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Selective αvβ3 integrin detection using [99mTc(N)PNP43]-tagged RGDechi Peptides: synthesis and pharmacological studies

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Introduction. The development of new integrin-selective molecules suitable for therapeutic or imaging purposes are currently of interest in development of effective personalized medical platforms.
Recently, a bifunctional chimeric echistatin-RGD-peptide, RGDechi, has been reported as a potent and selective antagonist of αvβ3, in which the echistatin portion is essential for such selectivity [1]. Herein, RGDechi and three truncated derivatives functionalized with a cysteine (**1-4**) (fig 1), were synthetized and labeled with the [99mTc][Tc(N)PNP43]-synthon ([PNP43=(CH3)2P(CH2)2N(C2H4OCH3)(CH2)2P(CH3)2]) (**99mTc1-4**) as basis for selective integrin recognition.
Methods. RGDechi and derivatives were synthetized and conjugated to cysteine to allow the labelling with the [99mTc][Tc(N)PNP]-synthon [2], and characterised by HPLC. The chemical identity of 99mTc-RGDechi complexes was determined by carrier-added experiments supported by radio/UV-HPLC and LC-MS analyses. Dilution and transchelation stability studies of 99mTc-RGDechi complexes were carried out. Biological properties and binding specificity studies to the receptors were assessed on a panel of cancer cells expressing different levels of αvβ3 and αvβ5. Finally, the pharmacokinetic profiles of the more promising candidates **99mTc1** and **99mTc2** were evaluated both on healthy and melanoma-bearing mice. Their metabolism and metabolite identification are also performed.
Results. Peptides were efficiently labelled with the [99mTc][Tc(N)(PNP)]-synthon. The compounds were stable at least for 18 hours in the reaction mixture. Dilution and transchelation studies demonstrated a high stability. In vitro binding data evidenced that the [99mTc][Tc(N)(PNP)]-synthon does not affect the biological properties of the peptides. The truncate **99mTc4**, which lack of the last five C-terminal amino acid, lost the selectivity to αvβ3. Biodistribution studies conducted on **99mTc1** and **99mTc2** showed that the compounds selectively localize in tumour models expressing αvβ3 and fails to accumulate in those expressing αvβ5 receptors [3].
Conclusion. 99mTc1-2 are able to discriminate between endogenously expressed integrins αvβ3 and αvβ5 and possess favorable pharmacokinetics characterized by low liver uptake and rapid elimination from non-target tissues resulting in positive target-to-non-target ratios. Results are promising; the presented construct can be considered the starting point for the development of agents for the selective detection of αvβ3 expression by SPECT.

References

[1] Del Gatto A, Zaccaro L et al, [2006], J Med Chem; 49(11):3416-20
[2] Bolzati C, Boschi A, et al, [2002], J Am Chem Soc; 124(38):11468-79
[3] Bolzati C, Salvarese N, et al [2018], J Med Chem; 21(8):9596-9610

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