CONNECTIVE TISSUE DISEASES

A mechanism of B cell hyperactivity in SLE

Researchers have identified a mechanism for B cell hyperactivity in patients with systemic lupus erythematosus (SLE). Published in *Science Translational Medicine*, the data show that microRNAs (miRNAs) miR-7, miR-21 and miR-22 enhance B-cell receptor signalling by suppressing the expression of *PTEN*, a process that could contribute to the characteristic production of autoantibodies in SLE.

Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase *PTEN* is a known tumour suppressor, but deficiency of the protein has also been shown to cause an SLE-like disease in mice.

“We relied on the mouse models to point us in the right direction,” comments Peter Lipsky, corresponding author of the study. By fluorescence-activated cell sorting, his team showed that B-cell expression (except memory B cells) of *PTEN* was lower in patients with SLE than in healthy donors.

Importantly, the researchers also identified an inverse correlation between the level of *PTEN* expression and SLE disease activity.

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SLE B cells stimulated *ex vivo* with IL-21, a known inducer of *PTEN*, had defective responses. There was also a defect in anti-IgM and CD40L-induced Akt phosphorylation in these cells. However, IL-21-induced *STAT3* and *PTEN* mRNA expression were not defective, indicating that the defect in the SLE B cells was not in signalling or transcription, rather, Lipsky says it “pointed toward an abnormality in miRNA regulation.”

Known regulators of *PTEN*, miR-21 and miR-22, were therefore considered as candidates for a role in SLE B-cell

activation. By TargetScan, the researchers also predicted miR-7 to be involved. All three miRNAs were found at a higher concentration in SLE B cells than in normal B cells and these miRNAs were shown to suppress *PTEN* expression. Finally, with an antagomir of miR-7, the team showed that miR-7 negatively regulates *PTEN* expression in human B cells and thereby identify a new candidate for therapeutic regulation.

Lipsky says of translating this ongoing research, “We are pursuing this in both mouse and human lupus to fine tune our understanding of the regulation of B cell activation and attempt to determine whether these findings provide the basis for a novel clinical intervention in lupus.”

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Original article Wu, X.-N. *et al.* Defective *PTEN* regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus. *Sci. Transl. Med.* doi:10.1126/scitranslmed.3009131