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**CD95-ligand on peripheral myeloid cells activates Syk kinase to trigger their recruitment to the inflammatory site.**

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**Abstract**

Injury to the central nervous system initiates an uncontrolled inflammatory response that results in both tissue repair and destruction. Here, we showed that, in rodents and humans, injury to the spinal cord triggered surface expression of CD95 ligand (CD95L, FasL) on peripheral blood myeloid cells. CD95L stimulation of CD95 on these cells activated phosphoinositide 3-kinase (PI3K) and metalloproteinase-9 (MMP-9) via recruitment and activation of Syk kinase, ultimately leading to increased migration. Exclusive CD95L deletion in myeloid cells greatly decreased the number of neutrophils and macrophages infiltrating the injured spinal cord or the inflamed peritoneum after thioglycollate injection. Importantly, deletion of myeloid CD95L, but not of CD95 on neural cells, led to functional recovery of spinal injured animals. Our results indicate that CD95L acts on peripheral myeloid cells to induce tissue damage. Thus, neutralization of CD95L should be considered as a means to create a controlled beneficial inflammatory response.