase sustained expression of these antisense RNAs [10]. Whereas the highly expressed antisenses RNAs repress neighboring gene or sense transcript expression, targeting those asRNAs that repress tumor suppressors like ANRIL repressing INK4A, INK4B and ARF can be a proposed prostate cancer treatment [11]. Exploiting asRNAs known to activate gene expression is also a captivating strategy. The intriguing finding of Uchl1 antisense playing a crucial role in promoting the

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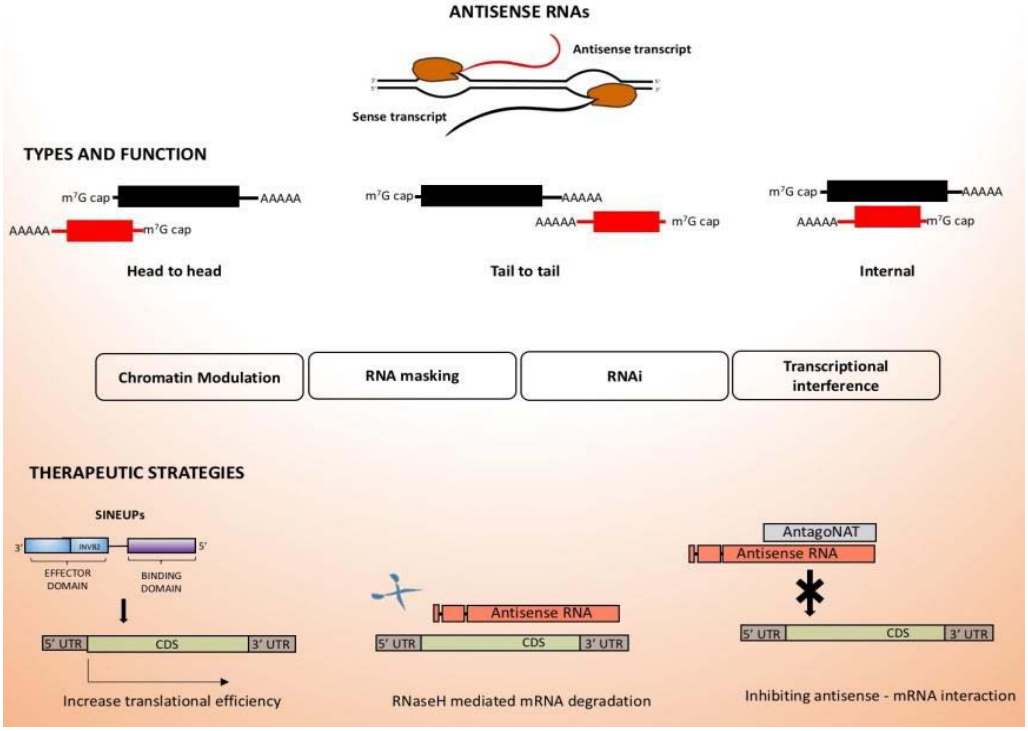

Figure 1: Biogenesis and functional mechanism of antisense RNAs and its therapeutic applications in cancer. Antisense RNAs originate from the same genomic region of a coding (or sense) mRNA but from the opposite strand. The types of asRNAs (*Head to head, tail to tail and internal*) depend on its transcriptional position to that of sense mRNA. Key mechanisms of asRNAs in gene regulation are chromatin modification, RNA masking, RNAi and transcriptional interference. Therapeutic application of asRNAs include use of SINEUPs, RNase H directed S/AS (sense/antisense) destabilization and targeting oncogenic asRNAs by antagoNATs.

translational efficiency of its sense partner leads to use of SINEUPs as a potent RNA based therapeutics [12]. The functional activity of SINEUPs depends on the combination of two RNA elements; a DNA binding domain for sequence specificity and an effector domain (inverted SINEB2 element) conferring the translational efficacy. Systematically designed, functionally consistent artificial SINEUPs may also increase protein levels in case of haploinsufficient tumor suppressors [13]. Use of antagoNATs has been yet another successful paradigm of upregulating protein expression influenced by an antisense. BDNF-AS was targeted by an antagoNAT with modified phosphorothioate-modified backbones and three locked nucleic acid (LNA) that in turn increased BDNF expression leading to an improved neuronal cell survival [14]. Despite appositeness of these commonly used strategies for knocking down asRNAs, there are few limitations to consider. For instance, when CRISPR/Cas9 was used to target lncRNAs about 80% knockdown was achieved, but most of asRNAs are bidirectional with shared promoter/enhancer elements and thus targeting an antisense will have an equal probability of its sense knockdown [15]. On the other hand, by using RNAi like siRNA/shRNA or ASO (Antisense Oligonucleotides) which is short complimenting DNA oligonucleotides can precisely target asRNAs however with a low but attainable efficiency. Several known asRNAs are projected as diagnostic and prognostic markers. HOTAIR is the most commonly upregulated asRNA with diagnostic importance in esophageal, colorectal, hepatocellular and cervical cancer and can strongly indicate overall survival in colorectal cancer patients [16]. ANRASSF1 and ANRIL were found to be significantly detectable in breast tumors with the later showed up to be a poor prognostic marker of cervical cancer [17,18]. With molecular mechanisms of limited asRNAs being revealed, a defined strategic approach of using these into clinics is at a premature stage. Nevertheless, the global-boom of non-coding RNA profiling with enriched reports on antisense RNAs in various tumors has a futuristic implication in diagnosis and therapy.

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