MicroRNAs and their signaling pathway in mycosis fungoides

Zhiyuan Sun, MD, Xiaona Yao, MD, Xing Ding, MD, Xun Li, PhD, Xuewen Tian, PhD

Abstract

Background: Oncogenic microRNAs, a kind of stable epigenetic inhibitors, often deregulated in Mycosis fungoides (MF) which affect the skin and tend to transform and spread.

Results: Previous studies investigating the de-expression of microRNA in MF patients skin biopsies identified that they were not only regulated by signaling pathway, but also regulated other signaling pathway. Furthermore, studies have elucidated the molecular mechanisms of the STAT signaling pathway that can promote a great diversity of miRNA expression via cytokine binding receptors, activating Janus kinase-3 and STAT proteins. But some non-STAT signaling pathway with microRNA de-expression in MF was incomplete.

Conclusion: Taken together, these studies demonstrate that microRNA may be used as the prognosis, progression and diagnose of MF, as they can not only control MF cell proliferation, but also induce MF cell apoptosis.

Abbreviations: CTCL = cutaneous T-cell lymphoma, JAK3 = Janus kinase-3, MF = mycosis fungoides.

Keywords: de-expression, microRNA, mycosis fungoides, signaling pathway, STAT

1. Introduction

Advanced mycosis fungoides (MF) or Sézary syndrome, major variants of cutaneous T-cell lymphoma (CTCL), are associated with 40% to 47% 5-year survival.[1] The annual incidence of primary cutaneous lymphomas is estimated to be 1:100,000, of which CTCL accounts for approximately 75% of cases; therefore, CTCL is a common type of primary cutaneous lymphomas.[2,3] Through the clonal proliferation of skin-invasive mature T-lymphocytes, CTCLs are characterized as non-Hodgkin’s lymphomas.[3] Mycosis fungoides (MF) is a common and indolent form of CTCL and is characterized by patches, plaques, or tumors containing epidermotrophic malignant CD4+CD45 RO+ helper/memory T-cells.[4] In the primary stage, MF appears as a flat erythematous skin lesion and resembles non-malignant psoriasis or eczema and can last for several years.[4] In later stages, tumor cells spread to other parts of the body as a fatal outcome. MF can develop into a leukemic variant, Sézary syndrome, in which cancer T-cells appear in the skin and blood, or shift to large cell lymphoma.[5] Skin cytokines orchestrate inflammation through their impact on the expression and function of other cytokines, and their downstream effectors (such as STAT and SOCS proteins, microRNA) are frequently observed.[6,7] MicroRNAs (miRNAs) are important molecular markers of MF progression and diagnose.[8]

miRNAs are a class of small non-coding RNAs with length of 18 to 22nt that are ubiquitous in eukaryotes and can regulate protein expression at the mRNA level.[9–11] Many studies have reported that MF alters miRNA expression, including reduced miR-191, miR-223, and miR-342, and increased miR-155.[12] These microRNA expression changes influence or influence signaling pathways such as STAT3, STAT5, or p53/Akt et al.[13,14]

2. MicroRNA expression and MF

It is important to understand how microRNA expression changes influence MF cell proliferation in order to develop them as a new target gene for the prevention and treatment of cancer. From Table 1, the expression of about 12 miRNAs whose function and characteristics were further analyzed by reliable experiments up-or down-regulated in MF skin biopsies...
or cells. Six miRNA expression upregulates and belongs to an oncogenic molecule. Another 6 miRNAs are downregulated and belong to the suppressor gene. Eight miRNAs can be used to evaluate MF progression; miRNA-122 and miRNA-214 are molecular markers of MF prognosis.[14,15] Moreover, miR-155, miR-203, and miR-205 in patient peripheral blood can be used as diagnostic markers,[16,17] that discriminated between malignant and benign skin inflammation with an accuracy of more than 90%.[18]

3. MicroRNA and STAT signaling pathway

The expression and function of STAT3, STAT4, and STAT5 have been extensively studied in MF, and these genes appear to play an important role in disease pathogenesis and can be used as important prognostic markers. The effectors (STAT3 and STAT5 et al) and the up-stream Interleukin-2 receptor common gamma chain, the associated Janus kinase-3 (Jak3) have attracted substantial interest. Interleukin-2 receptor common gamma chain-signaling cytokines, including IL-2, IL-4, IL-7, IL-15, and IL-21 are implicated in early pathogenesis and constitutive.[13,19] As shown in Figure 1, the deregulation of signaling pathways, including STAT, Src kinases, c-Myc, COX-2, NFκB, GATA3, TOX, and embryonic stem cell regulators, appears to play an important role in pathogenesis.[13,29] Deregulation of the p53 signaling pathway was also found in malignant T cells from patients with MF than from healthy donors. Further studies have proposed that the TWIST1 and BRD4 complex regulate miR-214 expression.[31]

4. MicroRNA and other signaling pathway

The deregulation of signaling pathways, including STAT, Src kinases, c-Myc, COX-2, NFκB, GATA3, TOX, and embryonic stem cell regulators, appears to play an important role in pathogenesis.[13,29] As shown in Figure 2, Fc receptor-like protein 3, along with T plastin, GATA-3, TOX, and miR-214, are promising therapeutic targets for many years in Sézary syndrome and can increase miR-21 expression by IL-21 activating IL-21R and STAT3, and then inhibit miR-21 in Sézary syndrome cell apoptosis.[24]

| miRNA type | Year | Biomarker use | Sample | Target/Pathway | Expression | Function | Ref. |
|------------|------|---------------|--------|---------------|-----------|---------|-----|
| miR-93     | 2021 | Progression   | Malignant T cells lines | p21 | down | Oncogenic molecule | [40] |
| miR-195-5p | 2020 | Progression   | Skin biopsies and cell lines | ARL2 | down | Oncogenic molecule | [41] |
| miR-106b   | 2020 | Progression   | Skin biopsies | P21/TXNIP | up | Oncogenic function | [42] |
| miR-337    | 2019 | /              | Malignant and non-malignant T cells | JAK/STAT | up | / | [36] |
| miR-214    | 2019 | Diagnose      | CD4⁺ T cells | TWIST1/BRD4/miR-214 | up | Oncogenic molecule | [31] |
| miR-155    | 2018 | Diagnose      | Malignant T-cell lines (MyLa2059, MyLa3675 and MyLa2000) and HH cells | SATB1/GATA3 | up | Oncogenic molecule | [25] |
| miR-155    | 2018 | Diagnose      | HUT102, HUT78 and HH cell lines | JAK/STAT, MAPK/ERK and PI3K/AKT | up | Oncogenic molecule | [16] |
| miR-155    | 2017 | Diagnose      | Peripheral blood | / | up | Oncogenic molecule | [16] |
| miR-155    | 2017 | Diagnose      | Peripheral blood | / | up | Downregulator gene | [43] |
| miR-155    | 2017 | Diagnose      | Skin biopsy, HH, HUT78, and MJ cell lines | CCR6 | down | Suppressor gene | [43] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | FORl-3, Tox | up | / | [15] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | STAT5/JAK3 | up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | p53 | up | Oncogenic molecule | [32] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | p53 | Down | Suppressor gene | [32] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | / | Up | Oncogenic function | [44] |
| miR-155    | 2017 | Diagnose      | Skin biopsies | / | up | Oncogenic molecule | [16] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | TOX | down | Suppressor gene | [30] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT4 | Up | Oncogenic molecule | [21] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
| miR-155    | 2017 | Diagnose      | Skin biopsies, HH and HUT-78 cell lines | STAT5 | Up | Oncogenic molecule | [27] |
inhibits tumor cell apoptosis by Akt/p53 signaling pathway,[14]
similarly miR-34a expression level was also increased by p53
signaling pathway in Se'zary syndrome patients skin biosies.[32]
However, miR-29a expression was lower in MF patients than in
healthy patients because of p53 signaling pathway inhibition.[32]

Earlier studies did not detect changes in p16 expression in all
MF cells until 2016.[33,34] Kitadate et al speculated that miR-16
directly or indirectly suppresses Bmi1, thereby enhancing p21
expression in MF cells based on their experiments results.[35] It
has been confirmed that microRNAs can directly regulate
receptor proteins. The miR-150 in MF cells was upregulated and
combined with the C-C chemokine receptor 6 “seed sequence”
mRNA of the 3-untranslated region (3-UTR) in advanced MF.
STAT3 expression can be significantly downregulated follow-
ing transfection with the miR-337 mimic, which potentially
targets the 3-UTR of STAT3.[36] MF progression can be estimated by
analyzing the upregulated expression of miR-155, miR-146a, 146b-5p, miR-342–3p, and let-7i* and down-
regulated expression of miR-203 and miR-205.[37] Subsequent
studies confirmed that miRNAs are potentially valuable tools for
the evaluation of disease progression in MF.[38,39]

5. Conclusions and perspectives
Collectively, the findings discussed in the present review provide
novel insights into the effect of microRNAs on MF cells, which
supports new concepts for the prognosis, progression, and
diagnosis of MF. As shown in Table 1, some miRNAs were
upregulated in the skin biosies of MF patients; however, some
miRNAs were downregulated. These miRNAs can be used as
biomarkers for disease diagnosis and as therapeutic targets.

MF cell proliferation and apoptosis involve the functional
cooperation of many signaling molecules. As summarized in
Figure 1, STAT signaling pathways, including STAT3, STAT4,
and STAT5, can promote a great diversity of miRNA expression
via cytokine binding receptors, activating Jak3 and STAT proteins.
Transcribed microRNAs regulate MF cell proliferation and
apoptosis via other signaling pathways or target molecules.

MicroRNA transcription can also be regulated by another
signaling pathway, as shown in Figure 2. However, these
signaling pathways can regulate microRNA expression and can
be regulated by microRNAs. It is not clear at the moment that
some important molecules are involved in this pathway. STAT3,
p53, TOX, and Bmi1 participate in these pathways and play an
important role.

These results indicate that cocktail therapy with microRNA
and other drugs may greatly reduce the risk of MF cell metastasis
in all types. The significance of miRNA as a molecular marker
may be used for prognosis, progression, and diagnosis of MF in
the future. Further studies are required to determine which of the
signaling pathways or miRNAs is most important for the
treatment or diagnosis of MF. In addition, many previous studies
have not established an integrated non-STAT signaling pathway.
Future studies investigating whole signal regulation in MF may
provide further insight into the mechanisms underlying its
activity.
Author contributions
Conceptualization: Xiaona Yao, zhiyuan Sun.
Data curation: Xiaona Yao, zhiyuan Sun.
Formal analysis: Xiaona Yao, zhiyuan Sun.
Funding acquisition: Xiaona Yao, Xuewen Tian, Xun Li.
Resources: Xing Ding.
Writing – review & editing: Xiaona Yao, zhiyuan Sun.

References
[1] Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol 2010;28:4730–9.
[2] Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood 2019;133:1703–14.
[3] Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154–8.
[4] Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798–812.
[5] Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479–84.
[6] Persson JL. miRNA in mycosis fungoides and skin inflammation. Apmis 2013;121:1017–9.
[7] Krejsgaard T, Lindahl LM, Mongan NP, et al. Malignant inflammation in cutaneous T-cell lymphoma—a hostile takeover. Semin Immunopathol 2017;39:269–82.
[8] van Kester MS, Ballabio E, Benner MF, et al. miRNA expression profiling of mycosis fungoides. Mol Oncol 2011;5:273–80.
[9] Jiang XI, Luo Y, Zhao S, et al. Clinical significance and expression of microRNA in diabetic patients with erectile dysfunction. Exp Ther Med 2015;10:213–8.
[10] Jia W, Wu Y, Zhang Q, et al. Expression profile of circulating microRNAs as a promising fingerprint for cervical cancer diagnosis and monitoring. Mol Clin Oncol 2015;3:851–8.
[11] Graziano A, Lo MG, Piva I, et al. Diagnostic findings in adenomyosis: a pictorial review on the major concerns. Eur Rev Med Pharmacol Sci 2015;19:1146–54.
[12] McGirt LY, Baerenwald DA, Vonderheid EC, Eischen CM. Early changes in miRNA expression are predictive of response to extracorporeal photopheresis in cutaneous T-cell lymphoma. J Eur Acad Dermatol Venereol 2015;29:2269–71.
[13] Sibbesen NA, Kopp KL, Latvinov IV, et al. Jak3, STAT3, and STAT5 inhibit expression of miR-22, a novel tumor suppressor microRNA, in cutaneous T-Cell lymphoma. Oncotarget 2015;6:20555–69.
[14] Manfe V, Biskup E, Rosbjerg A, et al. miR-122 regulates p53/Akt signalling and the chemotherapy-induced apoptosis in cutaneous T-cell lymphoma. Plos One 2012;7:1–11: e29541.
[15] Benoit BM, Jariwala N, O’Connor G, et al. CD164 identifies CD4(+) T cells highly expressing genes associated with malignancy in Sezary syndrome: the Sezary signature genes, FCRL3, Tox, and miR-214. Arch Dermatol Res 2017;309:11–9.
[16] Dusilkova N, Basova P, Polivka J, et al. Plasma miR-155, miR-203, and miR-205 are biomarkers for monitoring of primary cutaneous T-cell lymphomas. Int J Mol Sci 2017;18:2136.
[17] Ralliksaer U, Hagedorn PH, Banggaard N, et al. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). Blood 2011;118:5891–900.
