DEUTERIUM HAS A KEY ROLE IN TUMOUR DEVELOPMENT – A NEW SUBMOLECULAR REGULATORY SYSTEM

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Introduction

The deuterium/hydrogen (D/H) mass ratio is the largest among stable isotopes of the same element, causing differences in the physical and chemical behaviour between the two hydrogen isotopes. Although the concentration of D is more than 10 mM (150 ppm) in living organisms, the potential role of D was not investigated for six decades.

Aim

In order to reveal the possible role of naturally occurring D in living organisms, the consequence of the shortage of D was investigated in different biological systems.

Material and Methods

To reduce the D-concentration in different biological systems below the natural level we used deuterium-depleted water (DDW) in a range of 25 ppm and 135 ppm (D has a natural abundance in Earth’s oceans of about one atom in 6,420 of hydrogen, ~156.25 ppm on an atom basis).

Results

The experiments with DDW revealed that due to D-depletion the cell growth of various cell lines (PC-3, MDA, HT-29, M14) were inhibited in vitro. Deuterium depletion also inhibited the expression of genes (c-myc, c-Hras, Bcl-2, K-Ras, Gja1) having key role in tumor development. During the administration of DDW (85 ppm) to prostate cancer patients in a phase II, double blind clinical trial, the net decrease in the prostate volume was three times higher in the treated group (163 cm³ vs. 94 cm³, p = 0.019). During the extended follow-up of the 44 patients, in the first year [from the date of entering the trial], 2 patients (9.1%) died in the treated group and 9 patients (40.9%) in the placebo group (significantly lower mortality in the treated group. Fisher’s Exact Test, p = 0.034).

Conclusion

We suggest that cells are able to regulate D/H ratio and its changes can trigger molecular mechanisms having key role in cell cycle regulation. The decrease in D-concentration can intervene into a hitherto unknown submolecular regulatory system which can serve as a novel target in anticancer drug development. This approach to D-depletion of water and other molecules has broad potential to enhance the effectiveness of the currently available oncotherapies and results in innovative new medicines.

The effect of D-concentration on the growth rate of different cancer cell lines in vitro

In order to get more insight into the mechanism of action of D-depletion, the inhibitory effect was studied using the real-time, label-free measurement of the xCELLigence RTCA system (Roche Applied Sciences). The system measures electrical impedance changes across interdigitated micro-electrodes integrated on the bottom of tissue culture plates. A dimensionless parameter called sCell Index (sCI) is able to describe the viability of the cells and the cell count.

Phase II clinical trial

A double blind, four month long, randomized human phase II clinical trial was conducted on 44 prostate cancer patients. The daily water intake was replaced with DDW (85 ppm) D in 22 patients (treated group), while the other 22 patients (placebo group) took normal water. Treatment was carried out in addition to the conventional forms of treatments.

Clinical evidences

Both the net decrease in the prostate volume and the changes in PSA were significantly higher in those prostate cancer patients who underwent DDW-treatment in addition to the conventional therapies. The distribution of the best response (PB) to treatments differed significantly after four-month long DDW: placebo treatment in the test groups (7 subjects vs. 1 subject). All these results explain the impressive difference in the death rate in the two groups (2.6% treated vs. placebo group) within the first year (p = 0.034).

Conclusion

We suggest that the naturally occurring D plays a key role in cell-cycle regulation. Cells are able to regulate D/H ratio, and its changes can intervene into a hitherto unknown submolecular regulatory system (SMRS) in the signal transduction pathway. Cancer cells proved to be extremely sensitive to D-depletion, while non-cancer cells are able tolerate the decreasing D-concentration. D-depletion also inhibited the expression of the oncoproteins in the different organs of cancerous exposed mice. This approach to D-depletion of water and other molecules has broad potential to enhance the effectiveness of the currently available oncotherapies and results in innovative new medicines.

References