

## BACKGROUND

IL-1 receptor-associated kinases (IRAKs) are important mediators in the signal transduction of Toll-IL-1 receptor (TIR) family members. All TIRs with known function are involved in host defense mechanisms, either by the recognition of pathogens or as receptors for proinflammatory cytokines. They play a crucial role in the switch from innate to adaptive immunity in mammals, and the signaling cascades initiated by these receptors are implicated in a number of human diseases. The early signal transduction events triggered by the first step, the ligand-induced formation of a receptor complex. This complex can consist of a receptor and a coreceptor, such as IL-1RI and IL-1RAcP. Alternatively, several chains of one family member form a complex, as was reported for TLR4. In either case, the close proximity of the TIR domains of the individual receptor chains allows a homotypic interaction with the TIR domain of the adaptor molecules MyD88 or Mal. MyD88 can then in turn recruit an IRAK via a death domain-death domain interaction.<sup>1</sup>

There are four IRAKs: IRAK1, -2, -3(-M), and -4. IRAK-1 is activated at the receptor complex, becomes rapidly phosphorylated, and leaves the receptor complex to interact with the adaptor TRAF6. The IRAK-TRAF6 interaction is a key step in the assembly of a multiprotein signalosome, which includes the mitogen-activated protein kinase kinase kinase (MAPKKK) TAK1. This complex activates a number of downstream signaling cascades, including I $\kappa$ B kinases (IKKs), p38, and Jun-N-terminal kinases (JNKs), leading to the activation of transcription factors such as NF- $\kappa$ B and AP-1. Surprisingly, mice deficient in IRAK-1 are severely compromised in their ability to respond to IL-1, but the response is not completely abolished. This observation was explained by redundancy in the IRAK family: Two additional members IRAK-2 and IRAK-3(IRAK-M).<sup>2</sup> Both proteins behave much like IRAK-1 in overexpression studies and they can compensate for the loss of IRAK-1 in a mutant 293 cell line. The most striking difference among the three proteins is that only IRAK-1 has potent kinase activity.<sup>3</sup> However, IRAK-3 works as a negative Regulator of TLR/IL-1R Signaling in normal cells. IRAK-3 enhances the binding of MyD88 to IRAK-1 and IRAK-4 and prevents IRAK-1 phosphorylation.<sup>4</sup> In this way, IRAK-M traps both IRAK molecules in the receptor complex, preventing their dissociation. IRAK-4, a novel member of the IRAK family with unique functional properties. IRAK-4 shares the domain structure of the other IRAKs and it is able to activate similar signal transduction pathways, namely NF- $\kappa$ B and MAPK pathways. It rapidly and transiently associates with IRAK-1 and TRAF6 in an IL-1-dependent manner but it is not functionally redundant with IRAK-1. Most strikingly, IRAK-4 is an active protein kinase and requires its kinase activity to activate NF- $\kappa$ B.

IRAK-4 might act upstream of IRAK-1 as an IRAK-1 activator.<sup>5</sup>

### References:

1. Janssens, S. & Beyaert, M.: Mol. Cell 11:293-302, 2003
2. Kanakaraj, P. et al: J. Exp. Med. 187:2073-9, 1998
3. Li, X. et al: Mol. Cell. Biol. 19:4643-52, 1999
4. Kobayashi, K. et al: Cell 110:191-202, 2002
5. Li, S. et al: Proc. Natl. Acad. Sci. USA 99:5567-72, 2002

## TECHNICAL INFORMATION

### Source:

IRAK4 Antibody is a mouse monoclonal antibody raised against recombinant human IRAK4 fragments expressed in *E. coli*.

### Specificity and Sensitivity:

This antibody detects IRAK4 proteins in various cell lysate.

**Storage Buffer:** PBS and 30% glycerol

### Storage:

Store at -20°C for at least one year. Store at 4°C for frequent use. Avoid repeated freeze-thaw cycles.

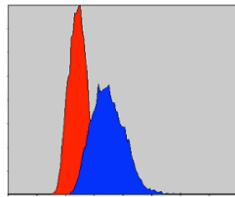
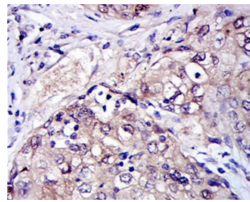
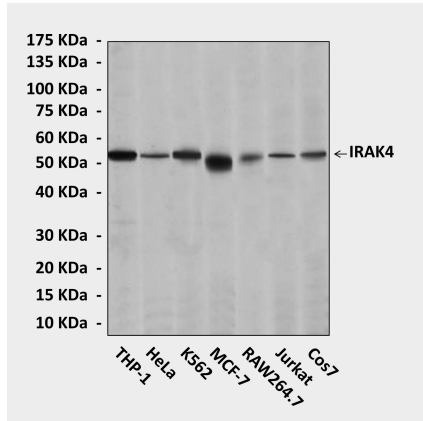
## APPLICATIONS

Application:	*Dilution:
WB	1:1000
IP	n/d
IHC (Paraffin)	1:50-200
ICC	n/d
FACS	1:50-200

\*Optimal dilutions must be determined by end user.



**QUALITY CONTROL DATA**



**Top:** Western blot detection of IRAK4 proteins in various cell lysates using IRAK4 Antibody. **Middle:** This antibody stains paraffin-embedded human lung cancer tissue in IHC analysis. **Bottom:** This antibody detects NFKB1 proteins specifically in HeLa cells by FACS assay (IRAK4 Antibody: Blue; negative control: Red).

