Mutation Research 717 (2011) 46–53

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

MicroRNAs in inflammation and response to injuries induced by environmental pollution

Enikö Sonkoly[a,b], Andor Pivarcsi[a,b,*]

[a] Molecular Dermatology Research Group, Unit of Dermatology and Venerology, Department of Medicine, Karolinska Institute, Stockholm, Sweden
[b] Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

ARTICLE INFO

Article history:
Received 31 August 2010
Received in revised form 2 February 2011
Accepted 7 February 2011
Available online 15 February 2011

Keywords:
miRNA
Inflammatory diseases
Immunity
Environmental pollution
Toxins
Carcinogenesis

ABSTRACT

MicroRNAs (miRNAs) are small noncoding RNAs that regulate basic biological processes by posttranscriptional suppression of their target genes. Altered miRNA expression may lead to widespread gene expression changes and has been implicated in pathophysiological processes such as cancer and inflammation. In this review, we summarize the present knowledge about the role of miRNAs in inflammation and in the response to environmental agents and pollutants, such as cigarette smoke, ethanol, carcinogenic chemicals such as benzo(a)pyrene (BaP) and dioxin, and UV radiation.

Contents

* Corresponding author at: Molecular Dermatology Research Group, Unit of Dermatology and Venerology, Center for Molecular Medicine (CMM) L8:02, Karolinska University Hospital, Stockholm, Sweden.
E-mail address: andor.pivarcsi@ki.se (A. Pivarcsi).

0027-5107/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2011.02.002

1. Introduction

MicroRNAs (miRNAs) are small, approximately 19–23 nt long, single-stranded non-coding RNAs that are encoded in the genome and regulate the expression of protein-coding genes [1]. MiRNAs have been implicated in the regulation of a wide variety of biological processes including development, cell differentiation and proliferation, as well as immunity and inflammation [2]. In this review, we will provide an overview of the involvement of miRNAs in inflammation and we will summarize the current knowledge on the association of miRNAs with exposure to environmental pollutants.

The first miRNA, named lin-4, was discovered in *Caenorhabditis elegans* in 1997 [3,4]. This gene regulated developmental transitions [4] and did not code for a protein but a long, non-protein coding transcript, which was processed into small functional RNAs. These small RNA molecules repressed the production of the lin-14 protein at the posttranscriptional level. Although at the time of this discovery, lin-4 was thought to be an exception, a few years later, hundreds of similar small functional RNAs were discovered in every multicellular organism analyzed, including plants, nematodes, arthropods and vertebrates [5]. In 2001, the term "miRNA" together with a systematic nomenclature was officially introduced to designate newly discovered small RNA-coding genes whose function is the regulation of protein-coding genes [5–7]. Today, we understand that miRNAs represent a novel layer in the regulation of the flow of genetic information and cellular functions. Similar to transcription factors, miRNAs are a critical component of the complex system, which defines the rate by which genetic information is expressed.

MiRNAs are encoded in the genomic DNA, and most of them are transcribed by RNA polymerase II. The produced long primary transcript (from few hundred to few thousands bases; *pri-miRNA*) is sequentially processed first in the cell nucleus and then in the cytoplasm to generate the mature, biologically active miRNA [8]. First, an RNase III enzyme, Drosha cleaves the primary transcript in the nucleus and generates an approx. 70 nt long RNA hairpin (*pre-miRNA*), which is then exported into the cytoplasm by Exportin 5. Another RNase III enzyme, Dicer, cleaves the miRNA hairpin into an approximately 22-mer RNA duplex. Most often only one of the two strands becomes the mature miRNA via separating from the other strand and incorporating into the RNA Induced Silencing Complex (RISC). This RNA-protein complex can bind to the 3′ untranslated region (3′UTR) of protein coding mRNAs present in the cytoplasm of the host cell and inhibit protein production via translational suppression, RNA-cleavage, or a combination of these two mechanisms [5,8]. Of note, not all nucleotides of the ~22 nt long miRNA participate in the base-paring, but 6–8 nt of the 5′ end of the miRNA (called the "seed") has a predominant role in defining the interaction, while the remaining nucleotides have complementary roles in this process [9].

A particularly interesting feature of miRNA-mediated gene regulation is that one miRNA can have dozens if not hundreds of functional targets within a cell type [6,7], each carrying the complementary sequences to the miRNA seeds in their 3′UTRs. To further add to the complexity of miRNA-mediated gene regulation, not only can one miRNA regulate hundreds of targets, but also each target can be regulated by multiple miRNAs simultaneously. This is made possible by the fact that mRNAs with long 3′UTRs may contain dozens or more miRNA binding sites [10]. The effect of multiple miRNAs targeting the same mRNA may be additive or synergistic, resulting in a higher degree of inhibition. In some aspects, the action of miRNAs can be compared to the action of transcription factors in terms of pleiotropy, although they act on different levels in the flow of genetic information.

Although bioinformatic predictions suggest that most of the genes are subject to miRNA-mediated regulation, there seem to be exemptions [10]. Genes which need to be transcribed constitutively at a high level, such as house-keeping genes, or antimicrobial peptides necessary in large amounts after induction, tend to have very short 3′UTRs presumably to avoid interference with miRNAs. Interestingly, cells can change the set of 3′UTRs utilized by mRNAs when they undergo activation. A large part of the transcripts in activated T cell switches to alternative set of 3′UTRs, most of which are shorter than the canonical ones, presumably to avoid miRNA-mediated regulation during T cell activation [11]. Recently it has been found that some pseudogenes (i.e. dysfunctional relatives of known genes that have lost their protein-coding ability and are generally thought to have no biological function) are expressed in tumor cells and can regulate the expression of their coding "pair" by luring away miRNAs targeting the corresponding region of the coding mRNA [12].

Since their discovery, miRNAs have been implicated in virtually every biological process investigated. MiRNAs regulate development, organogenesis, basic biochemical processes, signal transduction, cell proliferation, apoptosis and migration/invasion. Shortly after their discovery in human, deregulated miRNA expression was found in disease states such as cancer [13–18], developmental abnormalities [19], muscular [20,21] and cardiovascular disorders [22,23], schizophrenia [24] and in immune-mediated and inflammatory diseases [25–27]. More recently, miRNAs have also been implicated in the cellular response to environmental agents and associated diseases.

Since the 1970s there has been increasing global concern over the public health impacts attributed to environmental pollution. The World Health Organization (WHO) estimates that about a quarter of the diseases facing mankind today occurs due to prolonged exposure to environmental pollution. Several environmental chemicals including benzo(a)pyrene, dioxin, furan and conazoles are known to be carcinogenic, and exposure to ultraviolet (UV) radiation is a major risk for skin cancer. Exposure to airborne particulate matter (for example from diesel exhaust) has been associated with cardiovascular and respiratory diseases [28]. The adverse health effects of cigarette smoke are well-known and include smoking-related malignancies, chronic obstructive lung disease and cardiovascular diseases [29,30]. The mechanism by which these environmental exposures lead to impaired health and diseases is only partially known. While the capability of environmental exposures to produce DNA mutations has been a landmark for risk assessment and prevention, recent evidence suggests that some environmental factors cause epigenetic changes which may increase the risk of disease [31]. Most recently, environmental factors mentioned above have been linked to altered miRNA expression suggesting that miRNAs may be involved in the adverse health effects of these exposures.

2. MiRNAs in inflammation

The involvement of miRNAs in the regulation of immune system development was established already a few years after the discovery of miRNAs [32]. Not only can miRNAs regulate linage commitment during hematopoiesis, but they can also regulate the innate and adaptive immune responses upon encounter with pathogens or antigens, respectively [33–35]. In parallel with the investigation of their roles in the basic immune function, the attention of researchers turned to their potential roles in diseases in which the immune system malfunctions: chronic inflammatory conditions of various organs [2,26,36].

The first studies focused on the identification of deregulated miRNAs in various inflammatory diseases in comparison to