Thyroid status is a key modulator of tumor response to irradiation : determination of the underlying metabolic causes

B. F. Jordan[1], N. Christian[2], N. Crokart[1], V. Gregoire[2], O. Feron[3], and B. Gallez[1]

[1]Biomedical Magnetic Resonance Unit, Université catholique de Louvain, Brussels, Belgium, [2]Molecular Imaging and Experimental Radiotherapy Unit, Université catholique de Louvain, Brussels, Belgium, [3]Pharmacotherapy Unit, Université catholique de Louvain, Brussels, Belgium

Introduction:

In normal tissues, thyroid hormones (THs) play a major role in the metabolic activity and oxygen consumption of cells (1). Because the rate of oxygen consumption is a key factor in the response of tumors to irradiation, we hypothesized that THs may also affect the metabolic activity of tumor cells, and, hence, modulate the response to cytotoxic treatments.

Materials and Methods:

We measured the influence of thyroid status on the tumor micro-environment in a transplantable tumor model (TLT). Hypothyroidism and hyperthyroidism were generated in mice by chronic treatment with propyl thiouracil (PTU) and L-thyroxine (2). Local pO_2 was measured using electron paramagnetic resonance (EPR) (3). The rate of oxygen consumption by tumor cells from hypo- and hyperthyroid mice was measured using high frequency EPR (3).

Results:

Thyroid status significantly modified tumor pO_2 , with mean values of 11.5 ± 3.2 mmHg vs 2.3 ± 0.6 mmHg for treated and control mice respectively (Fig.1). Mechanistically, this was the result of the profound changes in oxygen consumption rates: tumor cells from hypothyroid mice consumed oxygen slower than tumor cells from euthyroid mice, which in turn consumed oxygen slower than cells from hyperthyroid mice (The mean slopes were -0.86±0.16 µM/min, -1.41±0.11 µM/min, and -1.91 ±0.15 µM/min, respectively, Fig.2). Thyroid status did not affect tumor growth in this tumor model. However, thyroid status was associated with a significant change in tumor radiosensitivity as the regrowth delay was increased by a factor of 1.6 in hypothyroid mice compared to euthyroid mice (Fig.3), an observation that is consistent with the tumor oxygenation status.

Discussion:

We demonstrate here that a transient induction in hypothyroidism during the course of a radiotherapeutic regimen could be of significant benefit for cancer patients. Importantly, we also suggest that correction of a hyperthyroid state would be of crucial importance before starting radiation therapy. Finally, we provide a rationale for these observations by showing the involvement of tumor metabolic parameters, such as oxygen consumption rate. In conclusion, this study provides unique insights into the impact of modulating tumor oxygen consumption and could have major implications in the management of cancer patients with thyroid disorders.

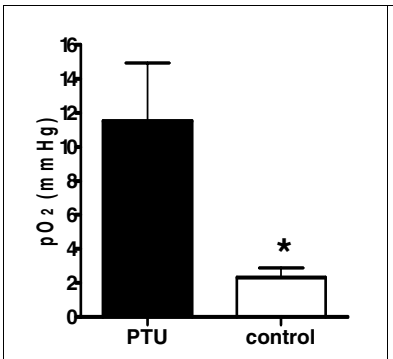

Fig.1

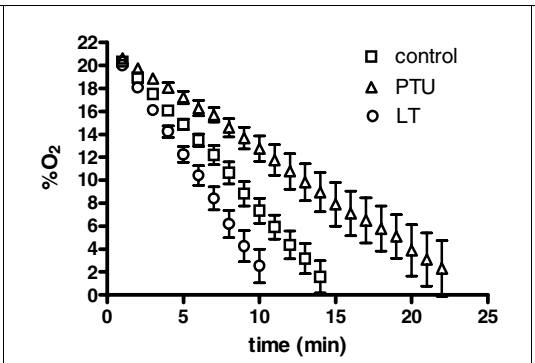

Fig.2

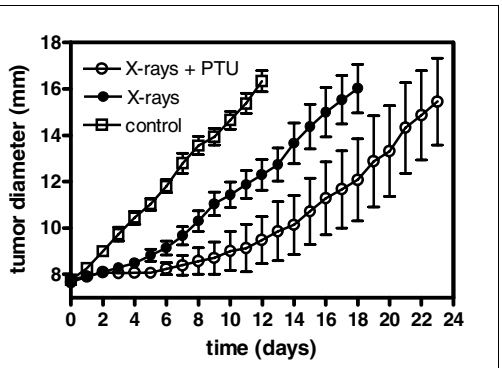

Fig.3

Fig.1 Mean TLT tumor pO_2 in control (n=3) and PTU-treated mice (n=6) as measured by EPR oximetry.

Fig.2 Effect of PTU (n=6) and L-Thyroxin (n=9) vs control (n=11) on TLT tumor cell oxygen consumption rate.

Fig.3 Effect of hypothyroidism (PTU treated mice) on TLT tumor regrowth. Mice were untreated (control); treated with 10 Gy of X-rays (X-rays), or treated with PTU in drinking water for 3 weeks before irradiation with 10 Gy of X-rays. Each point represents the mean tumor diameter ± sem (n=8/group).

References:

(1) Gredilla R, Lopez Torres M, Portero-Otin M, Pamplona R, Barja G. Mol Cell Biochem 2001;221:41-8.
(2) Theodossiou C, Skrepnik N, Robert EG, et al. Cancer 1999; 86:1596-601.
(3) Gallez B, Baudelet C, Jordan BF. NMR Biomed 2004;17:240-62.