Journal of Genetics and Cell Biology
JGCB, 2(3): 100-103
www.scitcentral.com

ISSN: 2639-3360

Review Article: Open Access

The Contribution of miR-34a-5p and miR-34a-3p to the Signaling Pathway of p53

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Received April 24, 2019; Accepted May 14, 2019; Published December 07, 2019

ABSTRACT

In contrary to the common belief that only one strand of the pre- miRNA is active (usually the 5p one that is the more abundant) while the second one (miRNA*) is discarded, functional 5p and 3p have been observed for many miRNAs. Among those miRNAs is miR-34a which is a target gene of the tumor suppressor p53. In this paper we review the role that miR-34a-5p and miR-34a-3p play in the signaling pathway of p53 by targeting overlapping sets of genes (MDM2 and THBS1), where THBS1 is involved in cancer relevant processes, and MDM2 is linked to p53 and miR-34a by a type 1 incoherent FFL that represent a novel mechanism for accelerating the response of p53 to external stress signals.

INTRODUCTION

microRNAs (miRNAs) are small non-coding RNAs that negatively regulate gene expression post transcriptionally by base-pairing to the 3'UTR of target mRNAs leading to repression of protein production or mRNA degradation [1]. They are involved in many biological processes, in particular cancer-relevant processes.

The biogenesis of miRNAs can be summarized as follows: a primary transcript (pri-miRNA) is first generated by RNA polymerase II. Then the primary transcript is processed by the microprocessor complex containing the RNase III enzyme Drosha to an approximate 70-nucleotide pre-miRNA hairpin (the precursor-miRNA) [2-4]. Pre-miRNAs are subsequently exported to the cytoplasm by exportin 5 (XPO5) [5,6] where their terminal loops are excised by the RNase III Dicer to give rise to a double stranded 22 nt stem composed of 5' and 3' strands representing 5p and 3p, respectively. While one of the two strands (the passenger strand miRNA*) is discarded, the other one (the guide) miRNA is then embedded into the RISC (RNA Induced Silencing Complex) to complementary target mRNA for post-transcriptional gene silencing [7]. p53 has been dubbed "guardian of the genome" [8] or gatekeeper [9] due to its central role in maintaining the genomic stability and tumor suppression [10-12]. It has been found to be mutated in about half of the human cancers [13,14]. Since its discovery p53 has been subject to a tremendous amount of work making it one of the most extensively studied gene. Its tumor suppressive role consists in inducing anti-proliferative cellular responses to a variety of stress signals, namely a cell-cycle arrest, senescence or an apoptosis. p53 can then be activated in response to DNA damage, hypoxia or aberrant growth signals resulting from deregulated expression of oncogenes [15-17].

miRNAs have been shown to be important components in the p53 network Their interactions with p53 have been demonstrated through the identification of several miRNAs as direct target genes of p53. By inducing the expression of specific miRNAs that have a tumor suppressive function a novel mechanism for tumor suppression for p53 has been then revealed. In particular the role of the miR-34 family has been reported in several studies [18].

miR-34 FAMILY AND THE p53 PATHWAY

Since it was believed that according to the thermodynamic stability of the pre-miRNA cells preferentially select the less stable one of the two strands (the guide) and destroy the other one (the miRNA*), early works on miRNAs have focused on the guide strand (which was usually considered as the 5p one because it was found to be more abundant than its counterpart miRNA* in humans [19]). However, even though miRNA* are less abundant they are often present and remain functional because they conserve their seed sequences and have been isolated from RISC [20,21]. The interplay between the 5p and 3p strands from the same

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Citation: Chafik A. (2019) The Contribution of miR-34a-5p and miR-34a-3p to the Signaling Pathway of p53. J Genet Cell Biol, 2(3): 100-103.

precursor has been shown by targeting overlapping sets of genes when the abundances of the two strands are similar [22]. In some cases the two arms function in opposing ways (e.g. miR-28 [23] and miR-125 [24]), while in others they function in joint fashion (e.g. miR-199 [25] and miR-155 [26]).

In mammalians miR-34 family consists of miR-34a, miR-34b and miR-34c that are encoded by two different genes. miR-34a is encoded by an individual transcript in chromosome 1 and expressed in a majority of tissues, while miR-34b and miR-34c share a common primary transcript in chromosome 11 and are mainly expressed in lung tis- sues. Several studies have reported that the members of miR-34 family were direct target genes of p53 and their up regulation induces apoptosis and cell-cycle arrest [27-33]. Indeed, Ectopic expression of miR-34 induces cell cycle arrest in both primary and tumor-derived cell lines [33]. Inactivation of miR-34a strongly attenuates p53-mediated apoptosis in cells exposed to genotoxic stress [29]. miR-34b/miR-34c were also down-regulated in p53-null human ovarian carcinoma cells and both cooperate in suppressing proliferation of neoplastic epithelial ovarian cells [28]. Since cell-cycle arrest and apoptosis are the responses of p53 to the stress signals, these facts imply that miR-34 mediate the tumor suppressive functions of p53. On the other hand the members of the miR-34 family can have decreased expression in cancer because of the inactivating mutations of p53 or the expression of viral inhibitors of p53, but also as a consequence of their own mutational or epigenetic inactivation.

Since 30% of all genes and the majority of the genetic pathways are regulated by miRNAs [12,34,35], we can expect some miRNAs to regulate p53 and its pathway. This hypothesis has been verified and some miRNAs have been identified as regulators of p53. Furthermore, miR-34a, which is a transcription target of the p53 protein, was also found to positively regulate p53 activity and function in apoptosis through its direct negative regulation of SIRT1 [36]. SIRT1 is a negative regulator of p53, which physically interacts with p53 and deacetylates Lys382 of p53 [37].

THE ROLE OF THE COMMON TARGET GENES MDM2 AND THBS1

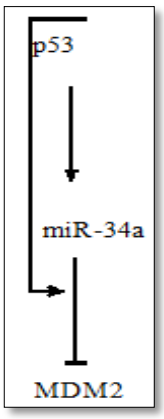
We begin by using DIANA-miRPath v3. 0 which is a miRNA pathway analysis web-server, providing accurate statistics utilizing predicted or experimentally validated miRNA interactions derived from DIANA-TarBase [38]. In the p53 signaling pathway we obtain the target genes of the different miRNAs that we found. Then we use the cytoscape 3.4.0 software to visualize the interactions where the relevant genes are involved, by taking the IntAct 1 to be our source of interactions.

For miR-34a the list of target genes contains 30 genes for miR-34a-5p and two for miR-34a-3p (MDM2 and THBS1) that are also target genes of the miR-34a-5p.

By loading the list of the 30 target genes of miR-34a-5p (containing also the two targets of miR-34a-3p) in Cytoscape 3.4.0 and searching the interaction in IntAct we obtain a network composed of 2492 nodes and 6493 edges.

In order to find the pathways in which the THBS1 gene is involved we use the BINGO application of Cytoscape and the relevant GO terms that are overexpressed in cluster containing the THBS1 gene. According to this analysis we can deduce that the THBS1 gene is involved in regulating tumor suppression processes.

MDM2 and p53 are linked by a negative feedback loop. However, since MDM2 is a target gene of miR-34a which means that it is negatively regulated by this miRNA, we can represent the interaction between the three molecules (p53, MDM2 and miR-34a) as a Feed For- ward Loop (FFL). According to the signs of the three interactions (activation/repression) the present loop is a type 1 incoherent FFL 1 IntAct is one of the largest available repositories for curated molecular interactions data, storing PPIs as well as interactions involving other molecules. It is hosted by the European Bioinformatics Institute. IntAct has evolved into a multisource curation platform and many other databases curate into IntAct and make their data available through it [21].



The dynamics of this FFL can be described as follows: when p53 begins to accumulate as a response to stress signals MDM2 rst raises since it is positively regulated by this gene. miR-34a is one of the direct target genes of p53, thus, at some level of p53 the expression of miR-34a begins also to increase, when it reaches some cellular level MDM2 begins to decrease. It has been demonstrated that the response time of the type 1 incoherent FFL is smaller than the one of a single regulation system [39]. Thus in cases where speedy responses are needed this type of regulatory loop is more advantageous than the simple one. Thus the FFL constitute

another mechanism that accelerates the stabilization of p53 in response to external stimulus.

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