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EDITORIAL

FDG Accumulation in Tumor Tissue

GLYCOLYSIS AND CANCER CELLS

Enhanced glycolytic rate of cancer cells was first demonstrated more than a half century ago. Originally, decreased respiration and both aerobic and anerobic increased glycolysis were considered to form the most important and specific characteristics of cancer cells (*1*). Considerable efforts have been devoted to elucidate the role of increased glycolysis in malignant cell proliferation. Studies using Morris hepatoma cell lines revealed that the degree of increased glycolysis and the activity of key enzymes in glycolysis such as hexokinase correlated with the rate of tumor growth (*2*). However, none have been conclusive to determine whether a high glycolytic rate is es-

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sential for cancer cells or is a consequence of other metabolic processes. It was later found that many, but not all, tumor cells and proliferating normal cells exhibited high rates of aerobic glycolysis and that increased glycolysis is neither an essential property of proliferating cells nor a distinct borderline of malignancy from benignancy.

FLUORODEOXYGLUCOSE AND PET IN ONCOLOGY

Inhibition of increased glycolysis of cancer cells by structural analogs of glucose was one concept of cancer chemotherapy. 2-Deoxy-D-glucose (2DG), a substrate for hexokinase, has been proven to be the most promising antimetabolite of many glucose analogs investigated to inhibit glycolysis. Quantitative autoradiographic methods of ^{14}C-2DG have been developed to measure local cerebral glucose utilization (*3*). FDG has been synthesized as a positron labeled analog of 2DG and used for brain and myocardial metabolic studies. FDG was also used in experimental tumor detection studies (*4*), and initial clinical studies of brain tumors (*5*) and metastatic liver tumors (*6*) have shown successful results for this new tumor imaging principle: tumor metabolic imaging.

In the last decade, FDG has been used in nuclear medicine oncology to a greater extent, namely diagnosing various tumors. As expected from the history of cancer biochemistry, most of the malignant tumors showed high FDG uptake, but there have been cases of low FDG uptake in tumors.

In glioma studies, the degree of glucose utilization rate had a positive correlation to the pathologic grade of the glioma (*5*) and to patient survival time (*7*). In the meningioma study, the degree of glucose utilization had an inverse correlation to tumor doubling time (*8*). However, some authors could not observe the correlation between the rate of glucose utilization in the tumor and the grade of glioma (*9*).

Recently, new cell biological techniques of flow cytometry have been introduced, where DNA content of cells in suspension can be analyzed and the percentage of proliferating cells is calculated from the DNA histogram. The level of FDG accumulation in head and neck tumors showed a good correlation to the percentage of proliferative cells in the biopsied sample, but no correlation to the histologic grade (*10*). Similar observation has also been reported in malignant lymphoma (*11*). Another technique of immunohistochemical labeling with the antibody Ki-67 also provides a rough estimation of the growth fraction of the tumor. The Ki-67 labeling index in head and neck tumor showed a good correlation to FDG uptake of the tumor (*12*).

However, in a FDG and flow cytometry study of head and neck tumors, tumor uptake of FDG was separated into two groups. High FDG uptake tumors showed better correlation to the proliferation index by flow cytometry than the low FDG uptake tumors. When the two groups were put together, there was no linear correlation between FDG uptake and proliferation index (*13*).

IN WHICH FRACTION OF TUMOR CELLS IS FDG CONCENTRATED?

How does FDG uptake relate to the proliferation of tumors? In a culture study, Higashi et al. (*14*) demonstrated that FDG uptake did not correlate with the proliferative activity of human adenocarcinoma cells, but strongly related to the number of viable tumor cells. During the growth stages of lag, exponential and plateau phases, they found a discrepancy between the proliferative rates, assessed by both DNA flow cytometry and ^{3}H-thymidine incorporation, and ^{3}H-FDG uptake. Total ^{3}H-FDG uptake showed an increase parallel to the number of viable cells but ^{3}H-thymidine uptake underestimated the number of viable cells.

The innovative work of Higashi et al. has given a direct answer to the issue of tumor FDG uptake that has been questioned in clinical PET study for many years. Cultural studies give us a great advantage to see characteristics of tumor cells. It is not necessary to consider the effect of blood flow. Culture conditions such as medium, CO_2, pH, etc. can be under strict control. Because tumor cells have no interaction to the host tissue, cultural studies are the pure growth models and have an indispensable value. Higashi et al. evaluated the growth fraction by DNA flow cytometry and the S-phase fraction by ^{3}H-thymidine. Both fractions were highest in the lag phase and decreased to the lowest in the plateau phase. The uptake pattern was different from FDG uptake, where FDG uptake has shown to be a marker of viable cells fraction. This is a clear and important answer. Extrapolation to clinical PET study suggested that the degree of the correlation of proliferation index and FDG uptake of the tumor may be determined by the degree of the overlap of the two fraction of tumor cells proliferating and viable cells.

EVALUATION OF TUMOR TREATMENT RESPONSE IN VIVO

Comparison of FDG and ^{3}H-thymidine has been reported in radiotherapy evaluation studies using rat hepatoma in vivo (*15*). Quantitative histopathologic change and ^{11}C-methionine uptake have been studied in the same experimental system (*16*). From these two studies, we can reconstitute the correlation of FDG uptake, ^{3}H-thymidine uptake and viable tissue (Fig. 1). Tumor FDG uptake in vivo showed a linear correlation to the percentage of viable tissue after radiotherapy and was clearly distinguished from ^{3}H-thymidine uptake.

However, after radiotherapy of recurrent colorectal tumors, residual high FDG uptake by PET did not correlate with the viability of tumors (*17*). Secondary inflammatory reaction after radiotherapy has been suggested to induce false positive FDG

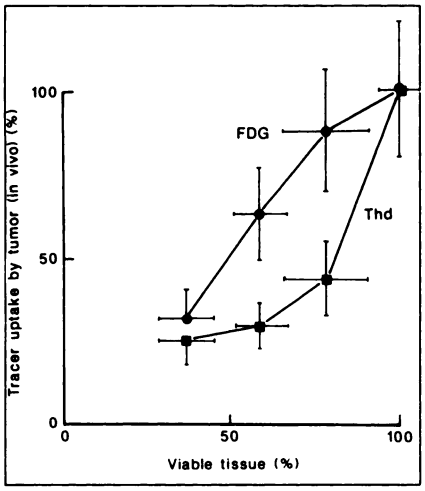

FIGURE 1. FDG uptake (●) and ^{3}H-Thd uptake (■) by AH109A tumor in vivo after 20 Gy irradiation were plotted against quantitative histopathologic data of viable tissue. The control data were assigned at 100%, and each point (1 day, 3 days, and 6 days after irradiation) was plotted as a relative value. The original tracer uptake data were expressed as radioactivity calibrated by injected dose, tissue weight and body weight. Reconstituted from the data in (*15*) and (*16*).

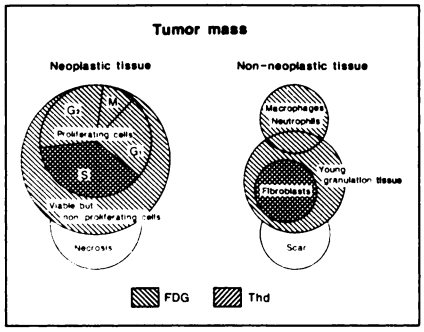

FIGURE 2. FDG and thymidine accumulation in various cellular elements in a tumor.

uptake in the treated tumor. FDG uptake by the non-neoplastic elements in a tumor has been evaluated with a autoradiography technique (*18*). In mouse mammary carcinoma, a syngeneic host, high FDG uptake was observed in macrophages infiltrating the marginal areas of necrosis as well as the newly forming granulation tissue around the tumor and the tumor cells. This study suggested that one should consider not only the tumor cells proper but also the non-neoplastic cellular elements, especially after treatment.

CONCLUSION

Components of tumor tissue can be classified as neoplastic and non-neoplastic tissues (Fig. 2). The former is divided into viable cells which are labeled with FDG and necrosis. Proliferating cells are a subset of viable cells. S-phase cells which are labeled with thymidine are a subset of proliferating cells. In the latter, proliferating fibroblasts were labeled with ^{3}H-thymidine. Both macrophages and young granulation tissue may concentrate FDG, but not the scar. Metabolic imaging of FDG-PET studies provides useful information in tumor diagnosis. Since in vivo tumors are composed of both neoplastic and non-neoplastic cell elements, studies on the contribution of both neoplastic and non-neoplastic cells to FDG uptake of tumor should be important.

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