TYROSINE KINASES IN AUTOIMMUNE DISEASES

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Myeloid leukocytessuch as neutrophils or macrophages are critical components of innate immunity but their improper activation may also lead to tissue damage during autoimmune inflammation. We have previously shown that certain neutrophil responses require Src-family kinases, Syk and PLCγ2. Therefore, we tested the role of tyrosine phosphorylation pathways in in vivo inflammatory reactions.Src-family kinases, Syk and PLCγ2 were all found to be required for autoantibody-induced inflammatory reactions such as the K/BxN serum-transfer arthritis or autoantibody-induced skin blistering disease in experimental mice.The genetic deficiency of those signaling molecules also prevented accumulation of myeloid cells at the site of inflammation. Given the role of tyrosine kinases in β_2 integrin-mediated leukocyte activation, we hypothesized that Src-family kinases, Syk and PLCγ2 are also required for β_2 integrin-mediated leukocyte migration. Surprisingly, neutrophil migration in a conventional Transwell assay did not require Src-family kinases, Syk or PLCγ2 even though it was strongly reduced by the genetic deficiency of the β_2 integrin-chain CD18. In addition, the Src-family kinase inhibitor dasatinib did not affect in vitro neutrophil migration. In vivo competitive migration assays (in which wild type and knockout cells are allowed to migrate to the site of inflammation within the same animal)also revealed that Src-family kinases, Syk and PLCγ2 were not required for neutrophil or monocyte migration in sterile peritonitis or autoantibody-induced arthritis models. On the other hand, tyrosine kinases were required for immune complex-induced cytokine production by neutrophils and macrophages.Taken together, Src-family kinases, Syk and PLCγ2 are required for neutrophil activation and cytokine production but do not play any direct role in CD18-mediated migration of myeloid cells to the site of inflammation.