Microbubbles conjugated with cyclo(CGGRRLGGC)

MB_{RRL}

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Chemical name:	Microbubbles conjugated with cyclo(CGGRRLGGC)	
Abbreviated name:	MB_{RRL}	
Synonym:		
Agent Category:	Peptide	
Target:	Unknown	
Target Category:	Receptor binding to tumor-derived endothelial cells	
Method of detection:	Ultrasound (US)	
Source of signal:	Microbubbles	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available in PubChem.

Background

[PubMed]

Ultrasound is the most widely used imaging modality (1), and its role in non-invasive molecular imaging is expanding with ligand-carrying microbubbles (2). Microbubbles are spherical cavities filled with a gas encapsulated in a shell. The shells are made of phospholipids, a surfactant, denatured human serum albumin, or a synthetic polymer. Ligands and antibodies can be incorporated into the shell surface of microbubbles, which are usually 2–8 μm in diameter. Microbubbles provide a strongly reflective interface and resonate to ultrasound waves, and they are used as ultrasound contrast agents in imaging

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of inflammation, angiogenesis, intravascular thrombus, and tumors (3-5). They also have the potential to be 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, interleukin-1, and other cytokine and chemokine secretion. Leukocyte emigration from blood is dependent on the leukocytes rolling along endothelial cell surfaces and subsequently adhering 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, vascular cell adhesion molecule-1, integrins, and selectins. Chemokines are chemotactic to leukocytes at sites of inflammation and tissue injury (9). Angiogenesis is a process of development and growth of new blood vessels from pre-existing vessels. Tumor growth depends on the formation of new blood vessels from angiogenesis. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) enhance angiogenesis. Expression of VEGF receptors is higher on the cell surface of tumor-derived endothelial cells than on the cell surface of normal endothelial cells.

Microbubbles conjugated to peptides or to antibodies against integrins, cell adhesion molecules, and VEGF receptors have previously been studied for the non-invasive assessment and imaging of angiogenesis (10-13). A peptide specific to tumor vasculature and containing Arg-Arg-Leu (RRL) was identified by screening a peptide display library panned against tumor cells derived from SCC-VII murine squamous cell carcinomas (14). Weller et al. (12) studied ultrasonic imaging of tumor vasculature using microbubbles conjugated with biotinylated c(CGGRRLGGC) (MB_{RRL}) in mice bearing human tumor xenografts.

Synthesis

[PubMed]

For targeted microbubbles, Weller et al. (12) prepared biotinylated microbubbles by sonication of an aqueous dispersion of decafluorobutane gas, phosphatidylcholine, polyethylene glycol-stearate, and phosphatidylethanolamine-biotin in a 2:1:1 ratio by weight. Microbubbles were combined with streptavidin, washed, and conjugated with MB_{RRL} or control peptide c(CGGGGGGGC) ($MB_{control}$). The microbubbles are 3.2 ± 1.0 μm in diameter. The peptide/microbubble ratio was estimated with flow cytometry to be ~60,000 (10).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Weller et al. (12) reported that MB_{RRL} or $MB_{control}$ (3.33×10^6/ml) perfused through the flow chamber coated with endothelial cells at a wall shear rate of 100 s^{-1} for 3 min. There was a significantly ($P < 0.01$) greater number of MB_{RRL} attached to tumor-activated

endothelial cells (2.4 ± 0.6 microbubbles/cell) than to normal endothelial cells (0.8 ± 0.1 microbubbles/cell). $MB_{control}$ attachment to both activated and normal endothelial cells was minimal (0.3–0.4 microbubbles/cell).

Animal Studies

Rodents

[PubMed]

Weller et al. (12) performed ultrasound assessment of MB_{RRL} binding in five mice bearing Clone C tumors (transfected with bFGF), six mice bearing PC3 tumors, and six normal mice. There were intense acoustic signals in both tumors at 2 min after MB_{RRL} injection compared with mild contrast in tumors injected with $MB_{control}$. There was little difference in myocardial signal intensity between MB_{RRL} and $MB_{control}$ in normal mice. The mean video intensity for normal myocardium was 0.5 ± 1 units, whereas the mean video intensity for the tumors was 5 ± 1 units ($P = 0.0001$). Postmortem histology demonstrated that the density of RRL binding was concentrated at the tumor periphery. No blocking studies or other studies to validate the mechanism were reported.

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 HL-58865

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