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THE FUTURE OF PSMA-TARGETING 64CU-RADIOPHARMACEUTICALS: A SHORT REVIEW OF RECENT PRECLINICAL RESEARCH

Abstract

Development and testing of prostate-specific membrane antigen (PSMA)-targeting radionuclide therapy (TRT) for prostate cancer diagnosis and endo-radiotherapy have seen great success in nuclear medicine. Among such radionuclides, 64Cu was deemed to be a good choice due to its moderate half-life (12.7 h) and high resolution. In this review we will give short view of the preclinical research projects to date and future directions of PSMA-targeting 64Cu radiopharmaceuticals for prostate cancer, with special emphasis on tailoring of PSMA-targeting 64Cu-radiopharmaceuticals which have tough pharmacokinetic properties.

I. Introduction

Prostate cancer is the sixth leading causes of cancer death in men worldwide in 2021 [1]. In fact, approximately 450,000 men in Europe have been diagnosed with prostate cancer in 2018 [2]. Investigation and application of PSMA-TRT for prostate cancer diagnosis and endo-radiotherapy have seen great success in Nuclear Medicine [3]. Copper (Cu) can react with many chelator systems due to its well-established coordination chemistry, and it can be linked to antibodies, proteins, peptides, and other biologically relevant small molecules. Radiopharmaceuticals labeled with 64Cu having longer half-life (12.7 h) can be used in delayed imaging, potentially leading to higher tumor-to-background contrast [4].

In this review we will give short view of the preclinical research projects to date and future directions of PSMA-targeting 64Cu radiopharmaceuticals for prostate cancer. Scheme of the overview is demonstrated in Figure 1.

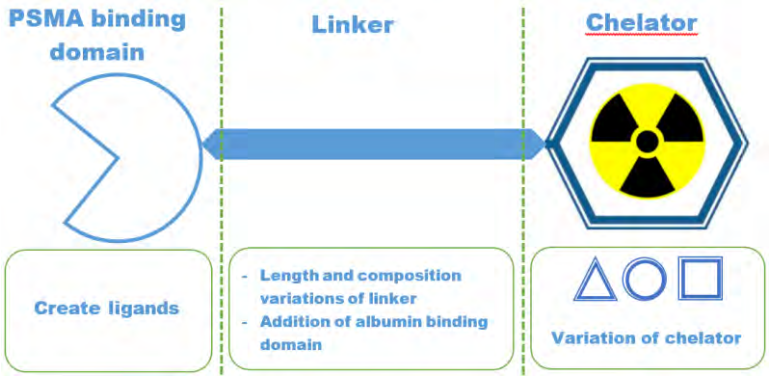

Fig. 1. Scheme of overview on preclinical research regarding the improvement of PSMA-targeting 64Cu-radiopharmaceuticals

II. PSMA-targeting Ligands

PSMA, as an antigen protein and an enzyme, has served as a target of interest for theranostic agent development. Small molecule inhibitors of PSMA gain huge interest to develop PSMA-targeting imaging agents, therapies, and/or theranostic agents, particularly for prostate cancer due to PSMA characteristics of rapid extravasation, quick diffusion in extravascular space, and efficient blood clearance [5].

Further investigation showed that the binding site enables to reach the active site through a tunnel in the PSMA extracellular domain and keep the bulky metal chelate moiety outside due to further optimization of the linker between the PSMA binding motif and the chelator. Among varieties of structures of PSMA inhibitors reported to date, the urea-based structure show the desired high binding affinity and stability [6].

III. Chelator Selection on 64Cu-labeled PSMA Ligands

The choice of a suitable chelator is very important in the design of a successful 64Cu-labeled radiopharmaceutical. 64Cu-chelate complex must have high stability in vivo because exchange of any 64Cu with endogenous metal ions in vivo, or transmetallation of 64Cu from the radiotracer to endogenous ligands in vivo will make the image quality decrease [7].

The ubiquitous chelator, NOTA, and new entrants such as, CB-TE2A, Diamsar, and NODAGA and have recently been determined to be excellent 64Cu chelators. NOTA can radiolabel with 64Cu at room temperature in 30 – 60 minutes, making it compatible with heat sensitive antibody vectors [8].

Several researches have been conducted to investigate the effect of chelating agent toward 64Cu labeled PSMA-targeting probes. Liu et al. reported 64Cu labeled radiotracer with a NOTA-conjugated precursor showed lower radioactivity accumulation in liver, and the uptake of 64Cu labeled NOTA-

conjugated radiotracer in kidneys was higher than other organs, which was different from DOTA-conjugated radiotracer. Wüstemann et al. reported that in vitro internalization rate facilitated by the CHX-A”-DTPA chelator was higher than facilitated by PSMA-617. Thus, the selection of chelator can effect on the pharmacokinetic properties of PSMA-targeting ligands [9].

IV. Linker Modification on 64Cu-labelled PSMA Ligands

There are evidences that PSMA-binding is not only caused by the PSMA-binding motif in these molecules, but also the hydrophobicity, linker lengths, and overall structure is thought to influence PSMA binding efficacy [2]. Hydrophobic linker modifications with multiple aromatic rings in the linker fragment improved the hydrophobic interaction with S1 accessory pocket suitable for PSMA-specific cell surface binding and cell internalization [10].

Santos et. al reported that the addition of spacer 4-aminomethyl- (cyclohexane)carboxylic acid in the linkers had positive effect on increased high potential affinity, high PSMA-specific uptake, fast clearance, and rapid kidney excretion [11]. In another report showed that FPyl substitution toward FBOA on EuE-k-[18F]-FBOA significantly gave positive benefits to hydrophilicity and the PSMA-binding affinity compared with its FBOA counterpart [12].

In addition, the binding of PSMA-targeting tracers to, for example, salivary gland is also thought to be due to the hydrophobic character of the linker [13]. Therefore, linker modifications on PSMA-targeting 64Cu radiopharmaceuticals for prostate cancer will significantly effects to the, biodistribution, binding affinity, and overall pharmacokinetic properties of small molecule inhibitors targeting PSMA.

V. Addition of an Albumin-binding Domain 64Cu-labelled PSMA Ligands

The investigation of modifying radiopharmaceuticals with an albumin-binding entity has recently recently gained growing interest. Müller et al. proved that the adding an albumin binding domain increased the circulation time and decreased normal tissue binding of radiolabeled compounds [2, 14]. PSMA-targeting radioligands modified with these entities showed enhanced blood circulation and, as a consequence, considerably increased accumulation in the tumor tissue, which correlated with better therapeutic outcomes in preclinical settings [15].

Albumin-binding 64Cu-based PSMA Ligand for imaging was studied by Umbricht et al. who designed albumin-binding PSMA ligands based on the glutamate−urea-binding entity and NODAGA chelator which was labeled with 64Cu (64Cu−PSMA−ALB-89).

The results demonstrated 64Cu−PSMA−ALB-89 showed increased in vivo stability as compared to outperformed previously developed PSMA ligands for 64Cu labeling. In view of nuclear medicine application, albumin-binding PSMA ligands were developed to enhance the blood circulation time and to increase tumor accumulation of radioactivity [16].

VI. Conclusion

Improving existing 64Cu PSMA-targeting ligands, investigating with various chelators, loking for suitable linker and enhancing tumor accumulation of radioactivity are points of interests in preclinical research of PSMA ligands labeled with 64Cu. The recent preclinical research projects discussed here and the ongoing preclinical research will delivery define the future of PSMA-targeting 64Cu-radiopharmaceuticals.

REFERENCES

1. R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, Cancer statistics, 2021 // CA: A Cancer Journal for Clinicians. - 2021, vol. 71, No. 1, pp. 7–33.
2. E. A. M. Ruigrok, W. M. Van Weerden, J. Nonnekens, and M. De Jong, The future of PSMA-targeted radionuclide therapy: An overview of recent preclinical research // In Pharmaceutics. – 2019, vol. 11, No. 11, pp. 560
3. J. Czernin and J. Calais, (177)Lu-PSMA617 and the vision trial: One of the greatest success stories in the history of nuclear medicine // Journal of Nuclear Medicine. - 2021, vo. 62, No. 8, pp. 1025–1026.
4. A. A. Niccoli, G. L. Cascini, C. Altini, D. Paparella, A. Notaristefano, and G. Rubini, The copper radioisotopes: a systematic review with special interest to 64Cu // Biomed Research International. - 2014; vol. 2014, pp. 786463.
5. S. Debnath, N. Zhou, M. McLaughlin, S. Rice, A. K., Pillai, G. Hao, and X. Sun, PSMA-targeting imaging and theranostic agents—current status and future perspective // International Journal of Molecular Sciences. - 2022, vol. 23, No. (3). Pp. 1158.
6. M. Benešová, M. Schäfer, U. Bauder-Wüst, A. Afshar-Oromieh, C. Kratochwil, W. Mier, U. Haberkorn, K. Kopka, and M. Eder, Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer // Journal Nuclear Medicine. - 2015, vol. 56, pp. 914–920.
7. G. R. Mirick, R. T. O'Donnell, S. J. DeNardo, S. Shen, C. F. Meares, and G. L. De Nardo, Transfer of copper from a chelated 67Cu-antibody

conjugate to ceruloplasmin in lymphoma patients. // Nuclear Medical Biology. 1999, vol. No. 26, pp. 841-845.
8. E. W. Price, and C. Orvig, Matching chelators to radiometals for radiopharmaceuticals // In Chemical Society Reviews. – 2014, vol. 43, No. 1, pp. 260–290.
9. S. Ait-Mohand, P. Fournier, V. R. Dumulon-Perreault, G. E. Kiefer, P. Jurek, C. L. Ferreira, F. O. Be´nard and B. Gue´rin, Evaluation of 64Cu-labeled bifunctional chelate-bombesin conjugates // Bioconjugate Chemistry. - 2011, vol. 22, No. 8, pp. 1729–1735.
10. H. J. Wester, and M. Schottelius, PSMA-targeted radiopharmaceuticals for imaging and therapy // Seminars in Nuclear Medicine. - 2019, vol. 49, No. 4, pp. 302–312.
11. M. Benesova, U. Bauder-Wust, M. Schafer, K. D. Klika, W. Mier, U. Haberkorn, K. Kopka, M. Eder, Linker modification strategies to control. the prostate-specific membrane antigen (PSMA)-Targeting and pharmacokinetic properties of DOTA-conjugated PSMA inhibitors // Journal Medical Chemistry. - 2016, vol. 59, No. 5, pp. 1761–1775.
12. H. T. Kuo, J. Pan, Z. Zhang, J. Lau, H. Merkens, C. Zhang N. Colp, K. S. Lin, and F. Bénard, Effects of linker modification on tumor-to-kidney contrast of 68Ga-labeled PSMA-targeted imaging probes // Molecular Pharmaceutics. - 2018, vol. 15, No. 8, pp. 3502–3511.
13. S. Robu, A. Schmidt, M. Eiber, M. Schottelius, T. Günther, B. H. Yousefi, M. Schwaiger, and H. J. Wester, Synthesis and preclinical evaluation of novel 18 F-labeled Glu-urea-Glu-based PSMA inhibitors for prostate cancer imaging: A comparison with 18 F-DCFPyl and 18 F-PSMA-1007 // European Journal of Nuclear Medicine and Molecular Imaging Research. - 2018, vol. 8, No. 1, pp. 30.
14. S. S. Huang, X. Wang, Y. Zhang, A. Doke, F. P. DiFilippo, and W. D. Heston, Improving the biodistribution of PSMA-targeting tracers with a highly negatively charged linker // Prostate. - 2014, vol. 74, No.7, pp. 702–713.
15. C. Muller, H. Struthers, C. Winiger, K. Zhernosekov, and R. Schibli, DOTA conjugate with an albumin-binding entity enables the first folic acid-targeted 177Lu-radionuclide tumor therapy in mice // Journal Nuclear Medicine. - 2013, vol. 54, No. 1, pp. 124–131.
16. R. Hasler, R. Schibli, C. A. Umbricht, M. Benes, N. P. Meulen, Van Der, and C. Mu, Design and Preclinical Evaluation of an Albumin-Binding PSMA Ligand for 64 Cu-Based PET Imaging // Molecular Pharmaceutics. – 2018, vol. 15, No. 12, pp. 5556-5564.