SLP76 works best in platelets when all three are phosphorylated, and mutations at all three tyrosines block platelet activation. Bezman et al. now find that the tyrosines selectively transmit signals from one or the other receptor.

This partiality became evident when the group created mutant mice defective either in Y145 or in both Y112 and Y128. Platelets from the Y145 mutants did not spread, aggregate, or degranulate—effects mediated by GPVI signals. These defects were associated with an inability to recruit and activate the known downstream molecules PLCγ2 and Vav1. These defects were milder in platelets from the dual mutant, which bound to both PLCγ2 and Vav1, but these cells were less sticky and did not form stable clots—effects attributed to αIIbβ3.

In T cells, mutations in any of the three SLP76 tyrosines cause defective T cell receptor signaling. But T cells that express two forms of SLP76—one mutated at Y112/128 and the other at Y145—remain functional, suggesting that the mutant SLP76s team up to recruit all the necessary molecules. Bezman et al. did not observe such complementation in platelets, however. T cells, which have many more immunoreceptors than platelets, might form larger signaling complexes in which different mutants are more likely to meet up and rescue each other.

**Twisted control**

Over-stimulated T helper (Th)-1 cells keep themselves in check by activating an internal brake, say Niesner et al. (page 1889).

Th1 cells activated by self-antigens can cause chronic inflammation, as seen in autoimmune diseases such as diabetes and rheumatoid arthritis. Niesner et al. were searching for genes that are highly expressed in such chronically activated Th1 cells in mice and discovered a transcriptional repressor called twist1. Now, the authors show that repeatedly activated Th1 cells avoid turning deadly by turning on twist1, which then inhibits NF-κB–dependent cytokine production.

Absent in naive mouse T cells, twist1 was switched on when these cells were stimulated with antigen in the presence of the Th1-polarizing cytokine IL-12 but not the Th2 cytokine IL-4. IL-12 activates the transcriptional activator STAT4, which then bound to and activated the twist1 promoter. Subsequent antigen stimulation increased twist1 expression in the Th1 cells, dampening their inflammatory cytokine production. The delayed induction of twist1 probably gives Th1 cells a chance to initiate inflammation before they are shut down.

An infusion of twist1-deficient Th1 cells worsened arthritis in mice, whereas a shot of Th1 cells overexpressing twist1 ameliorated disease. Before this finding can be clinically exploited, a twist in the human twist1 story needs to be sorted out: Th1 cells found in the diseased tissues of patients suffering from arthritis or chronic gut inflammation had plenty of twist1. Whether human twist1 also acts as a brake and, if so, how these disease-associated Th1 cells bypass it remains to be seen.

**Cranking out healthy platelets**

On page 1917, Nishikii et al. produce a plethora of platelets by picking perfect stem cell progenitors and preventing shearing of the platelets’ activating receptors.

Platelets for therapeutic use are currently filtered from donated blood, which increases the risk of infections and other side effects in patients who need frequent transfusions. Scientists have been trying to generate platelets from embryonic stem cell (ESC) lines instead, but their efforts have so far been stymied by two problems.

First, ESCs cultured with stromal cells produce a tiny platelet population that is quickly drowned out by other cell lineages. Nishikii et al. resolved this issue by using ESCs that had already differentiated into platelet-committed hematopoietic stem cells, which express the clot-promoting αIIbβ3 receptor.

The second and more worrying problem is that the ESC-derived platelets don’t aggregate properly. This defect was previously seen in vivo in long-lived platelets whose matrix-binding receptors had been sheared off by matrix metalloproteinases (MMPs). The group found that this also happened in vitro, and platelets cultured with MMP inhibitors formed clots in vitro and enhanced tissue repair in injured mice. This approach awaits testing in humans.