Microbubbles coated with antibody to intracellular adhesion molecule-1

MB$_{ICAM-1}$

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Chemical name:	Microbubbles coated with antibody to intracellular adhesion molecule-1	
Abbreviated name:	MB$_{ICAM-1}$	
Synonym:		
Agent category:	Antibody	
Target:	Intracellular adhesion molecule-1 (ICAM-1)	
Target category:	Adhesion molecule	
Method of detection:	Ultrasound (US)	
Source of signal:	Microbubbles	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about ICAM-1.

Background

[PubMed]

Ultrasound is widely used imaging modality (1) and is expanding its role in noninvasive molecular imaging with ligand-carrying microbubbles (2). Microbubbles are comprised of spherical cavities filled by a gas encapsulated in a shell. The shells are made of phospholipids, surfactant, denatured human serum albumin or synthetic polymer. Ligands and antibodies can be incorporated into the shell surface of microbubbles.

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Microbubbles are usually 2 to 8 μm in size. They provide a strongly reflective interface and resonate to ultrasound waves. They are used as ultrasound contrast agents in imaging of inflammation, angiogenesis, intravascular thrombus, and tumors (3-5). They are also potentially used for drug and gene delivery (6).

Endothelial cells are important cells in inflammatory responses (7, 8). Bacterial lipopolysaccharide, virus, inflammation, and tissue injury increase tumor necrosis factor α (TNFα), interleukin-1 (IL-1) and other cytokine and chemokine secretion. Leukocyte emigration from blood is dependent on their rolling along endothelial cell surfaces and subsequently adherence to endothelial cell surfaces. Inflammatory mediators and cytokines induce chemokine secretion from endothelial cells and other vascular cells and increase their expression of cell surface adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), integrins and selectins. Chemokines are chemotactic to leukocytes to sites of inflammation and tissue injury. The movements of leukocytes through endothelial junctions into the extravascular space are highly orchestrated through various interactions with different adhesion molecules on endothelial cells (9).

ICAM-1 is found on cell surface of endothelial cells and other vascular cells, such as smooth muscle cells and fibroblasts (10-14). It binds to counter-receptors on the cell-surface of leukocytes. IL-1 and TNFα increase ICAM-1 and other cell adhesion molecule expression on the vascular endothelial cells, leading to leukocyte adhesion to the activated endothelium. Microbubbles targeted with antibody against ICAM-1 are being developed as a noninvasive agent for ICAM-1 expression in vascular endothelial cells of dysfunctional endothelium (15-18).

Related Resource Links:

- Chapters in MICAD (ICAM-1)
- Gene information in NCBI (ICAM-1)
- Articles in Online Mendelian Inheritance in Man (OMIM) (ICAM-1)

Synthesis

[PubMed]

For targeted microbubbles, Weller et al. (17) prepared biotinylated microbubbles by sonication of an aqueous dispersion of decafluorobutane gas, phosphatidylcholine, polyethyleneglycol-(PEG-) stearate, and phosphatidylethanolamine-biotin in a 2:1:1 ratio by weight. Microbubbles were combined with streptavidin, washed, and conjugated with biotinylated mouse monoclonal antibody against ICAM-1(MB_{ICAM-1}) or isotype control monoclonal antibody (MB_{iso}). Control lipid microbubbles (MB_c) were also prepared. The microbubbles are about 3.4 ± 1.2 microns in diameter. An antibody to microbubble ratio was estimated to be 60,000 ± 5,000 by flow cytometry. Alternatively, the primary amino groups of antibody were covalently conjugated to the carboxylic groups on the

microbubble shell, which has been activated with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (15).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Villanueva et al. (15) reported that MB_{ICAM-1} (1–10 x 10^8/ml) perfused through the flow chamber coated with endothelial cells at a wall shear rate of 25 s^{-1}. There was a significantly greater number of MB_{ICAM-1} attached to IL-1 activated endothelial cells (8.0 ± 3.5 microbubbles/cell) than to normal endothelial cells (0.21 ± 0.09 microbubbles/cell). The number of adherent MB_{ICAM-1} to activated endothelial cell decreased to 2.6 ± 0.3 and 0.8 ± 0.4 at 100 and 1000 s^{-1}, respectively. The number of MB_{ICAM-1} adherent to normal endothelial cell was only 0.1 at 1000 s^{-1}. MB_c and MB_{iso} attachment to both activated and normal endothelial cells were minimal (0.03-0.05) at 25 s^{-1} and there were no significant changes at higher wall shear rates.

Weller et al. (16, 17, 19) confirmed that microbubble shell antibody density and wall shear rate are critical parameters controlling microbubble targeted adhesion. Microbubble adhesion was significantly greater with greater anti-ICAM-1 antibody density of the microbubbles and greater ICAM-1 expression on the cell surface of the endothelial cells. On the other hand, microbubble adhesion to endothelial cells was inversely proportional to the wall shear rate. Therefore, accumulation and retention of MB_{ICAM-1} is possible under physiologic flow conditions and is strongly influenced by shear stress and surface density of the target receptor.

Animal Studies

Rodents

[PubMed]

Weller et al. (16) performed ultrasound assessment of acute cardiac transplant rejection with 2.5x10^6 MB_{ICAM-1} by triggered myocardial contrast echocardiography in rats. Cardiac ultrasound imaging of rejecting allograft transplants (10 ± 4 U, n = 8) showed that video intensity signal was significantly higher (P<0.01) than control isograft transplants (1 ± 4 U, n = 7) for MB_{ICAM-1}. On the other hand, MB_c exhibited a minimal contrast in both the allograft and isograft transplants. Postmortem histology confirmed that the rejecting allograft transplants had a significantly higher ICAM-1 expression than the control isograft transplants.

Reinhardt et al. (18) performed ultrasound assessment of ICAM in experimental autoimmune encephalomyelitis (EAE) in rats by sensitive particle acoustic quantification (SPAQ), which allows qualification of microbubbles in high concentration and resolution in µm (20). EAE was induced by transferring myelin basic protein activated T-cells intravenously into rats. On day 4, the brain and spinal cord was excised 30 min after

injection of MB_{ICAM-1}. Registration of acoustic counts during the first scan of the brain and the spinal cord revealed a significant higher ICAM-1 expression in AT-EAE rats ($P < 0.001$, $n = 6$) that received MB_{ICAM-1} (~10,000-15,000 acoustic counts) than AT-EAE rats ($n = 4$) that received unspecific MB_{iso} (~500 acoustic counts). In addition, only a marginal signal was detected in healthy controls ($n = 4$, ~500 acoustic counts) that received MB_{ICAM-1}. Pretreatment of EAE rats with anti-ICAM-1 antibody or methylprednisolone (a therapeutic drug) before MB_{ICAM-1} injection decreased the acoustic counts by >75%. The whole brain scan of living anesthetized rats after injection of MB_{ICAM-1} confirmed the ex-vivo experiments that healthy control rats ($n = 3$) showed only a marginal acoustic signal, whereas EAE rats ($n = 3$) exhibited a strong acoustic signal similar to the ex-vivo EAE brain.

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

HL58865

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