Seminars in Oncology 43 (2016) 209–214

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

MicroRNAs in chronic lymphocytic leukemia: miRacle or miRage for prognosis and targeted therapies?

Katrien Van Roosbroeck[a], George A. Calin[a,b,c,*]

[a] Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX
[b] Center for RNA Interference and Non-Coding RNAs, The University of Texas MD Anderson Cancer Center, Houston, TX
[c] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

ARTICLE INFO

Keywords:
MicroRNA
Chronic lymphocytic leukemia
Biomarker
Targeted therapy
miR-34 mimic

ABSTRACT

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease and has a highly variable clinical course with survival ranging from a couple of months to several decades. MicroRNAs (miRNAs), small non-coding RNAs that regulate transcription and translation of genes, have been found to be involved in CLL initiation, progression, and resistance to therapy. In addition, they can be used as prognostic biomarkers and as targets for novel therapies. In this review, we describe the association between miRNAs and the cytogenetic aberrations commonly found in CLL, as well as with other prognostic factors. We describe the presence of miRNAs as extracellular entities in the plasma and serum of CLL patients and discuss their role in resistance to therapy. Finally, we will explore the potential of targeted miRNA therapy for the treatment of CLL, with a special emphasis on MRX34, the first miRNA mimic that is currently being evaluated for clinical use.

1. Introduction

MicroRNAs (miRNAs) are small, non-coding RNAs of 19-25 base pairs long. Their main function is the regulation of gene expression by either mRNA degradation or inhibition of translation, but other functions, such as mRNA stabilization, translational activation and RNA decoy, have been described as well [1]. By now, it is well established that miRNAs are important in almost all cellular processes, including differentiation, proliferation, cell cycle regulation, and apoptosis, processes that are deregulated in human cancers [2]. It was in chronic lymphocytic leukemia (CLL), the most common adult leukemia in the Western world, that the first miRNAs involved in human diseases were described. We showed that a cluster containing miR-15a and miR-16-1 was frequently deleted or downregulated in CLL, and that this downregulation correlated with allelic loss at 13q14, a region deleted in the majority of CLL cases [3]. After this initial report, many more studies correlated abnormal miRNA expression with cancer, resulting in more than 16,000 publications so far.

In this review, we will describe the association between certain miRNAs and the cytogenetic aberrations commonly found in CLL, as well as with other prognostic factors. Furthermore, we will discuss their importance as circulating miRNAs in CLL and their role in resistance to chemotherapeutic agents that are used to treat CLL. Finally, we will describe the potential of targeted miRNA therapy for the treatment of CLL.

2. miRNAs associated with common cytogenetic aberrations in CLL

The prognosis and outcome of patients with CLL is highly variable and has been found to be largely dependent on cytogenetic abnormalities that occur in the tumors. The majority of patients with CLL (~80%) can be categorized in five distinct cytogenetic prognostic subgroups: deletion of the long arm of chromosome 13 (del13q), deletion of the long arm of chromosome 11 (del11q), deletion of the short arm of chromosome 17 (del17), trisomy of chromosome 12 (tri12), and normal cytogenetics and normal fluorescent in situ hybridization analyses (NL cyto/FISH). For some abnormalities, the target protein-coding or non-coding gene has been identified (Fig. 1), while others are still under intensive investigation to unravel the biological significance of the aberrations.

Del13q is the most common cytogenetic abnormality (~55% of patients) and a good prognostic factor (median survival of 133 months) [4]. Detailed analyses of the deleted 13q14 region failed to

* Corresponding author. Departments of Experimental Therapeutics and Leukemia, Unit 1950, The University of Texas MD Anderson Cancer Center, 1881 East Rd, Houston, TX 77054. Tel.: +713 792 5461; fax: +713 745 4526.
E-mail address: gcalin@mdanderson.org (G.A. Calin).

http://dx.doi.org/10.1053/j.seminoncol.2016.02.015
0093-7754/