Journal of
Bioequivalence & Bioavailability
ISSN: 0975-0851

Jeyapalan and Yang, J Bioequiv Availab 2011, 3:8
DOI: 10.4172/jbb.100000e7

Editorial Open Access

Regulation of microRNA Functions by Non-coding RNAs

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Recently, there has been an increased interest in the function of non-coding RNA transcripts. The term non-coding RNA (ncRNA) is given to a functional RNA molecule that is not translated into protein. Originally non-translated regions of the genome were considered "junk DNA" based on the fact that they did not code for proteins and were thought to serve no purpose. However, their importance has been revealed in recent years. The 3'untranslated region (3'UTR) is an example of a type of ncRNA. The impact of the 3'UTR on miRNAs was originally introduced by our laboratory. We hypothesize that in the presence of the 3'UTR, endogenous miRNAs would bind to sites on the 3'UTR when the binding affinity is sufficiently high. This would arrest the normal function of the endogenous miRNAs and free the potential targets (mRNAs) of these miRNAs. As a consequence, the freed mRNA will be translated to proteins.

The effect of the 3'UTR on miRNAs is naturally occurring in the form of pseudogenes. These pseudogenes are an important component of the genome because they have been discovered to be as abundant as functional genes. It has been estimated that there are approximately 20,000 putative pseudogenes in the human genome [1]. This was recently described by Poliseno and coworkers, in which a PTEN pseudogene, PTENP1, was discovered to regulate PTEN cellular levels and suppress growth [2].

To study the effects of 3'UTR, we have developed different approached to examine how the 3'UTR may modulate miRNA activities. Initially, we exogenously over-expressed the 3'UTR of versican in vitro and in vivo and reported that over-expression of the 3'UTR resulted in an altered cell morphology and increased cell-cell adhesion in vitro and organ-organ adhesion in vivo [3]. Furthermore, we found that versican 3'UTR is able to antagonize miR-199a-3p function in regulating expression of two matrix proteins versican (VCAN) and fibronectin (FN), resulting in enhanced cell-cell adhesion and organ-organ adhesion. Recently, we expanded our research in this field and found that expression of the versican 3'UTR also lowers the steady state expression of miR-199-3p [4]. We have also applied this idea to the 3'UTRs of nephronectin and CD44. In the study of the 3'UTR of nephronectin, we showed that expression of nephronectin containing the 3'UTR enhanced osteoblast differentiation as compared with expression of nephronectin without the 3'UTR [5]. It promoted nodule formation and osteoblast differentiation due to endogenous miR-378 being bound and increased GALNT7 and increased nephronectin glycosylation and protein secretion. Direct evidence was obtained by expressing the 3'UTR alone, which promotes osteoblast differentiation [6]. In the studies of CD44 3'UTR, we introduced the CD44 3'UTR into human breast cancer cell line MT-1 and found that there was a decreased rate of cell proliferation and cell survival, while an increased amount of endothelial cell activities and angiogenesis [7]. These phenotypic characteristics can be explained due to the involvement of three miRNAs (miR-216a, miR-330 and miR-608), which bind both to the CD44 and CDC42 3'UTRs. The introduction of the exogenous 3'UTR of CD44 resulted in the increased protein translation of CD44 and CDC42, both of which play important roles in cell cycle regulation.

Significantly, Chin and co-workers have found that variation due to single nucleotide polymorphisms located in miRNA binding sites of 3'UTR affects miRNA target expression and function. The 3'UTR of KRAS contains a single nucleotide polymorphism correlated with an increased risk of non-small cell lung cancer [8]. This single nucleotide polymorphism prevents let-7 from binding, which results in the over-expression of KRAS in lung cancer.

Regulation of miRNA activities by different non-coding oligonucleotides has been extensively investigated including decoys, sponges, locked nucleic acids, and antagomirs [9-12]. These chemically modified antisense oligonucleotides are meant to antagonize specific miRNAs and are very effective against a specific miRNA or members of a miRNA family, for example, the let-7 and miR-17-92 clusters. However, since multiple miRNAs can target one gene, and antagonizing one miRNA may not relieve enough translational repression exerted by other miRNAs targeting the same gene, different approaches need to be investigated. The use of the 3'UTR may achieve the need as a 3'UTR of an mRNA with similar effects can be used to antagonize miRNAs of interest. These miRNAs may play similar role in producing the same phenotype. The importance of the 3'UTRs is beginning to be understood as they are modulators of miRNAs and are believed to play important roles in maintaining homeostasis. miRNAs can also be degraded through binding with the 3'UTR, which will protect target mRNAs from translational repression.

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Received September 14, 2011; **Accepted** September 16, 2011; **Published** September 18, 2011

Citation: Jeyapalan Z, Yang BB, (2011) Regulation of microRNA Functions by Non-coding RNAs. J Bioequiv Availab 3: v-vi. doi:10.4172/jbb.100000e7

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