5. Genetics and gene regulation

A68 MICRO RNA ANALYSIS REVEALS NOVEL GENES IN HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS: MIR-21 AFFECTS PDCD4 EXPRESSION AND REGULATES ABERRANT T CELL RESPONSES

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Objective MicroRNAs (miRNAs) are potent negative regulators of gene expression involved in innate and adaptive immune responses. The authors examined whether miRNAs are implicated in immune deregulation and lymphocyte hyperactivity in human systemic lupus erythematosus (SLE).

Methods TaqMan miRNA arrays were used to study the expression of 365 miRNAs. Expression of miRNAs and their gene targets were assayed by real-time PCR and western blot, respectively. miRNAs silencing by transfection with antago-miRs was performed to assess the effect of miRNAs on anti-CD3/anti-CD28-induced T cell proliferation and cytokine production.

Results A total of 27 miRNAs were differentially expressed in peripheral blood mononuclear cells of patients with SLE and healthy individuals. miR-21, miR-25, miR-106b and miR-148b were highly correlated with SLE disease activity ($r^2 > 0.85$), with miR-21 displaying the strongest correlation. SLE T lymphocytes had increased basal and activation-induced miR-21 expression, correlating with decreased expression of its gene target PDCD4 and enhanced proliferation upon anti-CD3/CD28 activation. This effect was reversed by silencing miR-21 which resulted in increased PDCD4 expression. Importantly, restoration of PDCD4 levels by silencing miR-21 suppressed the production of interleukin 10 and the expression of membrane CD40 ligand by activated SLE T lymphocytes.

Conclusion miR-21 is a key regulator of the apoptosis-related protein PDCD4 and may be involved in multiple immune processes such as proliferation, costimulation and cytokine production. Deregulated miR-21 expression associated with decreased PDCD4 levels may contribute to aberrant T cell responses in human SLE.