^{125}I-Labeled mouse anti-human carbonic anhydrase IX monoclonal antibody

^{125}I-MAb

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Chemical name:	^{125}I-Labeled mouse anti-human carbonic anhydrase IX monoclonal antibody	
Abbreviated name:	^{125}I-MAb	
Synonym:		
Agent Category:	Antibodies	
Target:	Carbonic anhydrase IX (CA IX)	
Target Category:	Enzymes	
Method of detection:	Single-photon emission computed tomography (SPECT) or planar imaging	
Source of signal / contrast:	^{125}I	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available.

Background

[PubMed]

^{125}I-Labeled mouse anti-human carbonic anhydrase IX (CA IX) monoclonal antibody (MAb), abbreviated as ^{125}I-MAb, is a probe developed by Li et al. for molecular imaging of tumor hypoxia (1).

CA IX is a membrane-associated glycoprotein that consists of an extracellular catalytic domain, a transmembrane anchor, and a short C-terminal cytoplasmic tail (2, 3). The

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expression of CA IX is largely restricted to the epithelial cells of the gastrointestinal tract, especially the gastric epithelial cells where CA IX catalyzes the hydration of carbon dioxide to bicarbonate and protons (1, 4). CA IX is one of the two CA isoforms (IX and XII) in the CA family that are overexpressed in various solid tumors (3). The CA IX overexpression is closely related to the activation of hypoxia-inducible factor-1 (HIF-1) and the inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene due to hypoxia or the mutation of the VHL gene (5, 6). In this process, HIF-1 upregulates the expression of CA IX while the VHL protein downregulates the expression of CA IX by involving in the degradation of HIF-1 α-subunits. In some renal cell carcinomas, CA IX could be significantly overexpressed (up to 150-fold) because of the VHL mutation and constitutive HIF-1 activation (2, 3, 6).

The direct outcome of CA IX overexpression is the acidification of the tumor microenvironment, leading to extracellular pH values of ~6.5 in contrast to 7.4 in normal tissues (4). The acidic microenvironment has been shown to be associated with tumorigenic transformation, chromosomal rearrangements, extracellular matrix breakdown, and tumor cell migration, invasion, and resistance to radio/chemotherapy (2, 3, 5). CA IX may also play a role in tumor cell growth by providing bicarbonate to the synthesis of pyrimidine nucleotides.

Because of these facts, CA IX has been investigated as a marker for cellular hypoxia and tumor prognosis and as a target for tumor imaging and therapy (7, 8). For these purposes, a large set of chemical inhibitors and several MAb have been developed (7-9). Ahlskog et al. described the generation and characterization of two high-affinity human MAb (A3 and CC7) specific to the extracellular domain of human CA IX (7). The radionuclide-labeled chimeric antibody cG250 and its Fab and F(ab')2 fragments have been tested by Divgi et al. as molecular probes for imaging clear-cell renal carcinomas and HT29 human colorectal tumor xenografts (10). Li et al. investigated the biodistribution of ^{125}I-MAb in animals bearing HT29 tumor xenografts (1). The results from these studies suggest that anti-CA IX MAb can selectively recognize CA IX in tumor cells and preferentially localize at sites of hypoxia in tumors after intravenous administration. This chapter summarizes the data obtained with ^{125}I-MAb.

Related Resource Links:

Nucleotide and protein sequences of human carbonic anhydrase IX

Nucleotide and protein sequences of hypoxia-inducible factor-1 (HIF-1)

Nucleotide and protein sequences of von Hippel-Lindau (VHL) tumor suppressor gene

Carbonic anhydrase-targeted clinical trials in clinicaltrials.gov

Articles on carbonic anhydrase IX in Online Mendelian Inheritance in Man

Synthesis

[PubMed]

Mouse anti-human CA IX MAb (the clone information not reported) is commercially available. Li et al. labeled the antibody with no-carrier-added Na^{125}I using the Iodogen method (1). The time of labeling reaction was 10 min, and the radiochemical purity of ^{125}I-MAb was 98%. ^{125}I-MAb was stable in new-born calf serum and phosphate-buffered saline for 96 h without obvious decrease in its radiochemical purity (>90%). The radiochemical yield and specific activity were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The expression of CA IX in HT-29 tumor xenografts was analyzed with immunohistochemistry of tumor sections, which showed that CA IX was predominantly expressed in the areas adjacent to necrosis but not in the areas of necrosis (1).

Animal Studies

Rodents

[PubMed]

Biodistribution studies were performed in athymic male mice bearing HT-29 xenografts after tail vein injection of 1.295 MBq (35 μCi) ^{125}I-MAb (n = 5 mice/time point) (1). During the first 12 h, a relatively high uptake of ^{125}I-MAb was observed in the tumors as well as in the liver, kidney, spleen, lung, and intestine. At 24 h, the uptake of ^{125}I-MAb in the normal organs decreased, whereas it reached the highest level (4.9 ± 1.2% injected dose per gram tissue (ID/g)) in tumors. The uptake value was significantly higher in tumors than in normal tissues ($P < 0.05$). However, the highest tumor/muscle ratio (8.16) was observed at 12 h after injection. The uptake in the thyroid was 0.4 ± 0.1% ID/g at 12 h and increased to 1.4 ± 0.04% ID/g at 96 h after injection, indicating metabolic de-iodination of the ^{125}I-MAb.

Binding of ^{125}I-MAb with whole blood cells *in vivo* was evaluated at 24 h after injection of 3.7 MBq (100 μCi) ^{125}I-MAb (0.1 ml) into an athymic mouse *via* the tail vein (1). The mouse was euthanized and blood cells were collected and washed completely to remove the unbound ^{125}I-MAb. The radioactivity in the blood was higher than in tumors and other organs (see Figure 2 in Li et al. (1)) and this value in the fraction of blood cells was 5.5% of the blood activity at 24 h after injection, indicating that a small fraction of ^{125}I-MAb diffused into blood cells.

Planar imaging was performed at 48 h after injection of 5.55 MBq (150 μCi) ^{125}I-MAb (0.1 ml) *via* the tail vein (1). Preferential accumulation of ^{125}I-MAb in the tumors was detected. A medium accumulation of radioactivity was also detected in the thyroid. Blocking studies were performed with injection of 100-fold molar excess of unlabeled antibody at 24 h before injection of ^{125}I-MAb. The results showed that unlabeled MAb effectively blocked the accumulation of ^{125}I-MAb in the tumor. The radioactivity in the thyroid was also decreased significantly, but no explanation for the mechanism of the decrease.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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