Spleen tyrosine kinase (SYK) is known to have a crucial role in adaptive immune receptor signalling. However, recent reports indicate that SYK also mediates other, unexpectedly diverse biological functions, including cellular adhesion, innate immune recognition, osteoclast maturation, platelet activation and vascular development. SYK is activated by C-type lectins and integrins, and activates new targets, including the CARD9-BCL-10-MALT1 pathway and the NLRP3 inflammasome. Studies using Drosophila melanogaster suggest that there is an evolutionarily ancient origin of SYK-mediated signalling. Moreover, SYK has a crucial role in autoimmune diseases and haematological malignancies. This Review summarizes our current understanding of the diverse functions of SYK and how this is being translated for therapeutic purposes.