Inhibition of interleukin-1b-induced NF-kB activation by calcium/calmodulin-dependent protein kinase kinase occurs through Akt activation, associated with interleukin-1 receptor-associated kinase phosphorylation and uncoupling of MyD88.

陳炳常

Chen BC and Lin WW

摘要

Abstract

Calcium/calmodulin-dependent protein kinase kinase (CaMKK) and Akt are two multifunctional kinases involved in many cellular responses. Although Akt and Ca(2+) signals have been implicated in NF-kappaB activation in response to certain stimuli, these results are still controversial, and the mechanism(s) involved remains unknown. In this study, we show the roles that CaMKK and Akt play in regulating interleukin-1beta (IL-1beta)-induced NF-kappaB signaling. In human embryonic kidney 293 cells, IL-1beta induces IkappaB kinase beta (IKKbeta) activation, IkappaBalpha degradation, NF-kappaB transactivation, and weak Akt activation. A CaMKK inhibitor (KN-93) and phosphatidylinositol 3-kinase inhibitors (wortmannin and LY294002) do not inhibit IL-1beta-induced NF-kappaB activation. However, IL-1beta-induced NF-kappaB activity is attenuated by increased intracellular calcium in response to ionomycin, UTP, or thapsigargin or by overexpression of CaMKKc and/or Akt. Ionomycin and CaMKKc overexpression increases Akt phosphorylation on Thr(308) and enzyme activity. Under these conditions or upon overexpression of wild type Akt, IL-1beta-induced IKKbeta activity is diminished. Furthermore, a

dominant negative mutant of Akt abolishes IKKbeta inhibition by CaMKKc and ionomycin, suggesting that Akt acts as a mediator of CaMKK signaling to inhibit IL-1beta-induced IKK activity at an upstream target site. We have also identified a novel interaction between CaMKK-stimulated Akt and interleukin-1 receptor-associated kinase 1 (IRAK1), which plays a key role in IL-1beta-induced NF-kappaB activation. CaMKKc and Akt overexpression decreases IRAK1-mediated NF-kappaB activity and its association with MyD88 in response to IL-1beta stimulation. Furthermore, CaMKKc and Akt overexpression increases IRAK1 phosphorylation at Thr(100), and point mutation of this site abrogates the inhibitory effect of Akt on IRAK1-mediated NF-kappaB activation. Taken together, these results indicate a novel regulatory mechanism for IL-1beta signaling and suggest that CaMKK-dependent Akt activation inhibits IL-1beta-induced NF-kappaB activation through interference with the coupling of IRAK1 to MyD88.