

Important note: the Abstract/Summary in the online submission section is very poorly written. It needs to be replaced by the summary in the revised manuscript.

For the remaining manuscript:

There is much duplication of information in the first two sections of the manuscript, namely section 1, Introduction and section 2. Pathophysiology of RA. To make the text more focused, current section 1 can be deleted entirely and section 2 can be labeled as Introduction, followed by the section on miRNAs.

In addition, most of the text in the entire manuscript is still poorly worded. A large proportion of sentences are either incomplete or fragmented, with disordered phrases. That is another reason that authors should keep most of the miRNA information, but try to shorten or delete unwanted general information especially in sections 1, 2, and 5.

Some suggestions for revision are given below in red font. But these cover only a fraction of the text, so a thorough revision of the entire manuscript by a write proficient in English language is necessary.

Line 18- is a kind of (replace kind with type)

Line 19-20 - The disturbance of miRNA (replace disturbance with dysregulation)

Line 22-23- expanding the way of RA diagnosis and treatment (this sentence may be deleted as it does not add new information)

Line 32- RA treatment (change treatment to management)

Line 48, 49- **Revise that sentence as follows:** Furthermore, the immune pathology in RA can also involve extra-articular organs, resulting in pulmonary and cardiac dysfunction.

Line 54- Several potential factors have been implicated, such as cell-free DNA (cfDNA) [2] and macrophage polarization [3]. **Delete this sentence- the two references cited here have no relevance to disease pathogenesis in RA.**

Line 66- achieve a radical solution

Revise this part of sentence to: achieve an effective control of the disease process.

Line 67- producers; **change it to procedures**

Line 85- DICER - **Expand DICER and any other abbreviations on their first use.**

Line 106- Anebues- correct it to “avenues”

Line 155- neonatal disorganized blood vessels lack an intact structural and tissue basis. Delete this sentence as the neonatal period has no relevance here.

Line 189-190- Considering the belief that this division may fragment the expression of miRNAs in RA, however, a miRNA may be expressed simultaneously in multiple cells or processes of RA progression.

Replace this sentence with: This may seem repetitious, but we took into consideration the fact that a single miRNA may be expressed in multiple cells and/or affect multiple processes involved in RA progression.

Line 198- revised title to: 3.1. miRNAs in cells of the immune system in RA

Lines 222-224- revise that sentence as follows:

and promotion of oncogenic pathways (delete highlighted part) immune-associated pathways involved in autoimmune diseases such as RA [40]

Lines 253-255- revise that sentence there to read as “Naïve T cells, activated under a specific cytokine environment can express Foxp3 or RORyt transcription factor and differentiate into Treg or Th17 cells, respectively [49].”

Line 270-miRANs (correct it to miRNAs here and at few other places in the manuscript)

Line 306-307- revise that sentence as follows:

By targeting GATA3 and PTEN, miR-10b alters the balance between pathogenic and regulatory T cells, e.g., Th17 versus Treg cells, and Th1 versus Th2 cells.

Line 373- M1-type macrophages express highly expressed in RA and , initiate---

Revise this sentence as: M1-type macrophages are abundant in RA joints and their activation initiates ---

Line 376- change Whereas to Whereas

Line 390-391- The overexpression of miR-494 can inhibit the expression of inflammation factors and NF-κB induced by macrophages

Revise this sentence to: The overexpression of miR-494 in macrophages can inhibit NF-κB and the expression of inflammatory mediators

Line 417- They express autoantibodies such as RFs and ACPA

Revise it to: Following activation, these cells produce autoantibodies such as RFs and ACPA

Line 440- revise it to: However, this hypothesis remains specific verification

revise it to: However, this hypothesis needs verification

Line 443: revise title to 3.2. miRNAs in inflammation underlying RA

Line 447- inflammatory executive cells involved in RA:

Replace it with: effector cells involved in RA

Line 451- secrete numerous inflammatory factors and inflammasomes (delete highlighted part because inflammasomes are not secreted)

Line 483- BMSCs (expand this and other abbreviations on first use)

Line 524- revise title to: 3.3. miRNAs in angiogenesis underlying RA pathology

Line 559- revise title to: 3.4. miRNAs in fibroblast-like synoviocytes in RA.

This section should be moved with cells, right after immune cells (after line 442), which is just before discussion of inflammation (line 443).

Figure shown in this section is not needed. It does not add any useful information over what is already shown in Figure 1

Line 663- revise title to: 4. Role of miRNAs in RA diagnosis and therapy

Also, section 4.3 on biomarkers can be moved up before the section on miRNAs as drugs.

Line 668- or as miRNA analogs or antagonists. (delete this part of the sentence there, it has no connection there).

Line 718- 4.2. Exosome-derived miRAN (change to miRNA)

Line 789- 5. Conclusion and perspective

This section at present is lengthy and almost another summary of the whole article. It is not meant for that purpose. It can be shortened to 2 short paragraphs, maximum 3 paragraphs.

Only main conclusions to highlight some main aspects of miRNAs in RA should be mentioned here in one paragraph. Then perspective could be another paragraph.