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The In Scope series of product newsletters highlight products that are applicable for a particular research topic. Due to space constraints, only a select list of products are provided in the table on p. 4-5. For more information about additional products, refer to our web site, RnDSystems.com. Please inquire about availability with a customer service representative at 1-800-343-7475 or e-mail us at info@RnDSystems.com. New products are released daily, thus the available products listed within this issue are only current for the date provided.

Figure Legend

Schematic illustrating possible effects of ADAM33 dysfunction as it relates to asthma. Loss-of-function mutations may depress cytokine and growth factor receptor shedding (left) or gain-of-function mutations may boost cytokine and growth factor shedding (right). Either may result in the epithelial damage, basement membrane fibrosis, tissue inflammation, and smooth muscle hypertrophy and hyperplasia often observed in the airways of asthmatic patients.

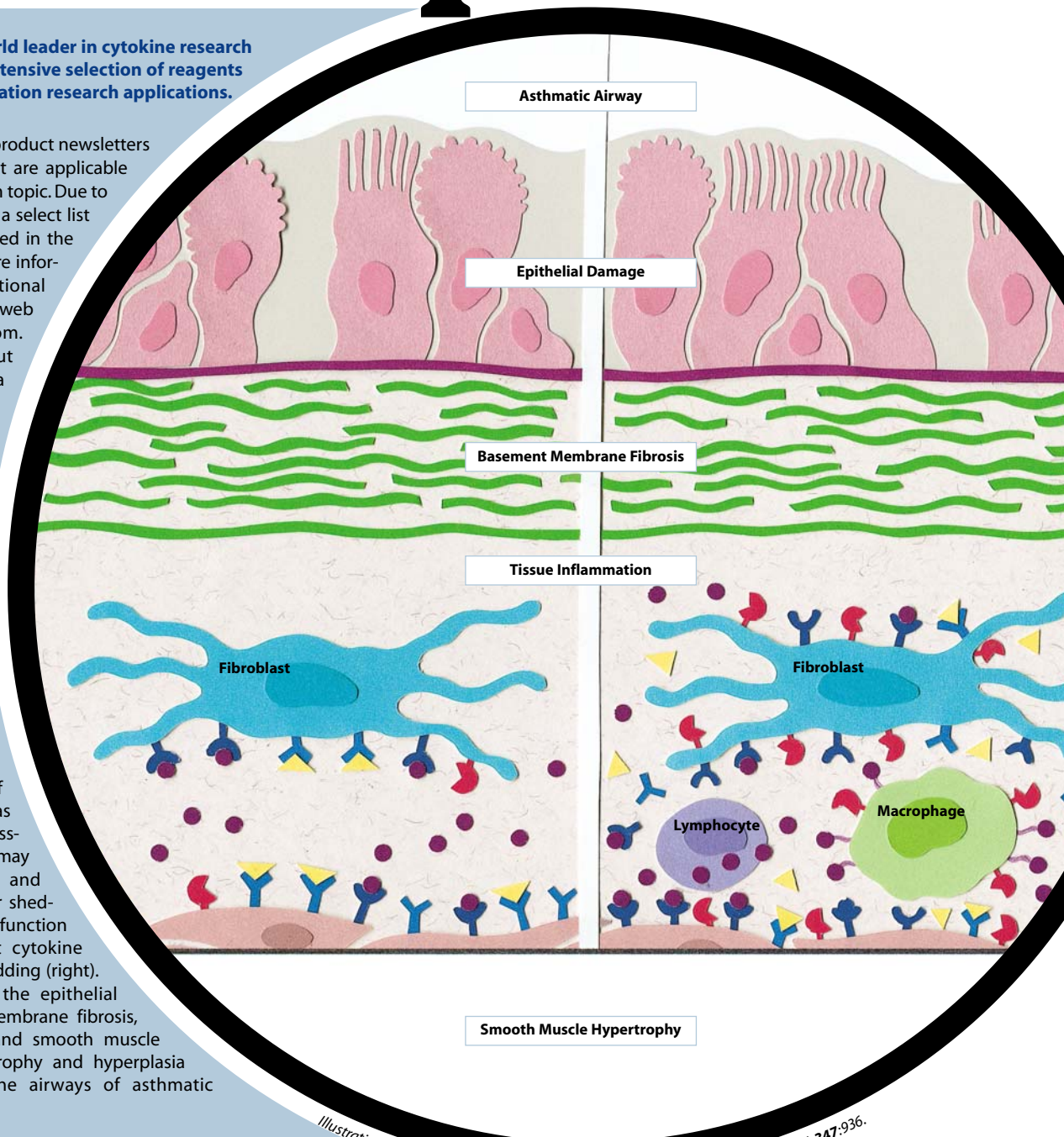


Illustration has been adapted from Shapiro, S.D. & C.A. Owen (2002) N. Engl. J. Med. 347:936.

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March 2003



everything cytokine & beyond

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The CXCR3 and CCR7 chemokine receptors, expressed on a variety of immune cell types mediate lymphocyte trafficking to inflammatory lesions and secondary lymphoid organs to initiate an immune response when bound by their corresponding ligands IP-10, I-TAC, MIG, 6Ckine, and MIP-3β.

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ADAM33 and Asthma

Although environmental factors certainly influence asthma, decades of genetic research have led to its description as a complex heritable disease. Progress has been slow, but evidence for the involvement of several specific genomic regions has finally emerged from linkage studies.¹⁻⁴ Particular genes responsible for asthma susceptibility, however, have remained elusive. Van Eerdewegh and colleagues identified the first of these genes, ADAM33.⁵

The human ADAM33 (a disintegrin and metalloproteinase 33) gene is located on chromosome 20 and encodes a series of specific motifs in an arrangement similar to that commonly found in ADAM family members.⁶ It possesses a type I transmembrane region with a relatively short cytoplasmic domain and several distinct extracellular regions including an EGF-like, a cysteine-rich, a disintegrin, and a metalloproteinase domain (Figure 1).^{6,7} Although many ADAM proteins have been identified, the specific functions for most are still unknown. Generally, ADAMs are thought to be involved in cell adhesion molecule, cytokine, growth factor, and receptor shedding from cell surfaces. Further, they have been implicated in inflammation and cell adhesion, signaling, proliferation, and death.⁷⁻⁹

Van Eerdewegh *et al.* performed two rounds of whole-genome linkage mapping using affected sibling pairs, selected candidate genes, and examined polymorphism frequencies in those genes to identify ADAM33.⁵ They then confirmed their findings via two types of linkage disequilibrium association mapping.^{2,5,10} Mutations in the ADAM33 sequence associated with increased susceptibility to asthma are described in the pro-, metalloproteinase, transmembrane, and cytoplasmic domains (Figure 1).⁵ ADAM33 is expressed by airway fibroblasts and smooth muscle cells.⁵ Data regarding the function of the ADAM33 gene product are not available yet, leading many to speculate as to its role in asthma. Its structure and expression pattern suggest involvement in airway remodeling,

perhaps via promotion of fibroblast and smooth muscle cell proliferation and/or through regulation of Th1/Th2 balance, possibly through alterations in cytokine shedding regulation (see cover figure).⁸

Other metalloproteinases have been associated with asthma as well. In particular, MMP-9 (matrix metalloproteinase 9) levels are increased in bronchial biopsies, bronchoalveolar lavage fluid, alveolar macrophage supernatants, and sputum of asthmatic patients. Further, lack of MMP-9 expression correlates with the lack of an asthmatic phenotype in a mouse asthma model. Currently, it is not clear whether these metalloproteinases are involved solely in the inflammatory aspects of asthma or whether they are also partly responsible for airway remodeling.^{8,11,12}

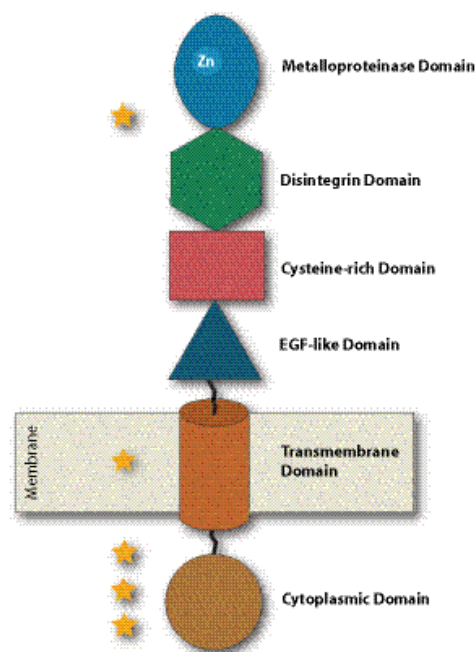


Figure 1. Schematic of the general structure of human ADAM33. Stars indicate general locations of known asthma-related polymorphisms (note: two in the pro-domain are not shown here).^{5,6}

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Immune Response to Insect Venom Immunotherapy

Allergic reactions to insect venom are very common and can range from mildly irritating to life-threatening in their severity. Venom immunotherapy (VIT) can prevent serious allergic responses in sensitized individuals. However, while nearly all patients are protected during VIT, a significant percentage relapse after VIT is discontinued. Administration of increasing doses of Hymenoptera insect venom or its major allergenic protein components induces several immune system adjustments in allergic patients. These mainly involve T cells, but also affect monocytes, mast cells, eosinophils, and basophils.¹

Venom-allergic patients produce the Th2 cytokines IL-4, IL-5, and IL-13 in response to venom exposure, whereas atopic and normal patients produce primarily the Th1 cytokines IFN- γ , IL-2, and TNF- α .^{2,3} During VIT, the venom specific Th2-dominated response shifts to a Th1-dominated response. This is the case for CD8⁺ cells as well as CD4⁺ T helper cells.⁴ A reduction in the number of IL-4 producing T cells is observed by the fifth day of VIT, followed by an increase in the number of IFN- γ and IL-2 producing T cells by six months.^{2,5} This leads to a decrease in allergen-specific IgE production and an increase in allergen-specific IgG₄ production.⁶ VIT also induces allergen-specific peripheral T cell anergy. During VIT, IL-10 is

initially produced by activated CD4⁺CD25⁺ allergen-specific T cells and later by B cells and monocytes.^{4,7} Elevated IL-10 levels promote a shift from allergen-specific IgE to normal IgG₄ production.⁷ Autocrine IL-10 blocks the CD28 costimulatory signal necessary for T cell activation.⁸ The T cell anergy involves reduced proliferative and cytokine responses. Reactivation of anergic T cells with IL-4 regenerates the Th2/IgE pattern, while either IL-2 or IL-15 regenerates the Th1/IgG₄ pattern.⁶ Loss of allergen-specific T cell anergy correlates with a failure of VIT (Figure 1).⁶

Other effects of VIT include monocyte activation with overproduction of IL-12 and TNF- α observed after at least two weeks of VIT.⁹ T cell IFN- γ and IL-10 also inhibit the release of histamine and sulfidoleukotriene from effector cells including mast cells and eosinophils.^{6,10} Several cell surface proteins are upregulated on basophilic granulocytes from allergic patients, including CD32, CD33, CD35, CD63, CD40 ligand, GM-CSF R α , gp130, IL-2 R β , and IL-4 R, while IL-5 R is downregulated. This activation state is initially exaggerated by VIT, but then subsides to nearly normal levels with continued treatment.¹¹ The surface markers CD11c, CD32, CD35, CD63, common γ chain, GM-CSF R α , gp130, IL-2 R β , and IL-4 R are downregulated following VIT.¹¹

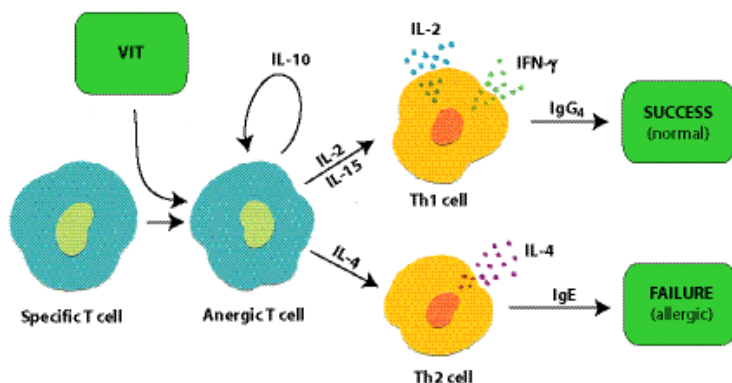


Figure 1. Allergic patients typically produce Th2 cytokines, while normal individuals produce Th1 cytokines in response to venom exposure. VIT switches the allergic patient from a Th2 to a Th1 phenotype and induces T cell anergy. If T cells remain anergic or are converted to a Th1 phenotype, then VIT is successful. VIT fails when anergic T cells are converted to Th2 cells.⁶

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Individual cytokine-secreting cells can be detected at frequencies well below 1 in 100,000, so *in vitro* cell expansion is not required before running an ELISpot assay. Unlike cytotoxicity assays, ELISpot results are highly reliable and reproducible.

The quality of the immune response (Th1- or Th2-dominated) is determined by the cytokine being secreted, and the magnitude (clonal size) is determined by the number of cells secreting that cytokine.

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Kit	Species	Kit	Species
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IFN- γ	• ♦ ♦ ♦ ♦ ★	IL-8	•
IL-1 β	•	IL-10	♦
IL-2	• ♦ ♦	IL-13	•
IL-4	• ♦	Latent TGF- β 1	•
IL-5	•	TNF- α	• ♦

• Human ♦ Mouse ♦ Rat ♦ Canine ★ Primate

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Name	Protein	Antibody	ELISA/Assays	mRNA Quantitation Kit	ELISA/Assay Development Kit	Primer Pair	Other
6Ckine/CCL21	• ◆	• ◆	•		◆		• CSP*
Akt		◦					
CCR1		•				• ◆ •	
CCR2		•				• ◆	
CCR3		• ◆				• ◆ •	
CCR4						• ◆ •	
CCR5		•				• ◆ •	
CCR7		•					
CD3		• ◆					• ◆ • T Cell Enrichment Column
CD23		•					
Common β Chain/IL-3 Rβ	◆	• ◆			◆		
Common γ Chain/IL-2 Rγ	• ◆	• ◆					
COX			◦				
COX-1				•			
COX-2				•			
CXCR1/IL-8 RA		•				• ◆ •	
CXCR2/IL-8 RB		•				• ◆ •	
CXCR3		•				◆ •	
EGF	•	•	•				
EGF R	•	•			•		
Eotaxin/CCL11	• ◆	• ◆	• ◆	•	•		• CSP,** • RD
Eotaxin-2/MPIF-2/CCL24	• ◆	• ◆	•		• ◆		• CSP**
Eotaxin-3/CCL26	•	•	•		•		• CSP**
ERK1		◦					
GM-CSF	• ◆ • ■ ▲	• ◆ • ■ ▲	• ◆ •	•	• ◆ •	•	• ELISpot, • FMAP
GM-CSF Rα		•					
I-309/CCL1	•	•	•		•		• RD
ICAM-1/CD54	• ◆ •	• ◆ •	• •	•	•	• ◆ •	
IFN-γ	• ◆ • ■ ▲ ◆ ◆ ■	• ◆ • ■ ▲ ◆ ◆ ■	• ◆ •	• ◆	• ◆ • •	• ◆ •	• ◆ • ◆ ◆ ELISpot, • FMAP
IFN-γ R1	• ◆	• ◆					
IFN-γ R2		• ◆					
IL-1β/IL-1F2	• ◆ • • ■	• ◆ • • ■	• ◆ • ■	• ◆ •	• ◆ •	• ◆ •	• ELISpot, • FMAP, • RD
IL-1 RI	• ◆	• ◆			•		
IL-1 RII	• ◆	• ◆	•				
IL-1 R3/IL-1 R AcP	•	•					
IL-1ra/IL-1F3	• ◆ ■	• ◆ ■	•		•		
IL-2	• ◆ • • ■	• ◆ • • ■	• ◆ •	• ◆	• ◆ •	• ◆ •	• ◆ • ELISpot, • FMAP, • RD
IL-2 Rα	•	•	•		•		
IL-2 Rβ		• ◆					
IL-4	• ◆ • • ■ ◆ ▲	• ◆ • • ■ ◆ ▲	• ◆ •		• ◆ • •	• ◆	• ◆ ELISpot, • FMAP, • RD
IL-4 R	• ◆	• ◆	•				
IL-5	• ◆ •	• ◆ •	• ◆		• ◆	•	
IL-5 Rα	•	• ◆					
IL-6	• ◆ • • ■	• ◆ • • ■	• ◆ • ■	•	• ◆ • ■	• ◆	• ◆ ELISpot, • FMAP, • RD
IL-6 R	•	•	•		•		
IL-8/CXCL8	• ■	• ■	• ■	•	• ■	•	• ELISpot, • FMAP, • RD
IL-9	• ◆	• ◆					
IL-9 R	•	•					
IL-10	• ◆ • • ■ ◆ ▲ □	• ◆ • • ■ ◆ ▲ □	• ◆ •	•	• ◆ •	• ◆ •	◆ ELISpot, • FMAP, • RD
IL-10 Rα	• ◆	• ◆					
IL-10 Rβ	•	•					
IL-12	• ◆ ■	• ◆ ■	•				
IL-12 p35						• •	
IL-12 p40	• ◆	• ◆	• ◆		• ◆	• ◆ •	
IL-12 p70		• ◆	◆		• ◆		
IL-12 Rβ1	•	•					
IL-13	• ◆	• ◆	• ◆		• ◆	• ◆ •	
IL-13 Rα1	• ◆	•					
IL-13 Rα2	• ◆	• ◆					
IL-18/IL-1F4	• ◆ • ■	• ◆ • ■	• ◆				

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Key

- Human
- ◆ Mouse
- Rat
- Cotton Rat
- Bovine
- Porcine
- ◆ Canine
- ▲ Feline
- Rhesus macaque
- ◻ Viral
- ◉ Primate
- Multi-species

* **Inflammation Research Chemokine Sampler Pack**
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 See page 2.

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CSP - Chemokine Sampler Pack
 ELISpot - ELISpot Kit
 FMAP - Cytokine Multiplex Assay
 RD - Receptor Detection Kit

Name	Protein	Antibody	ELISA/Assays	mRNA Quantitation Kit	ELISA/Assay Development Kit	Primer Pair	Other
IL-18 R α /IL-1 R5	•	• ◆					
IL-18 R β /IL-1 R7	•	•					
IL-18 BPa	•	•					
IL-18 BPc		◆					
IL-18 BPd	◆	◆					
IP-10/CXCL10	• ◦	• ◦	•		•		• CSP*
I-TAC/CXCL11	• ◆	• ◆	•		•		• CSP*
JE/CCL2	◆	◆	◆		◆	◆ •	◆ RD
JNK		◦					
KC	◆	◆	◆	◆ •	◆		
LTB ₄			◦				
MARC/MCP-3/CCL7	◆	◆					
MCP-1/CCL2	•	•	•	•	•	•	• RD, • CSP**
MCP-2/CCL8	•	• ◆			•		
MCP-3/CCL7	•	•	•		•		
MCP-4/CCL13	•	•	•		•		
MDC/CCL22	• ◆	• ◆	•		•		
MIG/CXCL9	• ◆	• ◆	•		•		• CSP*
MIP-1 α /CCL3	• ◆ ◦	• ◆ ◦	• ◆	•	• ◆		• ◆ RD
MIP-1 β /CCL4	• ◆ ◦	• ◆ ◦	• ◆		• ◆		• RD
MIP-3 β /CCL19	• ◆	• ◆			• ◆		• CSP*
MPIF-1/CCL23	•	•	•				• CSP**
MSK 1		◦					
MSK 2		◦					
β -NGF	• ◆ •	• •			• •	• ◆ •	
NGF R	• ◆	•				• ◆ •	
NO			◦				
iNOS		•	•	• ◆		• ◆	
p38		◦			◦		
PARP	◦	• ◆ ◦	◦				◦ Activated DNA
PGE ₂			◦				
PGF _{2α}			◦				
PGJ ₂			◦				
PIGF	•	•	•		•	• ◆	
PIGF-2	◆	◆	◆				
E-Selectin	• ◆ •	• ◆	• ◆	•		• ◆ •	
P-Selectin	• ◆	• ◆	• ◆	•		•	
RANTES/CCL5	• ◆ ◦	• ◆	• ◆	•	• ◆	•	• RD, • CSP**
SCF	• ◆	• ◆	• ◆		◆		• ◆ RD
SCF R	•	•					
Stat 1		• ◆					
Stat 3		• ◆					
Stat 6		• ◆					
TARC/CCL17	• ◆	• ◆	• ◆		• ◆		
TGF- α	•	•	•				
TGF- β 1	• ■	• ◦	•	•	•	• ◆	• RD
TGF- β 2	• ■	◦	•		•	•	
TGF- β RII	• ◆	• ◆					
TGF- β RIIIb	•						
TGF- β RIII	•	•					
TNF- α /TNFSF2	• ◆ • ◦ ■	• ◆ • ◦ ■	• ◆ • ◦ ■	• ◆ •	• ◆ • ◦ ■	• ◆	• ◆ ELISpot, • FMAP, • RD
TNF- β /TNFSF1	•	• ◆	•		•	•	
TNF RI/TNFRSF1A	• ◆	• ◆	• ◆		• ◆	• ◆	
TNF RII/TNFRSF1B	• ◆	• ◆	• ◆		• ◆	• ◆	
TXB ₂			◦				
VCAM-1	• ◆	• ◆	• ◆	•	◆	• ◆	
VEGF	• ◆ •	• ◆ •	• ◆	• ◆	• ◆ •	• ◆	• FMAP
VEGF R1/Flt-1	• ◆	• ◆	• ◆			• ◆	
VEGF R2/FIk-1/KDR	• ◆	• ◆	• ◆			• ◆	
VEGF R3	• ◆	• ◆				• ◆	

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- ◆ Mouse
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- Porcine
- ◆ Canine
- ▲ Feline
- Rhesus macaque
- Viral
- ⊕ Primate
- Multi-species

CSP - Chemokine Sampler Pack
 ELISpot - ELISpot Kit
 FMAP - Cytokine Multiplex Assay
 RD - Receptor Detection Kit

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Proinflammatory Cytokine Signaling via p38 MAPK

Two of the most important proinflammatory cytokines, IL-1 β and TNF- α , signal through two mitogen-activated protein kinase (MAPK) signal transduction pathways, the c-Jun NH₂-terminal kinase (JNK) pathway and the p38 MAPK pathway.¹ The p38 MAPKs are a family of four related Ser/Thr kinases: p38 α , p38 β , p38 γ , and p38 δ . Each isoform is activated by dual Tyr and Thr phosphorylation within the phosphoacceptor sequence Thr-Gly-Tyr, in the activation loop of the kinase subdomain VIII. Functional differences between the p38 isoforms are related in part to their differential expression. While p38 α is expressed ubiquitously, p38 β is expressed at highest levels in the brain and heart, p38 γ is expressed primarily in skeletal muscle, and p38 δ is enriched in endocrinologically active organs.² The most frequently studied family member, p38 α , was initially purified as a kinase critical to the proinflammatory IL-1 signaling cascade.³

Activation of all MAPKs is regulated by a three-tiered phosphorylation cascade comprised of an apical MAPK kinase kinase (MAP3K), a MAPK kinase (MEK or MKK), and a downstream MAPK. During an inflammatory response, IL-1 activates p38 MAPK by linking the MAPK cascade to the IL-1 receptor (IL-1 R) signaling pathway. Upon IL-1 binding, IL-1 R clusters with various adaptor molecules to form a receptor complex thought to consist of at least IL-1 R, IL-1 R3, MyD88, TRAF6, and the protein kinase IRAK.⁴ This complex appears capable of activating a number of distinct enzymes that function as MAP3Ks, including MEKK1-4, ASK1, and TAK1.⁵ While TAK1 is frequently linked to IL-1 signaling, it is currently unclear how many MAP3Ks may be utilized by the activated IL-1 R complex, and usage may depend upon cell type and physiological conditions. Following their phosphorylation, the MAP3Ks upstream of p38 MAPK then activate the dual specificity MAPK kinases MKK3 and MKK6. While MKK3 preferentially phosphorylates p38 α , p38 γ , and p38 δ , MKK6 can strongly phosphorylate all isoforms.⁶

All MAPKs are proline-directed kinases with specificity additionally conferred by MAPK docking sites present on physiological substrates. With a few exceptions, the p38 MAPK substrates that mediate proinflammatory signaling remain largely unknown.

p38 MAPK is known to phosphorylate several transcription factors, particularly activator protein-1 (AP-1). As homo- and/or heterodimers composed of bZIP factors from the Jun, Fos, and ATF families, AP-1 participates in the transcriptional induction of several cytokines, proteases, and cell adhesion molecules important in inflammation.^{7,8} All p38 isoforms phosphorylate the *trans*-activation domain of ATF-2, the AP-1 component most tightly linked to p38 MAPK activation.⁹ Also contributing to the strong and rapid induction of inflammatory response genes is p38 MAPK's post-transcriptional role in enhancing mRNA stability. The mRNAs encoding the AP-1 component c-Fos, the early response cyclooxygenase 2 (COX-2), and the chemokine IL-8 are all stabilized following p38 MAPK activation (Figure 1).^{10,11}

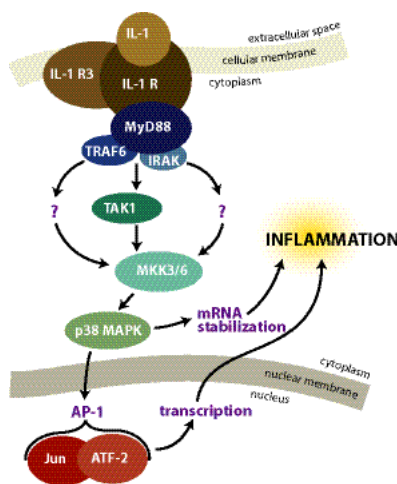


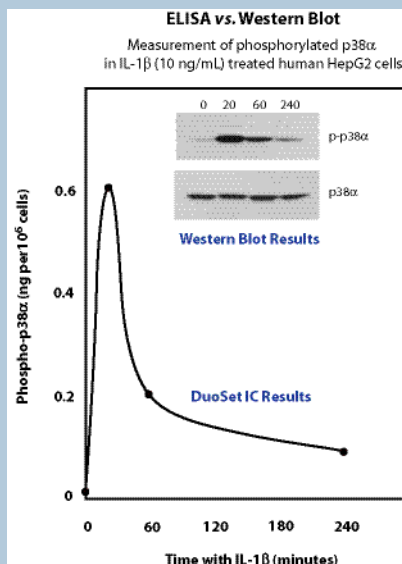
Figure 1. IL-1 signals via a receptor complex that includes IL-1 R, IL-1 R3, MyD88, TRAF6, and IRAK. This complex activates TAK1 as well as other MAP3Ks. TAK1 and others then activate MKK3 and/or MKK6, which in turn activate p38 MAPK. p38 MAPK then promotes the transcription and transcript stabilization of other proinflammatory factors.

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DuoSet® IC ELISA Development Systems

DuoSet IC ELISA Development Systems have been developed for several important intracellular factors involved in apoptosis and signal transduction. They offer a fast, economical, and quantitative alternative to western blot analysis that is more amenable to large-scale screening projects.



Available Kits

Analyte	Cat #
Bcl-2	DYC827
Bcl-x_L	DYC894
Caspase-9 (Active)	DYC830
Cytochrome c	DYC897
Phospho-p38α (T180/Y182)	DYC869
Total p38α	DYC8691
Phospho-p70 S6 Kinase (T389)	DYC896
Phospho-RSK1 (S380)	DYC892
SMAC/Diablo	DYC789
Survivin	DYC647

Kit Contents*

(Available in 2, 5, and 15 plate kit packs.)

- Coating Antibody
- Standard
- Biotinylated Detection Antibody
- Streptavidin-HRP

*The Caspase-9 assay is a novel and unique activity assay with different kit contents than those listed. See product insert for details.

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ELISpot

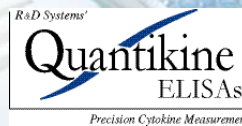
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