Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

MICRORNA-21 AND THE ROLE OF ANTI-APOPTOSIS IN HUMAN CANCERS

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ARTICLE INFO

Received:
19 Jan 2020
Received in revised form:
30 May 2020
Accepted:
09 Jun 2020
Available online:
28 Jun 2020

Keywords: *miR-21, anti-apoptosis, Bcl-2, PTEN, PDCD4.*

ABSTRACT

The dysregulation of miR-21 has been defined as the genome instability, an event of the hallmarks of cancer, is observed in human cancers. Additionally, the effect of dysregulation of miR-21 was observed in its target genes, which is involved in many signal pathways of tumorigenesis. Among them, particularly, miR-21 is strongly involved in the anti-apoptosis processes, also known as evading apoptosis. In the present study, we studied the experimentally validated miR-21 targets, including Bcl-2, PTEN, and PDCD4 gene, which are linked to anti-apoptosis in human cancers. Thus, miR-21 and its targeting apoptosis is a valuable therapeutic target in the development of human cancer treatment.

To Cite This Article: Minh Trong Quang, Kim My Thi Le, Tung Thanh Nguyen, Trinh Viet Nguyen, Tran Que Thi Tran, Hue Hong Thieu and *et al.*, (2020), "MicroRNA-21 and the role of anti-apoptosis in human cancers", ***Pharmacophore, 11(3),*** *78-81.*

Introduction

1. Onco-miR-21 involves in evading apoptosis - the event of hallmarks of cancer

In 1972, apoptosis, or "programmed cell death", was first used by Kerr et al. as the morphologically distinct form of cell death [1–4]. The process of apoptosis is reported as the highly regulated and controlled process that takes place normally during aging and development as a homeostatic mechanism to maintain the cell population in tissues [3, 5]. Since the discovery of apoptosis, it has played a significant role in the elimination of the damaged, infected, and mutated cells, which could potentially lead to pathology. Notably, damaged cells, which failed to undergo apoptosis, may lead to tumorigenesis [6]. Hence, the evading or reduction of apoptosis plays a key role in carcinogenesis. In the concept of hallmarks of cancer, which was updated by Hanahan et al. (2011), the characteristic of evading apoptosis - also known as anti-apoptosis, has been defined as one of the events of hallmarks of cancer [7, 8]. Moreover, in the updated hallmarks of cancer, mutation and genome instability, and tumor-promoting inflammation, were considered as the two additional characteristics of cancer progression [1, 9]. Concerning the aspect of genome instability, it leads to tumorigenesis by enabling the genome of cancer cells to escape their normal restraints. Among the genome instability, the abnormal expression of microRNAs (miRNAs) modulates the dysregulation of target genes in many biological pathways, including cell cycle defects, DNA damage repair regulatory defects, and apoptosis defects, and subsequently lead to tumorigenesis [10].

microRNA-21 (miR-21) locates at chromosome 17q23.2, which acts as an oncogene in the human genome. The significant upregulation of miR-21 has been demonstrated in many human cancers, including breast cancer [11, 12], hepatocellular carcinoma [13], nasopharyngeal carcinoma [14, 15], lung cancer [16], etc. Involving in hallmarks of cancer, notably, miR-21 was first identified as a vital anti-apoptotic factor in human glioblastoma [17]. Recently, large-scale experimental data showed that miR-21 plays an anti-apoptotic role in many human malignancies, including gastric adenocarcinoma [18], bladder cancer [19], lung squamous carcinoma [16], nasopharyngeal carcinoma [15], etc. Understanding the anti-apoptosis-

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related target genes of miR-21 will help increase our understanding of the miR-21 role in the characteristics of evading apoptosis in tumor cells and provide novel options for the targeting of cancer therapy.

2. Anti-apoptosis-related target genes of miR-21

2.1. Overexpression of anti-apoptotic protein: Bcl-2

The *B-cell lymphoma 2* (*Bcl-2)* gene encodes a 26-kDa protein that plays a vital role in the regulation of apoptosis via the intrinsic pathway as they regulate the caspase activity by helping to sequester cytochrome C in the mitochondria level through inhibition of the mitochondria-permeabilizing protein Bax [8, 20]. The overexpression of onco-miR-21 was reported to down-regulate Bax, up-regulate Bcl-2, and subsequently lead to the inhibition of apoptosis [8]. This disrupted balance of proapoptotic protein - Bax and anti-apoptotic protein - Bcl-2 were recorded in human glioblastoma U87MG cells [21]. It has been reported that the overexpression protects human glioblastoma U87MG cells against chemotherapeutic drug temozolomide induce apoptosis through the downregulation of Bax and upregulation of Bcl-2, and subsequently reduces the Bax/Bcl-2 ratio. These results highlighted that the overexpression of onco-miR-21 leads to the possibility of clinical resistance to chemotherapeutic therapy of temozolomide through the mechanism of evading apoptosis [21]. The anti-apoptosis potential of the overexpressed onco-miR-21 was also reported in MIA PaCa-2 pancreatic cancer cells [22], in which the experimental data revealed that miR-21 regulates the expression of Bcl-2, and Bcl-2 serves as one of the direct targets of miR-21, resulting in inhibiting the apoptosis in MIA PaCa-2 pancreatic cancer cell [22]. Since the miR-21 contributes to the evading apoptosis of many human malignancies through targeting Bcl-2, therefore, both miR-21 and bcl-2 may serve as valuable targets for developing novel cancer treatment in the future.

2.2. Inhibiting the expression of *PDCD4* - a mediator of apoptosis

Programmed cell death 4 (PDCD4) gene, locates at chromosome 10q25.2, its encoded protein binds to eukaryotic translation initiation factor 4A1 to regulate the translation, acts as a tumor suppressor gene and translation inhibitor [8, 23, 24]. The role of miR-21 and loss or suppression of PDCD4 expression has been recorded in many human tumors, such as non-small cell lung cancer [25], renal cancer [26], nasopharyngeal carcinoma [27], etc. through the seed-match type of 8mer 3'-UTR of PDCD4 and 5' miR-21. In the nasopharyngeal carcinoma, the association among LMP-1, miR-21, and PDCD4 expression was reported [27]. In their research, the overexpression of miR-21 was induced by LMP-1 through the PI3K/AKT/FOXO3a signaling pathway, subsequently, decreased the expression of PDCD4, and resulted in chemoresistance and apoptosis resistance in NPC cells [27]. Sheedy et al. (2010) reported that the PDCD4-deficient mice were protected against lipopolysaccharide-induced death via the regulation of PDCD4 expression after the stimulation of LPS [28]. In the signal pathway of NF-κB, the expression of miR-21 is induced by NF-κB, forming the negative feedback loop by targeting PDCD4. In this way, apoptosis is induced by PDCD4 via extrinsic signals [8]. Taken together, decreasing the expression of PDCD4 leads to the evading apoptosis as well as the drug-resistance in human cancer cells, therefore, inhibition of oncogenic miR-21 or up-regulation of PDCD4 may open up the new approach for the development of therapeutics for human cancers.

2.3. Down-regulation of *PTEN* tumor suppressor gene

The gene of phosphatase and tensin homologue (PTEN) enzyme, locates at chromosome 10q23.31, encodes a 403-amino acid PTEN protein containing a tyrosine phosphatase domain, was first identified as a tumor suppressor gene [8, 15, 29, 30]. It was well known that PTEN is involved in many biological processes, including apoptosis, cell proliferation, as well as angiogenesis through several signaling pathways [15]. PTEN controls the apoptosis through inhibiting the Akt pathway by reversing the phosphorylation of phosphoinositide 3 kinase (PI3K) [31]. The loss of PTEN has been investigated in many human oncogeneses [8, 15]. The effect of onco-miR-21 on the expression of PTEN was reported in many human malignancies, including nasopharyngeal carcinoma [15], cervical cancer [32], lung squamous carcinoma [16], hepatocellular cancer [33], etc. By informatics analysis, the seed-match type of 7mer-A1 was observed in the interaction between 3'-UTR of PTEN and 5' miR-21. The effect of miR-21 on the expression of PTEN was clearly reported by Ou et al. (2014). They used nasopharyngeal tissue and nasopharyngeal cell lines to show that miR-21 is significantly upregulated and inhibits apoptosis, which is linked to direct suppression of PTEN by miR-21 [15]. Xu et al. (2014) reported that miR-21 promotes the progression of squamous cell lung carcinoma through the negative regulation of PTEN expression and results in evading apoptosis. Their results demonstrated that miR-21 plays a vital role in squamous cell lung tumorigenesis and is involved in anti-apoptosis processes, as well as in mediating phenotypic characteristics of cancer cells including cell proliferation, invasion, and migration. In addition, miR-21 inhibits cell apoptosis linked to the PTEN expression. Overall, PTEN is directly linked to the intrinsic apoptotic pathway by mediating the expression of mitochondrial apoptosis factors and the extrinsic apoptotic pathway through the mediation of TNFα signaling [8].

Conclusion

The miR-21 upregulation has been shown to play an oncogenic role in the hallmarks of human cancers by targeting many pathways, including the evading apoptosis, genome instability. In the aspect of evading apoptosis, the effect of onco-miR-21 on the expression of its target genes, including Bcl-2, PTEN, and PDCD4 was shortly described in this article. The potential approach for therapeutics for human cancers, which focused on the miR-21 as well as their target genes will persist.

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