Mechanistic Study Comparing Radiolabeled and Fluorescent Glucose Uptakes by Cancer Cells for *In Vivo* Bioimaging

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Abstract: This study focuses on the differences in quantitative cellular uptakes between glucose analogs labeled with either fluorescence or radioactive isotopes, and their influences on tumor bioimaging via positron emission tomography (PET) and fluorescence imaging. The type of imaging probe drastically affected the localization and the kinetics of cellular uptake by various cancer cells in different conditions, which are critical parameters for tumor bioimaging.
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1. Introduction

Although both PET and fluorescence imaging based on glucose analogs have been used to study tumors *in vivo*, there have been some inconsistencies between them due to the lack of the mechanistic understandings underlying the uptake of the glucose-based probes. In this study, quantitative analyses of the localization and kinetics of glucose uptake by cancer cells when labeled with either radioactive isotopes or fluorescent molecules were performed. Understanding the mechanisms underlying this uptake phenomena will lead to a more accurate tumor bioimaging.

2. Methods

2-1. Fluorescence evaluation of glucose uptake and *in vivo* fluorescence bioimaging

After incubating starved ovarian cancer (SKOV3) or colorectal cancer (DLD1) cells with 100nM fluorescently-labelled 2-deoxyglucosone (2-DG-750) for 1 hour at different culture conditions (adhesive/non-adhesive states), the cells were separated into different components via centrifugation (10000g), and the fluorescence signals were measured using a plate reader (TECAN Spark 20M). Also, BALB/c mice grafted with each type of tumors were bioimaged with the intravenous injection of 10nmol 2-DG-750 using the *in vivo* imaging system (SHIMAZU Clairvivo-OPT plus).

2-2. Radioactivity evaluation of glucose uptake and PET imaging

Same as that in Section 2-1, but using fluorodeoxyglucose (FDG) (0.1MBq for cells and 10MBq for mice). The radioactivity was measured by gamma counter (COBRA Quantum 5003) and bioimaged via Clairvivo-PET (SHIMAZU).

3. Results and Discussions

The uptakes and the localizations of fluorescent and radiolabeled probes are summarized in Table 1. Certain combinations of probe type, cell type, and culture conditions induced better uptake of each type of probe. SKOV3 cells more efficiently absorbed fluorescent probes compared to radiolabeled probes and therefore were better imaged with fluorescence imaging than PET. The opposite was true for DLD1 cells, where they absorbed FDG much more efficiently. It is hypothesized that the difference was due to the molecular structures of 2-DG preventing complete internalization.

Table 1. Summary of normalized cellular uptakes of fluorescent and radiolabeled glucose analogs in the adhesive states.

	Total Uptake		Membrane-Bound	Cytosol	Organelles/Others
SKOV3 with 2-DG-750	4.4%	→	2.1%	2.1%	0.2%
SKOV3 with FDG	0.6%	→	0.2%	0.3%	<0.1%
DLD1 with 2-DG-750	3.3%	→	1.5%	1.7%	0.1%
DLD1 with FDG	7.6%	→	1.2%	6.2%	0.3%