^{125}I Labeled-mesenchymal-epithelial transition factor binding peptide

[^{125}I]-cMBP

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Chemical name:	^{125}ILabeled-mesenchymal-epithelial transition factor binding peptide	**Lys-Ser-Leu-Ser-Arg-His-Asp-His-Ile-His-His-His**
Abbreviated name:	[^{125}I]cMBP	
Synonym:		
Agent Category:	Ligand	
Target:	Mesenchymal-epithelial transition factor receptor (c-Met); hepatocyte growth factor receptor (HGFR)	
Target Category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{125}I	
Activation:	No	

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Studies:	• *In vitro* • Rodents	Structure of cMBP.

Background

[PubMed]

The hepatocyte growth factor (HGF) is the only known ligand of the mesenchymal-epithelial transition factor (c-Met) (also known as the HGF receptor) that has an important function, including cell development, proliferation, scattering, migration, and angiogenesis, all of which are necessary for the survival and repair of tissues (1). c-Met is known to mediate its activity through an intracellular tyrosine kinase (TK) that activates different signal transduction pathways, leading to initiation of the various cell processes (2). Also, deregulation of c-Met activity due to paracrine/autocrine activation, overexpression, or a mutation promotes the development of a neoplastic cell phenotype (2). Overexpression of c-Met and HGF has been associated with a poor prognosis and survival of the patient (3), suggesting that the c-Met receptor may be a suitable target for the detection of cancers at an early stage, which could help in the development of an appropriate treatment regimen to improve patient prognosis (4). c-Met is the target of several drugs under evaluation in clinical trials approved by the United States Food and Drug Administration. Investigators recently generated a monoclonal antibody (mAb) that inhibits the HGF–c-Met interaction and identified the active mAb against a surface epitope peptide as KSLSRHDHIHHH, which was designated as the c-Met binding peptide (cMBP) (5). The cMBP and its derivatives (containing a linker that was either a tri-amino acid linker, Gly-Gly-Gly (GGG), or an aliphatic carbon, 8-aminooctanoic acid (AOC)) were labeled with ^{125}I to generate ^{125}I-cMBP, 1^{25}I-cMBP-GGG, and ^{125}I-cMBP-AOC, and these agents were used to detect c-Met TK-positive tumor xenografts in mice (6). From this study the investigators concluded that although ^{125}I-cMBP was suitable for the imaging of c-Met TK-expressing tumors, the signal to background obtained from this nuclide was not very high, and the results could probably be improved by using another radionuclide and/or by modifying the linkers.

In an attempt to generate a c-Met–positive tumor imaging agent superior to ^{125}I-cMBP, ^{125}I-cMBP-GGG, and ^{125}I-cMBP-AOC, investigators conjugated a near-infrared (NIR) fluorescent dye, cyanine 5.5 (Cy5.5), to cMBP-GGG and cMBP-AOC to obtain cMBP-GGG-Cy5.5 and cMBP-AOC-Cy5.5 (4). The Cy5.5-conjugated cMBP derivatives were

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then evaluated for the NIR imaging of c-Met–positive xenograft tumors in a mouse model.

This chapter describes the *in vitro* and *in vivo* characterization of only ^{125}I-cMBP. The other c-Met imaging agents (1^{25}I-cMBP-GGG, ^{125}I-cMBP-AOC, cMBP-GGG-Cy5.5, and cMBP-AOC-Cy5.5) are described in separate MICAD chapters (7-10).

Synthesis

[PubMed]

The synthesis of cMBP was described previously (4). Briefly, the cMBP peptide was synthesized using Fmoc chemistry, with a purity of 90%. The ^{125}I labeling of cMBP was done by the chloramine T method, and the reaction was terminated with sodium bisulfite. The radiochemical purity of the labeled compound was reported to be between 90% and 95% at 24 h after the labeling as determined with instant thin-layer chromatography (ITLC). The stability of ^{125}I-cMBP in human serum was reported to be 90% at 1 h and 88% at 4 h as determined with ITLC.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using human glioblastoma U87MG cells, the 50% inhibitory concentration of cMBP was determined to be 1.5 μM (6). In a blocking study, the cells were exposed to ^{125}I-cMBP (2 pmol) in the presence of excess unlabeled cMBP (1 nmol), and a significant ($P = 0.049$) reduction in cellular binding of the radiochemical was observed compared with controls (6). Also, a scrambled peptide, containing amino acids similar to the cMBP, had no effect on the binding of ^{125}I-cMBP to the cells. Almost no ^{125}I-cMBP was internalized by the cells as determined with cell internalization studies (6).

Animal Studies

Rodents

[PubMed]

The biodistribution of ^{125}I-cMBP was studied in mice ($n = 5$ animals/time point) bearing U87MG cell xenograft tumors (6). The animals were injected with the radiochemical through the tail vein and euthanized at predetermined time points from 30 min to 24 h after the treatment. Tissues and organs of interest were subsequently removed from the animals; accumulated radioactivity was measured with a gamma counter, and the accumulated radioactivity data was presented as percent of injected dose per gram tissue (% ID/g). A high uptake of radioactivity by the pancreas was reported (47.28 ± 4.39% ID/g at 30 min, 58.37 ± 26.05% ID/g at 6 h, and 1.15 ± 1.89% ID/g at 24 h). The tumor uptake was 9.3 ± 0.78% ID/g at 30 min and decreased to 0.19 ± 0.31% ID/g by 24 h. A

high uptake of the label by the kidneys was also observed (17.18 ± 1.12% ID/g at 30 min, 7.32 ± 3.17% ID/g at 6 h, and 0.29 ± 0.40% ID/g at 24 h). All other organs showed a similar distribution of radioactivity at the different time points (for details, please see Table 1 of Kim and Park, et al. (6)). The tumor/blood ratio was reported to be 1.89 at 4 h after treatment with the radiolabel. Because of the high uptake of ^{125}I-cMBP by the pancreas, the expression of c-Met in this organ was investigated using the reverse-transcriptase polymerase chain reaction. A low expression of c-Met was observed in the pancreas, indicating that the uptake of ^{125}I-cMBP by this organ was not c-Met–mediated, and accumulation of label in this organ was non-specific. No blocking studies were reported.

From these studies, the investigators concluded that although ^{125}I-cMBP was taken up by c-Met–expressing tumors, it was not a suitable imaging agent because it generated a high background due to accumulation in other tissue and organs of the animals (6).

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.

Supplemental Information

[Disclaimer]

No information is currently available.

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