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The Enemy Within: Regulation of Host Genes by Intronic microRNAs

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MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules capable of negatively regulating the expression of target genes. This highly conserved method of gene regulation is accomplished via miRNA incorporation into a protein complex, mainly consisting of Argonaute proteins, where the miRNA binds a complementary region, typically within the 3' UTR of an mRNA. Due to their critical gene regulatory function, miRNAs play an important role in many diseases, including cancer.

Studies have shown that the majority of mammalian miRNAs are located within the introns of genes. These miRNAs are therefore referred to as intronic miRNAs [1]. Introns, although originally thought to be merely nonsense spacing elements in gene structure, have received extensive attention in recent years due to the discovery of important functions for these sequences. Further studies have demonstrated that intronic miRNAs are often co-expressed and therefore may share similar transcriptional regulatory mechanisms with their host genes in humans [2]. This correlation of expression suggests that these intronic miRNAs may have functions either similar, or opposite, to that of their host genes. Borchert and others have described how intronic miRNAs can be transcribed independently from the host gene, either by RNA polymerase II or III [3]. This independent transcription phenomenon is intriguing because miRNAs could then function and be regulated without any association with their protein-coding host genes. The questions of why these microRNAs are encoded within introns and how these intronic miRNAs relate to the function of their host genes beg to be answered by researchers. Certainly, there are intronic miRNAs that have functions completely unrelated to that of their host genes. Furthermore, there are some examples of intronic miRNAs that act in synergy with their host genes. Yet a third area of study is miRNAs which act in a way that is functionally opposed to the normal function of the host genes. Here we will highlight the role of those antagonistic intronic miRNAs, which are critical in the regulation of the expression and function of their host genes, and we will examine the implications of these intronic miRNAs in cancer development and progression.

Bioinformatic studies have demonstrated that approximately 20% of intronic miRNAs are predicted to target their host genes [4]. Although target prediction methods are imperfect, this is a significantly greater percentage than can be attributed to mere chance. Additionally, one bioinformatic study utilized the GO Biological Process (GOBP) and KEGG ontologies, which associate genes with cellular processes and biochemical pathways, respectively, to survey for over representation of miRNA targets within host gene-associated pathways. In other words, this method examines how many of the predicted miRNA targets would be involved in the normal function of the host gene. This study demonstrated that host gene pathways were significantly over represented when analyzed for intronic miRNA targets. Interestingly, many malignancy-related pathways ranked high [4], supporting the importance of intronic miRNA regulation of cancer-associated pathways.

At least two major mechanisms explain how a miRNA can negatively regulate its host gene or host gene function. First, the intronic miRNA can directly target the 3′ UTR of its host gene. This would lead to translational repression or direct mRNA degradation of the host gene and therefore, less of the total protein product will be expressed. One example of direct host gene targeting is miR-338-3p, which inhibits its host gene *AATK*, a kinase which plays a role in differentiation and apoptosis, by binding to its 3′ UTR [5]. Such an interaction forms a "first-order" negative-feedback circuit for fine-tuning host gene expression. The second mechanism by which a miRNA can negatively regulate its host gene function is by targeting a gene whose product is a downstream effector of the host gene product. In this way, the miRNA would effectively diminish signaling through a certain pathway directly activated by, or involved in; host gene function. Such regulation could be termed "second-order" negative feedback. One such example that exists in the prostate cancer KEGG pathway is miR-641, which is intronic to its host *AKT2*. The PI3K/AKT pathway plays a critical role in cancer development. Although miR-641 is not predicted to target its host, *AKT2*, its predicted targets (which include *PI3K, EGFR, PTEN, PDK1, RAS, MEK,* and *ERK*) are in functional synergy with its host, giving credence to the second-order negative feedback circuitry line of evidence. In the non-small cell lung cancer signaling pathway, miR-634 plays a similar role, participating in second-order negative feedback [4]. Thus, intronic miRNAs display targeting patterns that, not only alter the host's expression level, but can also alter the functional environment that the host exists in.

Extraordinarily precise control of genes is essential for cellular homeostasis and maintenance of a disease-free state. It is entirely reasonable to hypothesize that the function of a normal growth-promoting host gene may be negatively regulated or fine-tuned by intronic miRNA. In such a case, the miRNA would be an intrinsic protective mechanism by which cells can avoid transformation and resist becoming cancerous. Since loss of negative feedback control is a well-established mechanism by which malignancies develop, loss of such a tumor suppressor-type miRNA could cause oncogenic function in an otherwise normally-functioning gene. Even if such a loss was not the cause of cancer initiation, miRNA processing has been shown to be disturbed in cancer [6]. If expression levels of intronic miRNAs are reduced, as shown by some researchers [7,8], then proliferation-promoting signaling pathways may lose inhibition and result in uncontrolled cell proliferation and tumor growth. Additionally, if amplification of a growth-related host gene occurred, perhaps the signaling propagated by that gene would overpower the antagonistic ability of the intronic miRNA and cells may still become cancerous.

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Since we now know the role of intronic miRNAs in gene regulation is very important to normal cellular function, studies elucidating the roles of intronic miRNAs are integral to basic research today. Such consideration should prompt us to pay close attention to study design. For example, *in vitro* studies in which a gene is over expressed by inserting only the gene coding sequence into an expression vector are inherently flawed if there are miRNAs known to be encoded within the introns of that gene, because the intronic miRNAs originating from those missing introns may have critical roles in first-order or second-order negative feedback with respect to the expression and function of the host gene. It seems most likely that the majority of antagonistic intronic miRNAs would function as fine-tuning or dampening adjustments to the regulated proteome.

On the opposite end of the spectrum, studies of protein function derived from gene knockout strategy may need re-evaluation in the case that intronic miRNA loss due to the whole-gene knockout may have contributed to the biological phenotypes resultant from gene knockout [9]. However, because of the nature of miRNA, such studies are complex for several reasons. For example, one miRNA may have different roles in different cell types [10,11]. Secondly, there are likely different transcription factors responsible for regulating the specific locus of an intronic miRNA in different cell types. Thirdly, functional targets will differ in different cell types, depending on expression levels and sub-cellular localization of those targets. Therefore, all miRNAs, including intronic miRNAs, are subject to multiple layers of regulation. Antagonistic intronic miRNAs are an intriguing class of functionally important RNA molecules whose gene-tuning abilities need to be thoroughly elucidated and whose successful study will require a focused effort.

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