Sci Parasitol 20(1-2):25-32, August 2019
ISSN 1582-1366

Helminth-based therapy in Inflammatory Bowel Disease

Cristina-Sorina Cătană[1]*, Elena-Cristina Crăciun[2]*, Cristian Magdaş[3]*✉, Ioana Berindan-Neagoe[4,5,6], Vasile Cozma[3], Flaviu Tăbăran[7], Anamaria Cozma-Petruţ[8], Dan Lucian Dumitraşcu[9]

1 – Department of Medical Biochemistry, "Iuliu Haţieganu" University of Medicine and Pharmacy, 400349 Cluj-Napoca, Romania.

2 – Department of Pharmaceutical Biochemistry and Clinical Laboratory, "Iuliu Haţieganu" University of Medicine and Pharmacy, 400349 Cluj-Napoca, Romania.

3 – Department of Parasitology and Parasitic Diseases, University of Agricultural Sciences and Veterinary Medicine, Calea Mănăştur no 3-5, 400372 Cluj-Napoca, Romania.

4 – Research Center for Functional Genomics, Biomedicine and Translational Medicine, Institute of Doctoral Studies, "Iuliu Haţieganu" University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania.

5 – Department of Functional Genomics and Experimental Pathology, "Ion Chiricuţă" Institute of Oncology, 400015 Cluj-Napoca, Romania.

6 – MEDFUTURE – Research Center for Advanced Medicine, 400012 Cluj-Napoca, Romania.

7 – Department of Morphopathology, University of Agricultural Sciences and Veterinary Medicine, Calea Mănăştur no 3-5, 400372 Cluj-Napoca, Romania.

8 – Department of Bromatology, Hygiene, Nutrition, Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, 6 Pasteur, 400349 Cluj-Napoca, Romania.

9 – 2nd Medical Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, 400174 Cluj-Napoca, Romania.

** Authors with equal contribution*

Correspondence: Tel. 0040-264596384, Fax 0040-264593792, E-mail cmagdas@usamvcluj.ro

Abstract. Inflammatory bowel diseases (IBD) have a risk of severe evolution, therefore tremendous efforts are made to improve the treatment. Helminth-based therapy counts among the potential new treatment methods. The aim of this narrative review is to gain an overview of mechanisms by which the helminth therapy acts in IBD. Pertinent literature was searched in major databases and rigorously critically appraised. The discovery of microRNAs (miRNAs) modulated by the *Trichuris suis* products sheds light on another level of genetic and epigenetic alterations involved in IBD. High throughput technologies now allow for miRNA profiling studies that pinpoint miRNA differential expression across normal and chronically inflamed tissues. The complex interactive networks of miRNAs and target's gene and also miRNA profiling studies in IBD patients have revealed upregulated inflamma-miRs as well as downregulated miRNAs which could represent novel biomarkers of IBD, influential new mediators of this disease as well as therapeutic targets. This review concludes that treatment with *T. suis* may be effective in certain forms of IBD. The beneficial activity is explained by the modulation of miRNAs.

Keywords: Inflammatory bowel disease; MicroRNAs; Biomarkers; *Trichuris suis*.

Terapia pe bază de helminţi în boala inflamatorie a intestinului

Rezumat. Bolile inflamatorii intestinale (IBD) prezintă un risc de evoluţie severă, ca urmare, se depun eforturi intense pentru îmbunătăţirea tratamentului. Terapia pe bază de helminţi se numără printre potenţialele noi metode de tratament. Scopul acestui articol este de a oferi o imagine de ansamblu asupra mecanismelor prin care terapia cu helminţi acţionează în IBD. Literatura relevantă a fost căutată în baze de date majore şi evaluată riguros. Descoperirea micro ARN-urilor (miARN) modulate de produsele de excreţie ale helmintului *Trichuris suis* clarifică la un alt nivel modificările genetice şi epigenetice implicate în IBD. Tehnologiile moderne permit, în prezent, realizarea studiilor de stabilire a profilului miARN, care indică expresia diferenţiată a miRNA în ţesuturile normale şi în cele cu inflamaţie cronică. Analiza reţelelor interactive complexe dintre miRNA şi gena ţintă şi studiile profilului miRNA, la pacienţii cu IBD, au evidenţiat inflama-miR-uri supraexprimate precum şi miRNA-uri subexprimate, sugerând faptul că acestea ar putea reprezenta noi biomarkeri ai IBD, noi mediatori influenţi ai acestei boli, precum şi ţinte terapeutice. Articolul concluzionează faptul că tratamentul cu *T. suis* poate fi eficient în anumite forme de IBD, iar activitatea benefică se explică prin modularea miRNA-urilor.

Cuvinte cheie: Boli inflamatorii intestinale; MicroARN-uri; Biomarkeri; *Trichuris suis*.

Received 10.06.2019. Accepted 20.07.2019.

Introduction

Inflammatory bowel disease (IBD) describes a group of chronic inflammatory intestinal diseases with potential severe evolution and a certain risk for colorectal carcinoma (CRC) [Braicu et al., 2013]. Currently, IBD affects more than 1 million people in the United States and 2.5 million in Europe, respectively. It frequently occurs in the younger population and has a major impact on the individual's quality of life and working ability, thus resulting in substantial healthcare costs. Moreover, in 2015, ulcerative colitis (UC) and Crohn's disease (CD), which are the major phenotypes of IBD, emerged in newly industrialized countries in South America, Asia and the Middle East and evolved into a global disease with rising prevalence in every continent [Kaplan, 2015]. A commonality between UC and CD is a deregulated immune response in the gastrointestinal tract [Moldoveanu et al., 2015]. IBD develops due to complex interactions between the genome, the environmental stimuli, the microbiome and an improper mucosal immune response [Schaefer, 2016].

Modern therapy in IBD uses anti-TNF (tumor necrosis factor) drugs, which are very expensive and cannot completely control the inflammatory process [Cătană et al., 2015a; Kaplan, 2015; Fisher and Lin, 2015; Chira et al., 2016]. Likwise, the current diagnosis includes a range of invasive investigations [Tontini et al., 2015]. Previous research carried out on mice as well as clinical studies suggested that the helminth infection might prevent and even treat IBD. Since 2016, changes in intestinal microflora have been regarded as a new mechanism underlying IBD. In addition, researchers concluded that infecting the mice with one type of intestinal worm returned their mucus-producing cells to normal and shifted the bacterial composition in their guts [Leslie, 2016]. In this context, the helminth infection

might protect against inflammation in IBD, probably by modulating the immune system ("hygiene hypothesis") [Kaplan, 2015; Leslie, 2016].

The successful use of helminthic therapy for reducing inflammation was first recorded 40 years ago. Consecutive studies in animal and human models indicated that parasites could treat a wide range of chronic inflammatory diseases. However, available information regarding the effects of helminthic therapy in humans is limited. It is generally accepted that the majority of patients with inflammation-associated co-morbidities reacted positively to treatment with either *Trichuris suis* or *Hymenolepis diminuta*, the two most popular organisms frequently used by self-treaters [Liu et al., 2017].

Although the etiology and pathogenesis of IBD remains unsolved, research showed that inflammation and dysfunctions of innate and adaptive immunity, as well as the complex interaction between genetic factors cause the development of this pathological condition [Liu et al., 2017]. Therefore, the controlled re-introduction of helminthic therapy could represent a viable approach if certain molecular biomarkers able to predict and monitor treatment are used. An important genetic contribution to IBD could be represented by certain microRNAs (miRNAs).

MiRNAs in IBD

MiRNAs are a class of small non-coding single-stranded RNA molecules which have been highly conserved throughout evolution and which control protein production at the post-transcriptional level, thus being considered as promising biomarkers [Fisher and Lin, 2015; Cătană et al., 2017] (figure 1). In addition, a single miRNA can modulate multiple target genes and in its turn, a single target gene will admit numerous miRNAs with the capacity to control them. There are different miRNA expression patterns in IBD, which have been evaluated in blood, intestinal biopsies and saliva, respectively.

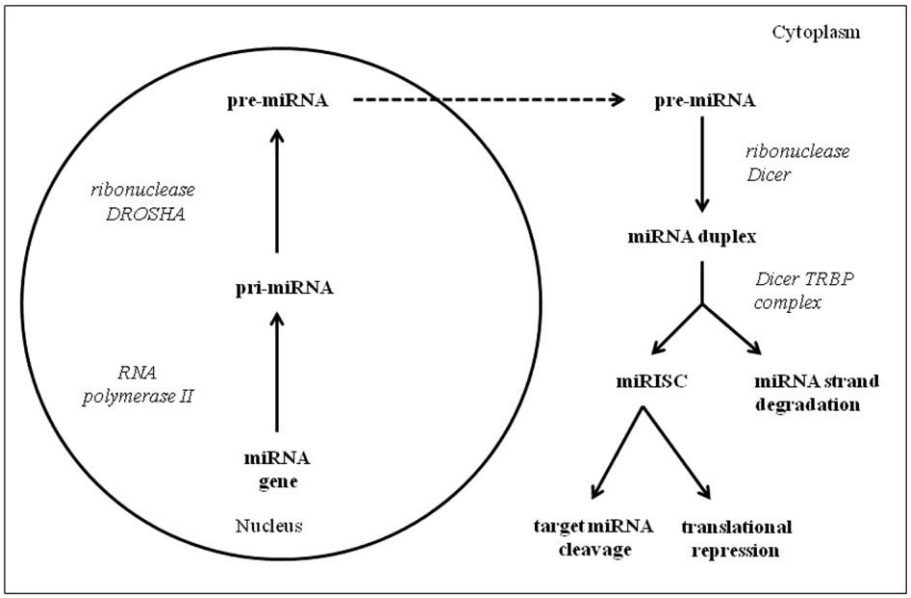

Figure 1. Biogenesis of miRNAs (adapted from Cătană, 2015)
Abbreviations: miRNAs – microRNAs; RISC – RNA-induced silencing complex;
TRBP – transactivating response (TAR) RNA – binding protein as a protein partner of human Dicer.

The stepwise miRNA biogenesis pathway starts in the nucleus and uses multiple RNA-binding proteins and two endoribonucleases. Firstly, the miRNA is transcribed as longer primary-miRNA by RNA polymerase II (RNA Pol II). The approximately 70-nucleotide (nt) long stem-loop primary-miRNA transcripts are processed by DROSHA RNase III enzyme into a precursor to generate the pre-miRNA structure. The pre-miRNA is exported to the cytoplasm where the

two strands of the duplex are separated from each other by the Dicer–TRBP complex. Next, the miRNA loaded to RNA-induced silencing complex (RISC) is complementary bound by specific miRNAs. Finally, the translation of target's mRNA is repressed inducing gene silencing [Cătană et al., 2015a; Schaefer et al., 2015].

MiRNAs as diagnostic and prognostic biomarkers in IBD

A considerable number of studies have indicated that dysregulations of miRNAs are associated with CD, UC or both. In addition, there is a correlation between changes in miRNAs profile and parasitoses such as echinococcosis or trichuriasis. Immune cells actively release miRNAs into extracellular surroundings. Since 2008, research has shown the presence of miRNAs in samples of plasma, serum, saliva andas tissues, serving as the primary diagnostic tool for different human diseases. The stability of circulating miRNAs is remarkable because they are either incorporated in exosomes and form a complex with an Argonaute protein or attached to high-density lipoproteins [Dong et al., 2017].

T. suis is an epidemic whipworm that gives clinical/subclinical infections in pigs and highly expressed circulating miRNAs such as ssc-let-7d-3p at 8 weeks postinfection, respectively [Dong et al., 2017, Gulati et al., 2016]. Subsequently other worm-derived miRNAs have been identified in body fluids and can be used as biomarkers in helminth infections or potentially in IBD treated with exogenous parasites-derived miRNAs. Helminth infections exhibit modulatory effects on host immune responses in humans, suppressing allergies and modifying susceptibility to microbial infections. The helminth-adjusted intestinal microbiome influences immunity during inflammatory diseases.

Inflamma-miRs have been involved in the regulation of immune and chronic inflammatory responses [Cătană et al., 2015b]. MicroRNAs are critical regulators of inflammation through the modulation pathway of NF-kB (nuclear transcription factor kappa B). Initially, researchers showed particularinterestin the inflammatory response and found an important role for several microRNAs, named "inflamma"-miRs, such as miR-31, miR-206, miR-424 and miR-146a, which are potential new biomarkers of IBD (table 1). Furthermore, the discovery of extracellular miRNAs led to the possibility that such small molecules may be used as patient monitoring tools [Fisher and Lin, 2015; Kalla et al., 2015]. The modified expression of miRNAs in inflamed colon tissues and circulating miRNAs, both stable and protected from blood RNA-ase, could serve as ideal biomarkers in IBD patients and lay the foundations for miRNAs-based therapy, diagnosis and monitoring [Kalla et al., 2015]. Furthermore, work has been extended to examine the importance of microRNAs in chronic inflammatory processes by using microarrays in mice, mouse mutants, blood stem cells and *in vitro* techniques, respectively. miR-155 and miR-146a, inflamma-miRs that are up-regulated in IBD are also positive regulators of T-cell responses [Kalla et al., 2015, Singh et al., 2014]. Studies have reported that in active UC tissues, miR-126 was significantly increased compared to the control group. Likewise, miR-132, which exhibits an anti-inflammatory effect, was up-regulated in the biopsies of IBD patients [Kalla et al., 2015]. Chronic inflammation is also characterised by an increase in the level of pro-inflammatory cytokines coded by genes activated by the critical NF-kB [Singh et al., 2014; Cătană et al., 2015a; Fisher and Lin, 2015].

Adenosine through adenosine A2a receptor (A2aAR) interferes with NF-kB signalling pathway. For example, overexpression of miR-16, down-regulation of A2aAR as well as the expression of pro-inflammatory cytokines such as IL-8 and IFN-γ have been identified in colonic epithelial cells in UC patients [Tian et al., 2016]. miR-21 and miR-29a were found to have elevated expression in human UC colonocytes while miR-106a, miR-16 and miR-21 were overexpressed in CD ileitis [Wu et al., 2011].

Table 1. Example of inflamma-miRNAs with altered expression involved in IBD

miRNA	Colon (Intestinal biopsy)/ Serum/Plasma	Target genes	Up/ Down regulated	References
miR-106a	**+/+/+**	ATG16L1; IL-10	up	[Sharma et al., 2009; Wu et al., 2011; Paraskevi et al., 2012]
miR142-3p***	+/-/-, saliva	ATG16L1	down	[Zhai et al., 2013; Schaefer et al., 2013]
miR142-5p***	+/+/+, saliva	ATG16L1	up	[Schaefer et al., 2013]
miR-93		ATG16L1	up	[Lu et al., 2014]
miR130a		ATG16L1		[Wang et al., 2018]
miR-4284	+/-/-	CXCL5	down	[Koukos et al., 2013]
miR-16	+/+/+	A2aAR	up	[Wu et al., 2011; Paraskevi et al., 2012; Majd et al., 2018]
miR-21***	+/+/+, saliva		up	[Wu et al., 2011; 30]
miR-30c***		ATG5		[Schaefer et al., 2013; Lu et al., 2014]
miR-31***	+/-/-, saliva	FIH1	up	[Schaefer et al., 2013; Olaru et al., 2011]
miR181a		ATG5		[Lu et al., 2014; Tekirdag et al., 2013]
miR-29a	+/+/+	IFNG (IFNγ); IL-12B (IL12p40)	up	[Wu et al., 2011; Paraskevi et al., 2012; Fasseu et al., 2010; Ma et al., 2011; Brain et al., 2013]
miR-126	+/+/+	IKBA (IκBα)	up	[Feng et al., 2012; Paraskevi et al., 2012]
miR-320a, 320b, and 320c	**+/-/-**	NOD2	down	[Pierdomenico et al., 2016]
miR-155*	**+/+/+**	SOCS1	up	[Pathak et al., 2015; Beres at el., 2016; Wang et al., 2010]
miR-124	**+/-/-**	STAT3	down	[Koukos et al., 2013]
miR-101**	+/+/+, saliva	-	up	[Schaefer et al., 2013]
miR-375*	**+/+/+**	-	up	[Schaefer et al., 2013]

* implicated in cancerogenesis
** altered in saliva in UC patients
*** altered in saliva in CD patients

Abbreviations: ATG16L 1 – autophagy-related 16-like 1; **CXCL5** – chemokine; **FIH1** – factor inhibiting hypoxia inducible factor 1; **IFNG (IFNγ)** – *Interferon gamma;* **IKBA** – regulatory protein that inhibits NF-kappa-B; **IL12B (IL12p40)** – interleukin 12B; **NOD2** – nucleotide binding oligomerization domain containing 2; **SOCS1** – suppressor of cytokine signaling 1**; STAT3** – signal transducer and activator of transcription 3; **A2aAR** – adenosine A2a receptor.

Inflammatory processes and endogenous inflamma-miRs are plastic as they may be shaped by adequate external interventions, which could lead to the disease-free phenotype by targeting central elements of the immune system [Cătană and Berindan-Neagoe, 2012; Fisher and Lin, 2015]. An absolute advantage of TSO (*T. suis* ova) therapy is the minimal risk of accidental colonization due to the particular life cycle of this helminth. No adverse effects, no high costs and no risk of immunosuppression were recorded after TSO administration in patients with chronic inflammation while the Th1/Th17 proinflammatory response shifted towards the more anti-inflammatory Th2 response [Rosche et al., 2013] (figure 2).

There is a link between Th1, Th2 and the responses to *T. suis* administration. Besides helminth-microbiota interactions, it is very important to make the difference between the phenotypes of the host's immune system, classified as Th1 or Th2 dominant, in the modulation of gut microflora by the experimental helminth infection [Kalla et al., 2015; Matijašić et al., 2016; Cătană et al., 2018].

Helminth products act in animal models as anti-inflammatory and immunosuppressive agents and inhibit the pro-inflammatory effects of microbial PAMPs (pathogen-associated molecular patterns).

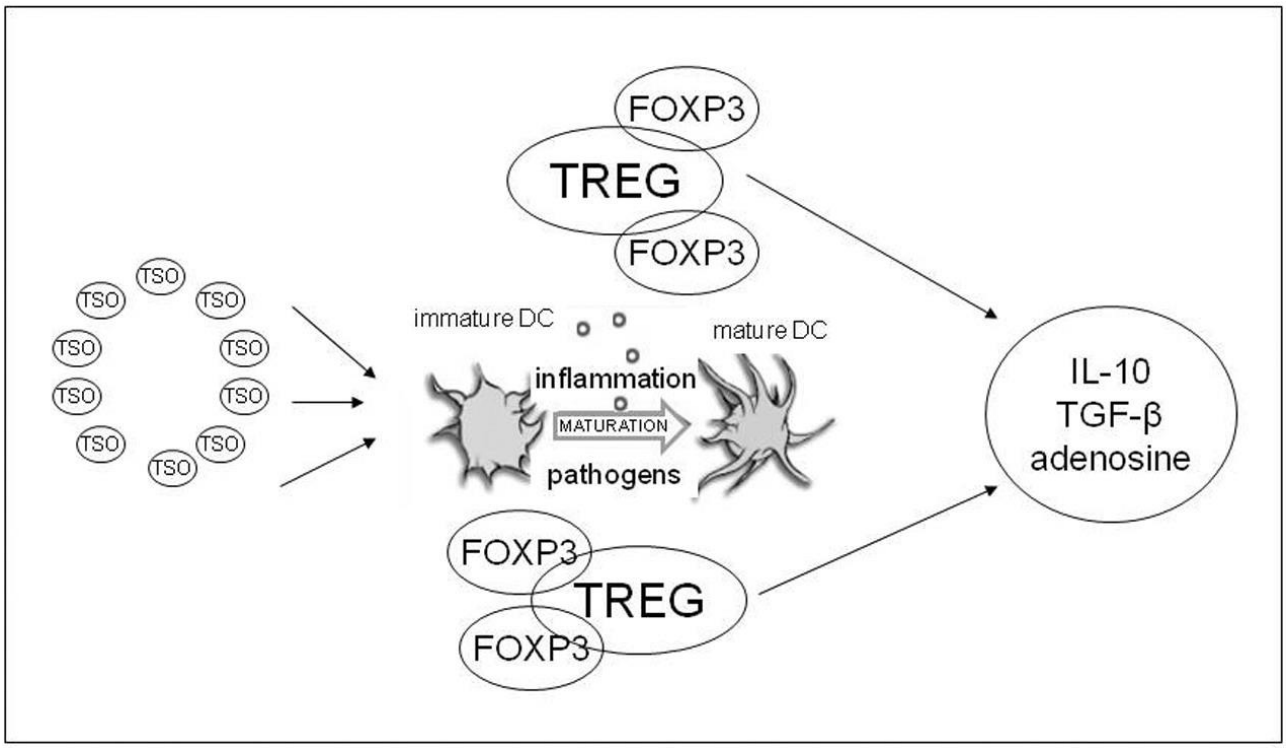

Figure 2. *T. suis* circuit that restraints inflammation in IBD.
Abbreviations: DC – dendritic cells; FOXP3 – forkhead box P3; IL – interleukin;
TGF – β- transforming growth factor; TSO – *Trichuris suis* ova; TREG – T regulatory cells.

Helminth infection leads to the maturation of DCs thus inducing the intestinal TREGs (CD4+Foxp3+) activation which blocks effector T cell reply. The most common and well-studied genetic variant of *ATG16L1* (rs2241880; leading to a T300A conversion) exhibits a strong association with risk for developing Crohn disease.

In conclusion, *T. suis* could modify the immunological status in experimental models of IBD, by inducing phenotypical changes associated with the inhibition and over-expression of serum and colonic miRNAs, which could further be a source of valuable biomarkers for affordable immunotherapy.

Conflict of Interest disclosure:

The authors declare that there are not conflicts of interest.

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