Medicine (diagnosis and treatment of cancer), Drug development

Novel targeted alpha therapy against cancer stroma

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Abstract

We have succeeded in developing a new concept radiotherapy drug (actinium-labeled fibroblast-activating protein inhibitor ([^{225}Ac]FAPI-04)) targeting cancer-associated fibroblasts in cancer stroma. When it was administered to pancreatic cancer model mice, selective accumulation in tumors and tumor growth inhibition were confirmed (Fig. 1). Cancer-associated fibroblasts create the environment necessary for the growth of cancer cells and also serve as a barrier to prevent anti-cancer agents from reaching the cancer cells. In this research, we have shown for the first time in the world that by attacking cancer with short-range radiation called alpha rays, it suppresses the growth of cancer cells.

Background & Results

Although the overall survival rate of cancer patients is improving, the 5-year relative survival rate of pancreatic cancer remains at a fairly low level of 10%, limiting the effectiveness of existing treatments. [^{225}Ac]FAPI-04, which was successfully developed in this research, can be administered to patients with intractable pancreatic cancer by targeting multiple metastatis. Furthermore, it has been reported that FAP is expressed in many cancer types other than pancreatic cancer, and in the future, the effectiveness of treatment for other cancer types will be verified. We would like to go for clinical application as a therapeutic drug against broad types of cancers.

Significance of the research and Future perspective

In recent years, treatment using alpha rays, which has a high therapeutic radiation effect, has attracted attention. General alpha-ray therapies have targeted specific molecules that appear on the surface of cancer cells. However, these molecules often differ depending on the type of cancer, and the degree of expression may differ at the site of metastasis. In addition, when performing treatment targeting cancer cells, the stroma surrounding the cancer cells may act as a barrier, and the anticancer drug may not be sufficiently distributed to the cancer cells. Especially in pancreatic cancer, since there are many components of this cancer stroma, existing treatments often fail and become intractable, and a new treatment strategy is required. Through joint research with the University of Heidelberg in Germany, we have succeeded in developing a new radiotherapy drug targeting cancer-associated fibroblasts (CAFs), which are the main constituents of cancer stroma. FAP (fibroblast activation protein) is strongly expressed in the CAFs of many cancers, while its expression in normal organs is low. In this study, an intravenous administration of a FAP inhibitor ([^{225}Ac]FAPI-04) labeled with the α-emitter actinium(^{225}Ac) showed significant tumor growth suppression in pancreatic cancer model mice. In the future, it is expected to become an epoch-making treatment for intractable cancer including pancreatic cancer.

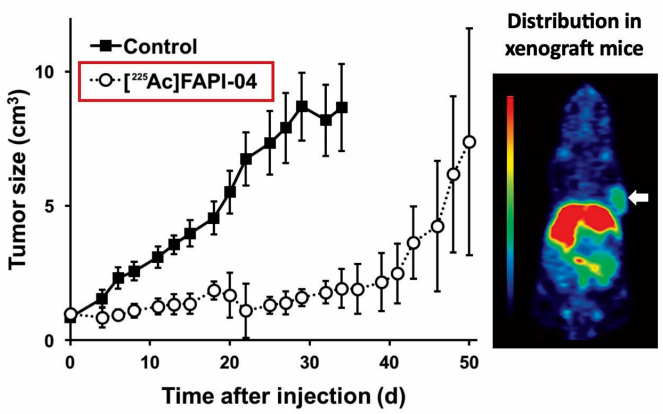

Fig.1. (a) Human pancreatic cancer cells were grafted onto mice, which were then given targeted alpha radiation therapy ([^{225}Ac]FAPI04). Compared with mice given a control treatment (black squares), mice given [^{225}Ac]FAPI04 (open circles) showed a marked decrease in tumor growth. (b) Mice were injected with diagnostic imaging probe ([^{64}Cu]FAPI-04) to enable positron emission tomography (PET) imaging. The imaging shown here indicates uptake of ^{64}Cu-FAPI-04 in the pancreatic cancer xenograft (arrow).

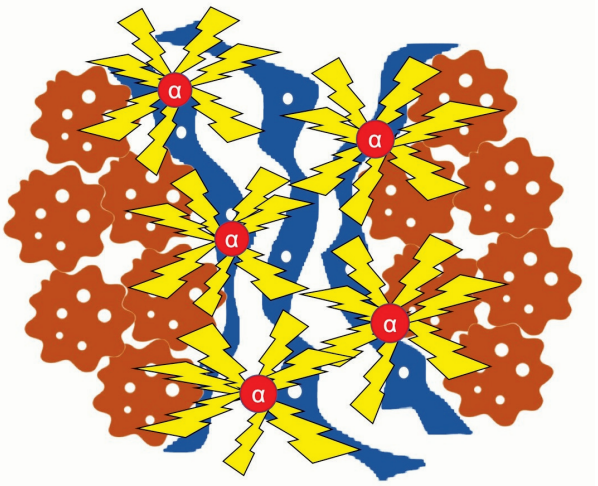

Fig. 2. Schema of cancer-associated fibroblasts (blue) and cancer cells (brown) in the cancer stroma: Therapeutic agent [^{225}Ac] FAPI-04 (red circle) irradiates alpha rays from the stroma.

Patent PCT/EP/2019/052952

Treatise Watabe, T; Liu, Y; Kaneda-Nakashima, K, et al. Theranostics Targeting Fibroblast Activation Protein in the Tumor Stroma: ^{64}Cu and ^{225}Ac-Labeled FAPI-04 in Pancreatic Cancer Xenograft Mouse Models. J Nucl Med. 2020 Apr; 61(4): 563-569. doi: 10.2967/ jnumed.119.233122.
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Keyword targeted alpha therapy, pancreatic cancer, cancer stroma, actinium