SYSTEMIC LUPUS ERYTHEMATOSUS

Defective T_{FH} cell checkpoint in SLE

> down-regulation of *P2RX7* might be linked to the increased number of T_{FH} cells in patients with SLE

T follicular helper (T_{FH}) cells are an integral part of barrier immunity and immune responses to infection, but can also aid autoantibody production in autoimmune diseases such as systemic lupus erythematosus (SLE). The results of a new study suggest that the dysregulation of T_{FH} cells that occurs in SLE could be the result of a defective T_{FH} cell checkpoint.

In the gut, T_{FH} cells respond to extracellular ATP released by microbes via P2X purinoceptor 7 (P2X7) signalling, which triggers cell death pathways in the presence of high concentrations of extracellular ATP. In the absence of P2X7, T_{FH} cells do not undergo cell death and provide deregulated help to B cells, resulting in increased production of antibodies. However, it is unclear if T_{FH} cells in germinal centres react to extracellular ATP in patients with SLE, and whether P2X7 signalling affects autoantibody production.

"We tested whether *P2rx7*$^{-/-}$ mice showed some defect in P2X7-mediated control of T_{FH} cells in the ATP-rich inflammatory environment that is generated in pristane-induced lupus (PIL)," explains co-corresponding author Fabio Grassi. "This experimental model allowed us to address

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T_{FH} cell-dependent pathogenetic aspects in mice on the C57BL/6 background, including *P2rx7*$^{-/-}$, *Icos*$^{-/-}$*P2rx7*$^{-/-}$ and *Cd4-Cre P2rx7*$^{fl/fl}$ mice, which would have been extremely difficult to address in murine models of spontaneous lupus."

P2rx7$^{-/-}$ mice with PIL had more severe disease, an increased number of T_{FH} cells in germinal centres and greater autoantibody production than wild-type mice with PIL, suggesting a role for P2X7 in regulating T_{FH} cell functions during disease. *Icos*$^{-/-}$*P2rx7*$^{-/-}$ mice, which lack T_{FH} cells and are unable to form germinal centres, produced fewer autoantibodies than *P2rx7*$^{-/-}$ mice upon disease induction. Further experiments in germinal centre-competent mice that lack P2X7 in T cells confirmed autoantibody production in *P2rx7*$^{-/-}$ mice with PIL to be T_{FH} cell-dependent.

The number of circulating T_{FH} cells able to respond to stimulation with a P2X7 agonist ex vivo was reduced in patients with SLE compared with healthy individuals and inversely correlated with the frequency of circulating T_{FH} cells. The amount of *P2RX7* mRNA in circulating T_{FH} cells from patients with SLE was also reduced compared with healthy individuals, suggesting that downregulation of *P2RX7* might be linked to the increased number of T_{FH} cells in patients with SLE.

Interestingly, T_{FH} cells from patients with primary antiphospholipid syndrome (APS) did not share the dysfunctional phenotype of T_{FH} cells from patients with SLE. "Patients with primary APS and SLE share SLE-susceptibility genes, yet patients with primary APS do not develop complete SLE," states co-corresponding author Pier Luigi Meroni. "Our study unravels a pathogenic pathway that operates in patients with SLE, but not in patients with primary APS."

"This study provides new mechanistic insights for P2X7-mediated regulation of T_{FH} cell homeostasis and function," comments Di Yu from the John Curtin School of Medical Research in Canberra, Australia, who was not involved in this project. "In my opinion, it strongly suggests that the defect in P2X7-mediated inhibition of T_{FH} cell generation can promote lupus, as shown in both a pristane-induced mouse model and using human samples. However, the reduced expression of P2X7 is likely to be one of many reasons for the hyperactive phenotype of T_{FH} cells in SLE."

Importantly, P2X7 signalling seems to affect the expansion of T_{FH} cells in autoimmunity, but not during immunization responses. No difference was seen in the number of antigen-specific $CD4^+$ T cells after immunization with ovalbumin in mice adoptively transferred with ovalbumin-peptide-specific T_{FH} cells from either congenic *P2rx7*-deficient or wild-type mice.

"The identification of P2X7 as a selective checkpoint inhibitor of T_{FH} cells suggests that restoring P2X7 activity in SLE could limit the progressive amplification of pathogenic autoantibodies but have no suppressive effects on adaptive immune responses against pathogens," says Meroni. "Rather, improving P2X7 activity should beneficially influence the reduced responsiveness of patients with SLE to vaccines."

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