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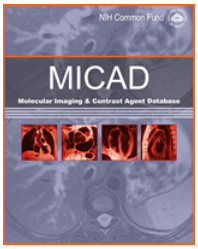

^{99m}Tc-Interleukin-18-binding protein-Fc-interlukin-1 receptor antagonist

^{99m}Tc-IL-18bp-Fc-IL-1ra

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Chemical name:	^{99m}Tc-Interleukin-18-binding protein-Fc-interlukin-1 receptor antagonist	
Abbreviated name:	^{99m}Tc-IL-18bp-Fc-IL-1ra	
Synonym:		
Agent category:	Polypeptide	
Target:	Interleukin-18 (IL-18) and IL-1 receptors	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging	
Source of signal:	^{99m}Tc	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about the IL-18bp.

Background

[PubMed]

Interleukin-18 (IL-18) is a proinflammatory cytokine produced by macrophages, epithelial cells, and activated T cells (1, 2), and it plays an important role in inflammation and immune response (3, 4). IL-18 induces production of tumor necrosis factor and IL-1 in mononuclear cells. A variety of normal and malignant cells can produce and respond to IL-18 through its receptor (IL-18R). A soluble secreted IL-18 binding protein (IL-18bp) was found to bind to IL-18 with high affinity (dissociation constant (K_d) = 0.4 nM) and to neutralize the biological effects of IL-18 by blocking its interaction with IL-18R (5, 6). IL-18bp-Fc is a 40-kDa glycoprotein with an immunoglobulin (Ig) domain.

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The interleukin-1 family of two proinflammatory cytokines, IL-1α and IL-1β, which bind to two IL-1 receptors (IL-1R1 and IL-1R2), and an IL-1R antagonist (IL-1ra), is mainly produced by activated macrophages and tissue macrophages (7). IL-1α and IL-1β are important mediators of the inflammatory response and hematopoiesis, and they are involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. IL-1 is involved in chronic inflammatory diseases and in neuropathological conditions (8, 9). The balancing action of IL-1 and IL-1ra plays an important role in the regulation of inflammation and immune responses (10). IL-1ra has been shown to be effective as an anti-inflammatory treatment in several chronic inflammatory diseases and stroke (11, 12). A human recombinant, non-glycosylated form of the human IL-1ra (rhIL-1ra, Anakinra) has been approved by the United States Food and Drug Administration for the treatment of rheumatoid arthritis (13).

IL-1 and IL-18 exhibit additive or synergistic effects in promoting pathophysiological processes observed in many inflammatory diseases (14). A dual domain IL-18bp-Fc-IL-1ra fusion protein was constructed by joining IL-18bp and IL-1ra cDNA to the Fc fragment of human IgG_1 cDNA in an expression plasmid (15). The amino-terminal segment binds to IL-18, and the carboxyl-terminal sequence binds to the IL-1R. Liu et al. (15) radiolabeled IL-18bp-Fc-IL-1ra with ^{99m}Tc *via* 2-iminothiolane reduction to produce ^{99m}Tc-IL-18bp-Fc-IL-1ra for use with single-photon emission computed tomography (SPECT) imaging of inflammation in mice.

Related Resource Links:

- Chapters in MICAD (IL-1, IL-18)
- Gene information in NCBI (IL-1á, IL-1â, IL-1R1, IL-1R2, IL-1ra, IL-18, IL-18R)
- Articles in Online Mendelian Inheritance in Man (OMIM) (IL-1á, IL-1â, IL-1R1, IL-1R2, IL-1ra, IL-18, IL-18R)
- Clinical trials (IL-1, IL-1ra, Anakinra, IL-18)
- Drug information in FDA (Anakinra)

Synthesis

[PubMed]

Liu et al. (15) reported the synthesis of ^{99m}Tc-IL-18bp-Fc-IL-1ra. IL-18bp-Fc-IL-1ra was incubated with 2-iminothiolane for 30 min at 37°C in phosphate-buffered saline (PBS, pH 7.4). A solution of 1,110 MBq (30 mCi) $^{99m}TcO_4$– was added to a mixture of $SnCl_2$ and glucoheptonic acid and incubated at room temperature for 5 min to produce ^{99m}Tc-glucoheptonate, which was then incubated with the thiolated IL-18bp-Fc-IL-1ra for 30 min at room temperature, with a radiolabel yield of 75%. ^{99m}Tc-IL-18bp-Fc-IL-1ra was purified on a PD-10 column, with >95% radiochemical purity. The specific activity was 7.4–8.3 MBq/μg (0.20–0.22 mCi/μg). ^{99m}Tc-IL-18bp-Fc-IL-1ra remained >95% intact for up to 5 h in both saline at room temperature and serum at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Liu et al. (15) performed binding competition experiments with ^{99m}Tc-IL-18bp-Fc-IL-1ra (2 nM) and IL-18bp-Fc-IL-1ra (0.1–10,000 nM) using rat leukocytes, which contain both IL-18R and IL-1R. The IC_{50} value for IL-18bp-Fc-IL-1ra was 73.56 nM.

Animal Studies

Rodents

[PubMed]

Liu et al. (15) performed *ex vivo* biodistribution studies in normal mice and mice with TPA-induced edema in the right ears (n = 3–5/group) at 3 h after intravenous injection of 74 MBq (2 mCi) ^{99m}Tc-IL-18bp-Fc-IL-1ra. The biodistribution pattern was similar for the TPA-treated mice and the normal mice, with the highest accumulation in the liver (23% injected dose/gram (ID/g), followed by the intestine (15% ID/g), kidneys (10% ID/g), spleen (3.6% ID/g), blood (1.1% ID/g), lung (0.8% ID/g), and stomach (0.7% ID/g). Low radioactivity levels (<0.4% ID/g) were found in the heart, skin, and muscle. In the TPA-treated mice, the inflamed right ears accumulated 1.80 ± 0.17% ID/g *versus* 0.48 ± 0.07% ID/g ($P < 0.01$) in the contralateral left ears. Pretreatment with excess unlabeled IL-18bp-Fc-IL-1ra 30 min before the tracer reduced the radioactivity levels to 1.09 ± 0.08% ID/g (right ears) *versus* 0.53 ± 0.13% ID/g (left ears) ($P < 0.05$). The levels of IL-1β and IL-18 were significantly increased in the TPA-treated ears compared with contralateral ears (IL-1β: 3,987 ± 40 pg/ml *versus* 556 ± 196 pg/ml, $P < 0.01$; IL-18: 223 ± 19 pg/ml *versus* 139 ± 12 pg/ml, $P < 0.05$). SPECT imaging at 3 h showed that the TPA-treated ears were clearly visualized, whereas the contralateral ears were almost invisible. Pretreatment with excess unlabeled IL-18bp-Fc-IL-1ra markedly reduced the radioactivity in the TPA-treated ears.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

R01 HL090716, P41 EB002035

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