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One step ahead: miRNA-34 in colon cancer-future diagnostic and therapeutic tool?

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ABSTRACT

The discovery that microRNAs (miRNAs) - short, non-coding RNA molecules which regulate gene expression - are implicated in many types of cancer has revolutionised cancer research, giving hope for a new perspective in diagnostics and treatment. Dysregulation of miRNAs occurs in various malignancies, including colorectal cancer (CRC). CRC is one of the leading causes of cancer-related death and in most countries its incidence is still rising. Among several miRNAs which have been linked to CRC, miR-34 has attracted particular attention. This miRNA is involved in the regulation of cell cycle and apoptosis through multiple signaling pathways such as p53, Ra and Wnt signaling. Understanding its role in CRC may facilitate its future use as a diagnostic tool and therapeutic target.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. The last global statistics were provided for 2012, with approximately 1.4 million new cases and 0.7 million deaths (Ferlay et al., 2013). In 2017 in the United States alone approximately 135,430 new cases and 50,260 deaths were reported, while in 2015 in China around 350,000 new cases and 190,000 deaths were noted (Chen et al., 2016; Siegel et al., 2017). The majority of cases occur in more developed regions, which points to the importance of environmental risk factors in colorectal carcinogenesis, such as improper dietary habits, insufficient physical activity, excessive body weight, smoking and alcohol consumption (Ferlay et al., 2013). The non-modifiable risk factors comprise age, genetic predisposition and intestinal inflammation. Inflammatory bowel disease (IBD) significantly increases the risk of cancer development, as the cumulative risk for colitis-associated cancer (CAC) equals 18% in ulcerative colitis (UC) and 8.3% in Crohn's colitis after 30 years of disease (Eaden et al., 2001; Canavan et al., 2006; Rubin et al., 2012).

MicroRNAs (miRNAs) are short, non-coding RNA molecules which regulate gene expression through binding to the target mRNA – usually at the 3′UTR, although interactions with 5′UTR and coding region have also been reported (Arora et al., 2013). These miRNA-mRNA interactions result in either degradation of mRNA or translational repression (Bajan and Hutvagner, 2014). Since miRNAs regulate basic cellular functions such as proliferation, differentiation and apoptosis, they may have a role in carcinogenesis. In fact, upregulation or downregulation of many miRNAs has been reported in various cancers (Ma et al., 2012; Zhu et al., 2014; Berindan-Neagoe et al., 2014; Guo et al., 2014; Yang et al., 2014, 2015; van Schooneveld et al., 2015). Depending on the function of miRNAs and their altered expression in cancer, some of the miRNA-encoding genes could be considered as oncogenes or tumor suppressor genes (Yamakuchi et al., 2008; Hermeking, 2010; Chi and Zhou, 2016).

Since miRNAs dysregulation was first detected in cancer, it has been extensively studied with the hope of discovering biomarkers for early diagnosis and prognosis, as well as new treatment possibilities. Over the years, more than 160 miRNAs were reported to be dysregulated in CRC, either within the cancer cells or in the peripheral blood. The most commonly reported include miR-20a and miR-31 (upregulated), miR-143 and miR-145 (downregulated) in tissue samples, while miR-92a was upregulated both in tissue and plasma (Luo et al., 2011). Moreover, the role of many miRNAs in CRC development with regard to their involvement in different cellular pathways was analyzed (for review see Chi and Zhou 2016). Additional evidence pointing to the importance of

Abbreviations: AOM, azoxymethane; APC, adenomatous polyposis coli; BTG-4, B-cell translocation gene; CAC, colitis associated cancer; CSCs, cancer stem cells; CRC, colorectal cancer; DSS, dextran sodium sulfate; GSK-3, glycogen synthase kinase-3; EMT, epithelial-mesenchymal transition; FU, fluorouracil; HA, hyaluronic acid; IBD, inflammatory bowel disease; iNOS, inducible nitric oxide synthase; KO, knockout; miRNAs, microRNAs; MM, multiple myeloma; MTA, methylthioadenosine; NO, nitric oxide; NOS2, nitric oxide synthase-2; SAMe, S-adenosylmethionine; siRNA, small interfering RNA; SIRT1, silent information regulator 1; SNALPs, stable nucleic acid lipid particles; TCF/LEF, T cell factor and lymphoid enhancer factor; UC, ulcerative colitis; WT, wildtype

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Table 1
The miR-34 expression in human CRC studies.

Reference	Number of patients (stage I/I/III/IV/adenoma tissue;number of samples)	Specimen	miR		Method
			subtype	expression	
Roy et al. (2012)	Not applicable	formalin-fixed paraffin-embedded tissues from normal colonic mucosa and colon tumors	miR34a miR34c	downregulated downregulated	Real time RT-PCR
Arndt et al. (2009)	45 (stage I, II, III, IV; 4:19:20:2)	Colon tumors	miR34a	upregulated	Real time Quantitative RT-PCR
Monzo et al. (2008)	22 (stage I and II 6:16:0:0)	Colon tumors	miR34a	upregulated	Real time RT-PCR
Gao et al. (2015)	10 (stage II and III)	Colon tumors	miR34a-5p	downregulated	Real time Quantitative RT-PCR
Tazawa et al. (2007)	25	Colon tumors	miR34a	downregulated	Real time RT-PCR
Ma et al. (2012)	30	Colon tumors	miR34a	downregulated	Real time RT-PCR
Bu et al. (2013)	5 (stage I, II, III, IV; 2:1:1:1)	Colon tumors	miR34a	downregulated	Quantitative RT-PCR
Zhang et al. (2014)	100 (stage I + II, stage III + IV; 44:56)	Colon tumors	miR34a	downregulated	Real time Quantitative RT-PCR
Akao et al. (2010)	63 (stage I, II, III, IV; 12:19:24:8)	Colon tumors	miR34a	downregulated	Real time Quantitative RT-PCR
Wang et al. (2012)	109 (stage III and IV)	Colon tumors	miR34a	upregulated	Taqman Real time PCR

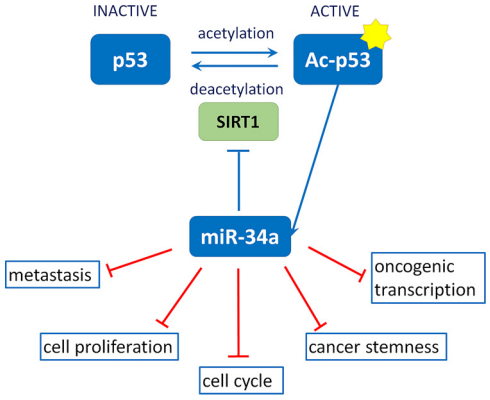

Fig. 1. The p53, SIRT-1 and miR-34a circuit. While acetylated p53 is the active form of this transcription factor, SIRT1 inhibits apoptosis through deacetylation of p53. Acetylated p53 induces miR-34a expression, which in turn inhibits SIRT1. Consequently, there is an increase in p53 acetylation, and increased p53 stability enhances miR-34a production. Therefore, miR-34a-mediated inhibition of SIRT1 can counteract the cancer process causing various effects on tumor cells. The positive feedback loop between p53, SIRT1 and miR-34a may thus become a new therapeutic target for the treatment of cancer.

miRNAs in CRC was provided by a study which reported that impaired DICER1 gene function and consequent downregulation of several miRNAs lead to cancer stem cell generation (Iliou et al., 2014). Among the studied miRNAs, miR-34 attracts particular attention (Table 1).

In this review we will analyze the role of miR-34 in the pathogenesis of CRC, its influence on the course of the disease and the pathways miR-34 is involved in.

2. The role of selected members of miR34 family in cancer: regulation of processes through different signaling pathways

The miR-34 family attracted attention when its members (miR-34a, miR-34b and miR-34c) were recognized as p53 targets. While miR-34a is encoded by its own gene and is expressed in all mouse tissues, with highest abundance in brain, miR-34b and miR-34c come from a single transcript and are mainly expressed in lungs. Except for the lung, where miR-34b/c are predominant, miR-34a is generally expressed at higher levels than the other members of the miR-34 family (Hermeking, 2010).

Overexpression of miR-34 leads to apoptosis and G1-phase cell cycle arrest, which suggests a link between miR-34 and p53. In fact, p53 regulates the expression of miR-34, as there are p53 binding sites within miR-34a and miR-34b/c promoter regions (He et al., 2007). Consequently, the antioncogenic action of miR-34 is regulated by p53.

Experiments based on ectopic introduction of miR-34 as well as bioinformatics approach allowed to identify numerous miR-34 targets, which primarily included mRNAs responsible for cell cycle control and response to DNA damage. Although miR-34a and miR-34b/c mostly target the same mRNAs, there is a difference in affinity for specific targets between miR-34 family members. Such system allows for an effective regulation of multiple processes by p53 (Hermeking, 2010). So far, over 77 of miR-34 targets have been validated, including factors controlling cell cycle (CDK4, CDK6, c-Myc, E2F3), apoptosis regulators (Bcl2, survivin, CREB), proteins engaged in invasion (c-Met, Axl receptor, RAS-oncogene homolog RRAS), factors related to epithelial-mesenchymal transition (EMT-inducing transcription factor SNAIL or zinc finger 281 protein), cancer stem cells formation (Notch1-4, WNT1, WNT3, β-catenin, CD44) and regulation of metabolism (hexokinase 1 and 2, glucose-6-phosphate isomerase, pyruvate dehydrogenase kinase 1, lactate dehydrogenase A) (Rokavec et al., 2014a).

Another miR-34 target, silent information regulator 1 (SIRT1), is involved in a feedback loop consisting of miR-34a, SIRT1 and p53, as demonstrated in an experiment conducted on the human colon cancer cell line, HCT116. SIRT1 is a NAD-dependent deacetylase involved in cellular response to oxidative stress and DNA damage. P53 is among SIRT1 target proteins, and deacetylation decreases p53 activity. Acetylated p53 induces miR-34a expression which inhibits SIRT1 and consequently activates p53-dependent apoptosis (Fig.1) (Yamakuchi and Lowenstein, 2009). It can be thus concluded that miR-34a regulates p53 activity through its direct target, SIRT1.

There are several arguments pointing to the role of miR-34 in cancer. Firstly, deletions in the regions where miR-34 genes are located (1p36 for miR-34a and 11q23 for miR-34b/c in humans) are detected in various types of cancer (1p36 deletion in neuroblastoma, glioma, melanoma, breast, colorectal, non-small cell and small cell lung cancers and 11q23 deletion in breast, lung, cervical and prostate cancers) (Agostini and Knight, 2014). Secondly, miR-34a downregulation is found in cancer cell lines (including breast, lung, colon, kidney, bladder and pancreatic carcinoma cell lines) and several types of primary cancer (such as colorectal, pancreatic, mammary, ovarian, urothelial, renal cell, nasopharyngeal and lung carcinomas and soft tissue sarcomas) (Toyota et al., 2008; Lodygin et al., 2008; Vogt et al., 2011; Siemens et al., 2013b; Wang et al., 2015a). The expression of miR-34a is also reduced in cancer stem cells (CSCs), in particular in glioblastoma, prostate, pancreatic and gastric CSCs, while its reintroduction suppresses EMT phenotype (Liu and Tang, 2011; Bao et al., 2012).