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Mini Review

A Long Non-coding RNA and its Potential Role in Human Myeloid Leukemia

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Abstract

Over the past ten to fifteen, lncRNAs have been discovered to be expressed widely in eukaryotes and function as regulators of many diverse biological processes. We have identified a novel long non-coding RNA (lncRNA) that, as our early evidence indicates, participates in maintaining the undifferentiated and proliferative state of human myeloid leukemia-derived cells. With the accumulating evidence that lncRNAs act in regulating genes required for proper cell differentiation, the enhanced expression of the lncRNA we identified in myeloid leukemias and its apparent role in maintaining the proliferative state of these cells is quite significant, both in terms of understanding lncRNA function, and the potential design of novel therapeutics for myeloid leukemias.

Keywords: Long noncoding RNA; Leukemia; Differentiation

Introduction

Over the past decade, long non-coding RNAs (lncRNAs) have been discovered to function as regulators of gene expression and numerous biological processes. They are transcribed from loci throughout the genomes of most eukaryotes [1-7]. and reports indicate that many lncRNAs are involved in the regulation of pluripotency and differentiation [8-14]. Although the mechanisms by which these lncRNAs function are still being explored, one model that has emerged states that nuclear lncRNAs modulate gene expression through interactions with histone modifying proteins and/or transcription factors [6-7, 12, 15-18].

Other lncRNAs function in the cytoplasm [19-21]. Lnc-MD1, for example, is a muscle-specific lncRNA that regulates muscle differentiation by binding to microRNAs (miRNA) and limiting their availability to regulate gene expression [9]. Another lncRNA, TINCR, is induced during epidermal differentiation and interacts with a number of differentiation-specific mRNAs to regulate their stability [10]. These, and other results, demonstrate that lncRNAs can act to regulate genes required for cell differentiation through multiple mechanisms [13, 21- 23]. Furthermore, enhanced expression of some lncRNAs have been shown to contribute to certain cancers as well. SAMMSON for example, is a lncRNA expressed at elevated levels in melanomas and its inhibition resulted in decreased viability of human melanoma-derived cells [24]. Likewise, numerous lncRNAs, including the one we describe here have been implicated in contributing to acute myeloid leukemia [25-28].

Identification of a lncRNA transcribed from exon 1 of the p53 gene

A few years ago, as described below, we identified a lncRNA, designated as lncRNAp53Int1, that exhibits enhanced expression in myeloid leukemias, that functions to maintain the proliferative state of leukemic cells [25]. To date, our findings indicate that lncRNAp53Int1 functions in the cytoplasm, and through interactions

with as yet unidentified RNA molecules or proteins, contributes to oncogenic transformation by suppressing the differentiation of myeloid progenitor cells. Inhibiting its activity or the activity of its targets is predicted to lead to differentiation and cessation of proliferation.

lncRNAp53int1 is linked to the differentiation of human myeloid leukemia cells

A number of years ago, we identified a transcription unit located in the 1st intron of the human p53 tumor suppressor gene that encoded a RNA transcript that had no identifiable open reading frame for protein synthesis [28]. This transcript was later classified as a lncRNA [19, 30-31] and is listed as GC17M015273 in the GeneCard Human Gene Database (http://www.genecards.org) and NONHSAG020729 in NONCODE v4 (http://www.noncode.org). The lncRNAp53Int1 transcript is approximately 1125 nucleotides in length, is polyadenylated, and contains no introns. While there appears to be no functional or regulatory relationship to p53 itself, the abundance of this lncRNA is significantly reduced during differentiation of human myeloid leukemia cells [25]. We hypothesize that lncRNAp53Int1 plays a crucial role in maintenance of the undifferentiated proliferative state in myeloid leukemia. That lncRNAp53Int1 is expressed in immature cell types is supported by lncRNA expression data collated in various publicly available databases. Although expressed in a variety of human tissues, tissues found to express the highest levels of lncRNAp53Int1 include those that contain proliferative and immature cell types such as lymph node, foreskin fibroblasts and umbilical endothelial cells.

Potential Therapeutics

Myeloid leukemias are characterized by genetic alterations that lead to a complete or partial block at various stages of myeloid differentiation and subsequent proliferation of myeloid progenitor cells [32-36]. That lncRNAp53Int1 appears to block differentiation of human myeloid leukemia cells is noteworthy because the ability to induce differentiation of acute myeloid leukemias is used as one therapeutic strategy [34, 37-40]. The discovery of a regulatory role for lncRNAp53Int1 in leukemia cell differentiation and the ultimate identification of its cellular targets could provide researchers with new pathways to target in the development of novel therapeutics for acute myeloid leukemias [41-42]. Silencing this lncRNA or one or more of its interacting molecules could potentially lead to an effective way to inhibit proliferation through the induction of terminal differentiation.

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Conflict of Interest

No conflict of interest.

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