

**P001** TNF-induced  $\beta_2$  Integrin Activation Involves Src kinases and a Redox-Regulated Activation of p38 MAPK in human neutrophils  
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We had shown that the "inside-out" signaling induced by TNF- $\alpha$  to activate  $\beta_2$  integrins is redox regulated. Kinases involved in this pathway were investigated by studying the effects of kinase inhibitors on neutrophil adhesion and on the expression of  $\beta_2$  integrin activation neopeptide 24. We here show that both p38 MAPK (inhibited by SB203580) and Src kinases (inhibited by PP2) are involved in  $\beta_2$  integrin activation by TNF and oxidants (diamide). PP2 blocked TNF-induced expression of 24 neopeptide and cell adhesion promoted by the integrin activating anti-CD18 KIM185 mAb, showing that both the "inside-out" and the "outside-in" signaling involve Src kinases. P38 MAPK was activated by TNF and oxidants in the presence of EDTA, thus independently of integrin engagement. P38 MAPK was not activated upon direct integrin activation by KIM185 mAb. Thus, p38 activation allows to distinguish the "inside-out" from the "outside-in" pathway resulting from integrin engagement. Finally, p38 MAPK activation by TNF was blocked by DPI (diphenyliodonium) and Nac (N-acetylcystein) and is thus redox-regulated. These results, demonstrate that TNF "inside-out" signaling leading to  $\beta_2$  integrin activation involves Src kinases and a redox-regulated activation of p38 MAPK.