Intrinsic T-cell regulator miR-142-3p/5p-a novel therapeutic target?

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COMMENT

Intrinsic T-cell regulator miR-142-3p/5p – a novel therapeutic target?

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies against various self-antigens. Systemic inflammation affects the skin, joints, central nervous system and, in particular, kidneys through so-called lupus nephritis (LN).[1] The exact pathogenesis of systemic lupus erythematosus remains unclear. However, a growing body of evidence suggests that B-cells, a source of autoantibodies and effector T-cells, contribute to the pathogenesis of SLE by secreting cytokines. T-cell/B-cell interaction via their costimulation is crucial for an orchestrated immune response. This interaction is modulated by IL-21-producing T-follicular helper (T_{fh}) cells, which are located mainly in germinal centers. T_{fh} cells are required to help B-cells secrete high-affinity IgG antibodies.[2]

The delicate balance between regulatory and effector cells is important for immune tolerance. Specialized cell subsets, such as regulatory T-cells (T_{regs}), defined as $CD4^+CD25^{high}CD127^{dim}FoxP3^+$ T-cells, and the more recently discovered regulatory B-cells (B_{regs}), can regulate the T-cell and B-cell immune response and hyperactivity. B_{regs} are widely defined as $CD19^+CD24^{high}CD38^{high}IL\text{-}10^+$ B-cells, but a unique phenotype is lacking. In addition to immunoregulation by cell–cell interactions and the ligation of costimulatory molecules, microRNAs (miRNAs) with immunomodulatory properties were described in a remarkable finding. miRNAs, which are single-stranded RNAs of ~22 nucleotides, are potent negative regulators of gene activity. Previous studies have demonstrated that miRNAs can regulate various immune cells, particularly T-cells. Thus, the role of miRNAs as potential biomarkers in several autoimmune diseases, including rheumatoid arthritis, psoriasis, and multiple sclerosis, was tested. Interestingly, few studies had investigated the role of miR-142-3p/5p in systemic lupus erythematosus before the present elegant study by Ding et al.[3] was published.

The authors demonstrated in a previous study that miR-142-3p/5p could reduce CD84, IL10, and SAP protein levels in the T-cells of SLE patients via its interaction with the 3′-UTR of the target mRNA.[4] In contrast, overexpression of miR-142-3p/5p reduced IgG production and significantly decreased the levels of CD40L, ICOS, IL-4, IL-10, and IL-21, which are crucial for T-cell activation. In the context of these data, miR-142-3p/5p expression was analyzed in $CD4^+$ T-cells from SLE patients, which were exposed ex vivo to mycophenolic acid (MPA).[5] Interestingly, this frequently used immunomodulating drug in clinical practice upregulated miR-142-3p/5p in $CD4^+$ T-cells.

MPA was suggested to increase H4 acetylation of a putative regulatory region of miR-142e. A more recent study in patients with granulomatosis with polyangiitis (GPA) demonstrated that miR-142-3p overexpression can also decrease T_{reg} function in patients with GPA. This impaired T_{reg} function might be explained by the ADCY9-dependent downregulation of cAMP, a pivotal axis that is prominent in the suppressive function of T_{regs}.[6] Thus, the upregulation and inhibition of the miR-142-3p pathway can affect the regulatory and effector cell compartments, respectively.

This study in the present issue is sound and unravels a new mechanism by which miR-142-3p/5p functions. Ding et al. used a sophisticated experimental approach to prove the hypothesis that the altered protein expression of B cell lymphoma 6 (BCL-6), which potentially binds to the miR-142-3p/5p promotor region, suppresses miR-142-3p/5p expression in the $CD4^+$ T-cells of SLE patients (Fig. 1). It was demonstrated before that the two known isoforms of MIR142 exhibit different expression patterns. Whereas miR142p3 is preferentially expressed by effector T-cells, T_{regs} express high levels of miR142p5.[7–9] This pattern is closely related to the differential impact of the miR142 isoforms on cellular cAMP levels. miR142p5 mainly inhibits the hydrolysis of cAMP via suppression of the enzyme phosphodiesterase-3b (PDE3b) and thereby upregulates cellular cAMP levels.[8] In contrast, miR142p3 attenuates cAMP generation by repressing adenyl cyclase 9 (AC9), an enzyme that enhances cAMP generation.[9] Thus, miR142p3 decreases the levels of intracellular cAMP in effector T-cells, promoting effector activity.

T_{regs} make use of a suppressive mechanism known as metabolic disruption. During metabolic disruption, cAMP is transferred from Tregs to target cells, inducing suppression and anergy. Therefore, miR142p5 is critical for T_{reg} function as high cellular cAMP levels are required for proper suppressive activity. A specialized T_{reg} subset, the so-called regulatory follicular T-helper (rTfh) cells, was previously shown to regulate Tfh cell and B-cell activity.[10] A hallmark of this subset of cells is their coexpression of BCL-6 and FoxP3. Ding et al. did not further differentiate between rTfh and Tfh cells. However, it would be interesting to know whether the impact of BCL-6 on miR142 depends on the cell subset i.e., whether the BCL-6-mediated regulation of miR142 is different in regulatory versus effector Tfh cells. Indeed, Dekkema et al. recently reported that in patients with autoimmune vasculitis, T_{regs} harbor higher levels of miR142p3, while miR142p3 levels in effector T-cells were similar

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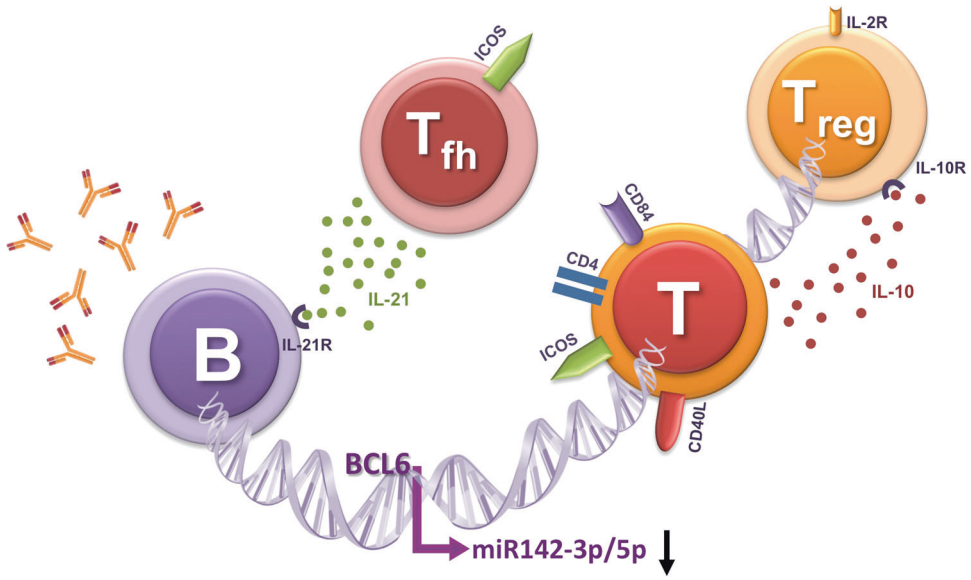

Fig. 1 This figure illustrates the interaction between B-cells and T-cells. Follicular T-helper (T_{fh}) cells and regulatory T-cells (T_{regs}) can promote and inhibit immune response, respectively. The B cell lymphoma 6 (BCL-6) protein potentially binds to the miR-142-3p/5p promoter region and suppresses miR-142-3p/5p expression, which in turn enhances the expression of costimulatory molecules (CD40L, ICOS, and CD84) and cytokines (IL-4, IL-10, and IL-21) by T-cells, increases IgG production by B cells, and modulates the suppressive function of T_{regs}

in patients compared to healthy controls.[6] The authors demonstrated that the transfection of healthy Tregs with miR142p3 inhibited their suppressive function. In addition to the lineage-specific regulatory effect of BCL-6 on miR142, it will be important to further elucidate whether specific isoforms of miR142 are dysregulated in SLE in future studies. These data would provide important insights into whether disturbances are dependent on T-cell lineage.

REFERENCES

1. Dolff, S., Witzke, O. & Wilde, B. Th17 cells in renal inflammation and autoimmunity. *Autoimmun. Rev.* **18**, 129–136 (2019).
2. Dolff, S. et al. Increase in IL-21 producing T-cells in patients with systemic lupus erythematosus. *Arthritis Res. Ther.* **13**, R157 (2011).
3. Ding S., et al. BCL-6 suppresses miR-142-3p/5p expression in SLE CD4(+) T cells by modulating histone methylation and acetylation of the miR-142 promoter. *Cell. Mol. Immunol.* https://doi.org/10.1038/s41423-019-0268-3 (2019).
4. Ding, S. et al. Decreased microRNA-142-3p/5p expression causes CD4+ T cell activation and B cell hyperstimulation in systemic lupus erythematosus. *Arthritis Rheum.* **64**, 2953–2963 (2012).
5. Tang, Q. et al. Mycophenolic acid upregulates miR-142-3P/5P and miR-146a in lupus CD4+T cells. *Lupus* **24**, 935–942 (2015).
6. Dekkema, G. J. et al. Increased miR-142-3p expression might explain reduced regulatory T cell function in granulomatosis with polyangiitis. *Front. Immunol.* **10**, 2170 (2019).
7. Kuchen, S. et al. Regulation of microRNA expression and abundance during lymphopoiesis. *Immunity* **32**, 828–839 (2010).
8. Anandagoda, N. et al. microRNA-142-mediated repression of phosphodiesterase 3B critically regulates peripheral immune tolerance. *J. Clin. Invest.* **129**, 1257–1271 (2019).
9. Huang, B. et al. miR-142-3p restricts cAMP production in CD4+CD25- T cells and CD4+CD25+ TREG cells by targeting AC9 mRNA. *EMBO Rep.* **10**, 180–185 (2009).
10. Clement, R. L. et al. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. *Nat. Immunol.* **20**, 1360–1371 (2019).-