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IMMUNOLOGY

Balancing immunoreceptor signalling

The Src-family kinases LYN and FYN differentially regulate immunoreceptor signalling by directing the phosphorylation of SH2 domain-containing protein tyrosine phosphatase 1 (SHP1, also known as PTPN6) at distinct sites, according to new research published in *Nature Communications*. The findings of this study shed light on the opposing, non-redundant roles of these two kinases in regulating homeostasis and inflammation.

The fine-tuning of signalling pathways downstream of immunoreceptor tyrosine-based activation motif (ITAM)-bearing receptors, such as T cell receptors, B cell receptors and Fc receptors, is important in maintaining homeostasis within the immune system. The binding of high-avidity ligands to these receptors induces activating signals, whereas the binding of low-avidity ligands can induce inhibitory signals by a mechanism known as inhibitory ITAM (ITAMi) signalling, in which SHP1 activity has been implicated.

> “FYN and LYN differentially control SHP1 activity by regulating its phosphorylation status”

To investigate the switch between ITAMi and ITAM signalling, Ben Mkaddem and colleagues focused on LYN and FYN. In both monocytic and lymphocytic cell lines cultured under ITAM and ITAMi-inducing conditions, *in vitro* knockdown of LYN expression inhibited ITAMi signalling but had no effect on ITAM signalling. Conversely, silencing FYN expression had no effect on ITAMi signalling, but converted ITAM signalling into ITAMi signalling.

The inhibitory signalling generated by silencing FYN was abolished when both FYN and SHP1 were knocked down, indicating a link between FYN and SHP1. In bone marrow-derived macrophages, the researchers found that FYN directed the phosphorylation of SHP1 at S591, whereas LYN directed the phosphorylation of SHP1 at Y536. Phosphorylation of SHP1 at S591 and Y536 is associated with the inhibition and activation of SHP1, respectively, suggesting that FYN and LYN differentially control SHP1 activity by regulating its phosphorylation status.

To explore the functional role of this regulation *in vivo*, Ben Mkaddem and colleagues used two mouse models: a model of nephrotoxic serum nephritis and the collagen antibody-induced arthritis (CAIA) model. LYN deficiency exacerbated nephritis and arthritis, and was associated with phosphorylation of SHP1 at S591, whereas FYN deficiency was protective and associated with SHP1 phosphorylation at Y536. In the CAIA model, treating transgenic mice, expressing either human Fcγ receptor IIA (hFcγRIIA) or human Fcα receptor I (hFcαRI), with antibodies that induce ITAMi signalling prevented disease development; this protection required LYN expression.

Translating these findings into humans, the researchers found that LYN, but not FYN, was recruited to FcγRIIA in the leukocytes of healthy individuals, which was associated with phosphorylation of SHP1 at Y536. However, the leukocytes of patients with lupus nephritis only weakly recruited LYN, but strongly recruited FYN to FcγRIIA, a situation that was associated with phosphorylation of SHP1 at S591. These findings support the role of LYN and FYN in controlling the balance between homeostasis and inflammation; an imbalance that could lead to the development of autoimmune diseases.

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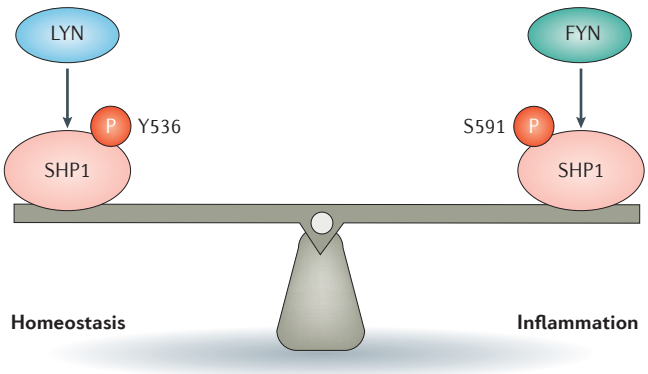

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