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Analysis of KiSS-1R Receptor Dynamics Through Kisspeptin-Derived Ligands for Breast Cancer Radiotheranostics

Currently, theranostic options for triple-negative breast cancer (TNBC) are critically lacking. As a promising strategy, the KiSS-1 receptor (KiSS-1R) has been reported for potential molecular imaging and targeted radionuclide therapy. The interaction of kisspeptins (KPs) and their receptor (KiSS-1R) is vital for the reproductive axis and has been reported to exhibit tumor-suppressing properties. Controversially, metastasis-promoting characteristics have been observed in various cancer types, e.g. TNBC. This led to the synthesis of radiolabeled metal-chelator conjugates of endogenous KP-10 (Gallium-68, Lutetium-177) and KP-54 (Gallium-68) for potential radiotheranostic application. However, these compounds suffer critically from proteolytic degradation and low tumor uptake, while the role of KiSS-1R in cancer biology remains unclear and must be investigated further.

For this purpose, DOTA- and Alexa-Fluor-488 (AF-488)-conjugated KPs were synthesized in high purities (>99%) and of (sub-)nanomolar affinities towards KiSS-1R, verified *via* functional Ca^{2+} release assays. Target expression analysis was conducted using commercial antibodies and synthesized ligands in native human and transfected cell lines expressing KiSS-1R. Conventional analysis methods failed due to rapid receptor internalization, but live cell imaging microscopy using AF-488 labeled KPs successfully visualized KiSS-1R on CHO-KiSS-1R cells.

Additionally, rapid internalization dynamics were verified through internalization assays using promising DOTA-KPs radiolabeled with Lu-177, obtained in high radiolabeling efficiency (>95%) and good radiolytic stability. Despite variable total uptake and internalization rates among different KPs, [^{177}Lu]Lu-KiSS-34-DOTA showed highest internalization of >40% of total uptake. Positron emission tomography (PET) studies with Ga-68 labeled DOTA-KPs in healthy BALB/c mice revealed [^{68}Ga]Ga-KiSS-34-DOTA as favorable due to improved solubility and *in vivo* stability compared to endogenous ligands, KP-10 and KP-54.

In summary, DOTA- and AF-488-conjugated KPs demonstrate functionality for receptor validation and interaction studies, suggesting potential in theranostic applications against TNBC. Further evaluation of KiSS-1R biology in native cancer cell lines remains essential before further translational approaches.

Research type

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