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Real-time metabolism with hyperpolarized NMR

Probing treatment response of glutaminolytic prostate cancer cells with hyperpolarized [5-¹³C]glutamine

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Non-invasive study of metabolism

A trick called “hyperpolarization” allows real-time NMR detection of reaction cascades in living cells. Systems function and responses to genetic, nutritional or toxic intervention can be directly visualized by fast and easy-to-interpret *in vivo* assays.

Hyperpolarized magnetic resonance spectroscopy (Hyperpolarized MRS) of ¹³C-labeled compounds can be used to estimate rates for specific enzymatic reactions *in vitro* and *in vivo*. Furthermore, for some hyperpolarized ¹³C-labeled substrates there is sufficient signal for the spatial distribution of both the substrate and its metabolites to be imaged *in vivo*.

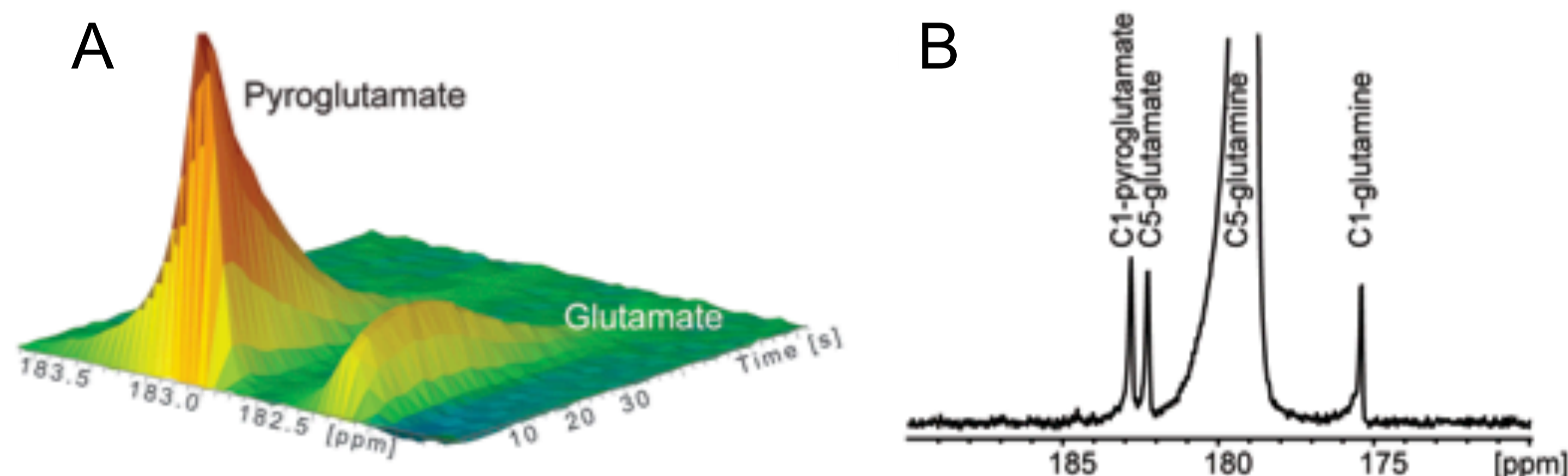
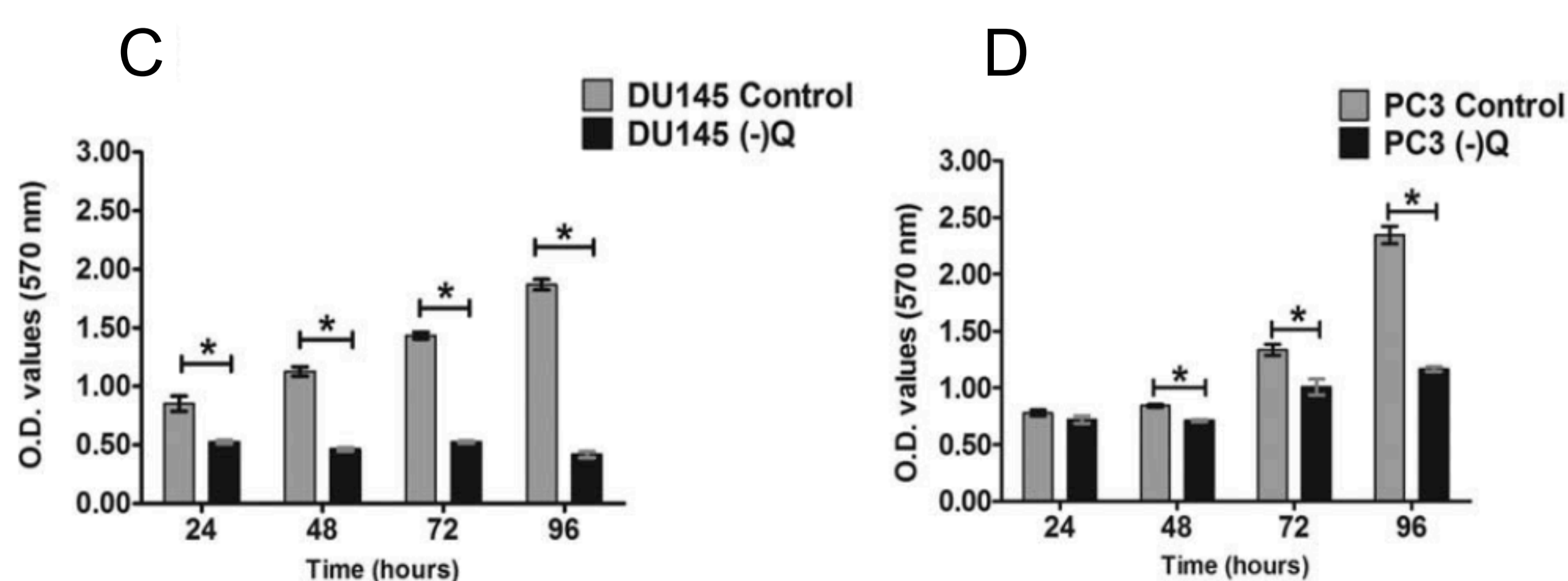


Fig. A Real time glutamine metabolism in DU145 a human prostate cancer cell line using [5-¹³C]glutamine. B) Single spectrum after 20 s from the dynamic series shown in A).

The real time conversion of glutamine to glutamate is easily followed.

Glutaminolytic phenotypes

For some cancer cells, activation of the PI3K signaling pathway is instrumental in causing increased levels of glucose. In other cancer cells, the same signaling pathway leads to an inefficient glutamine metabolism rather than excess glucose metabolism.



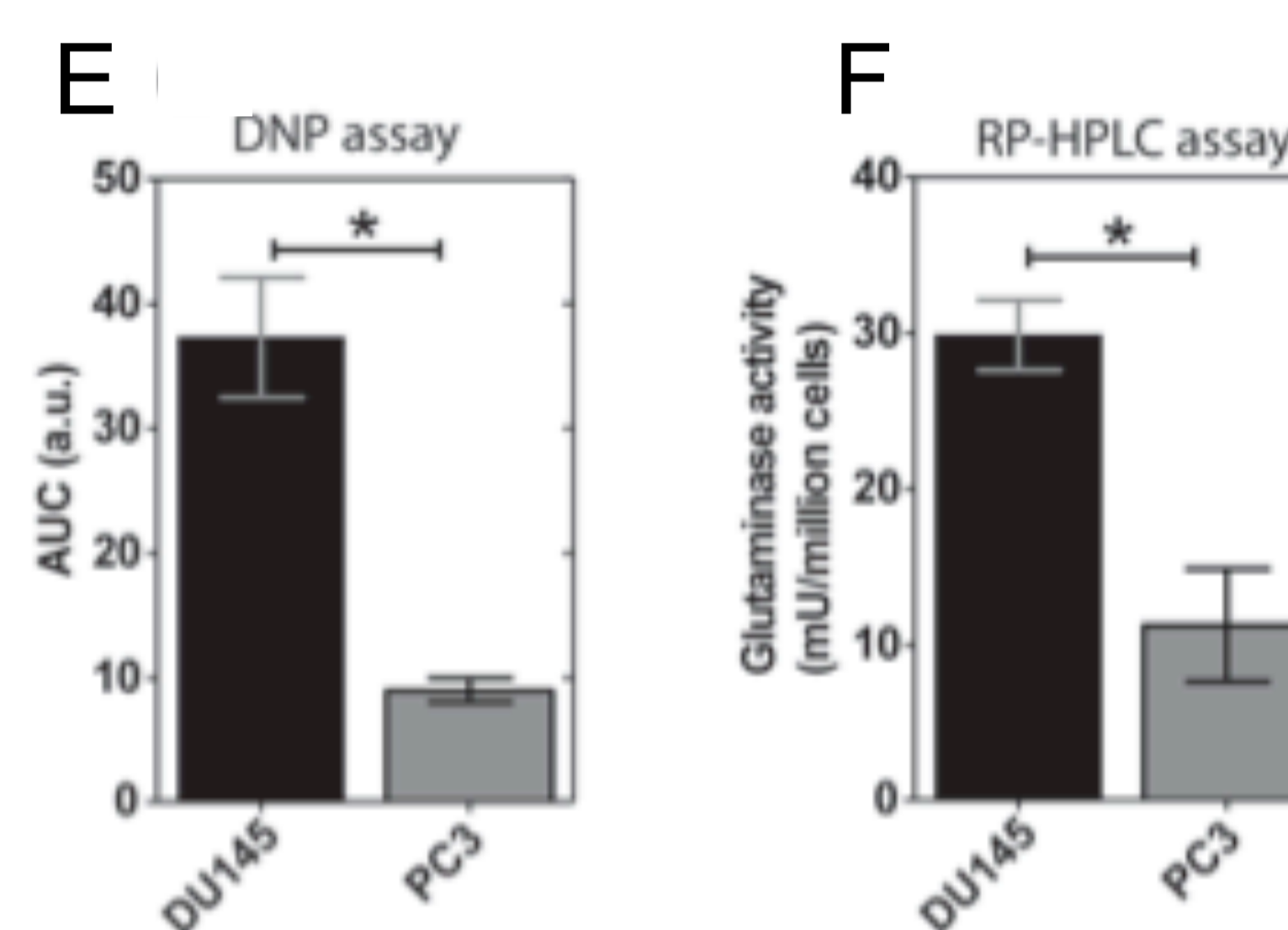
DU145 cells are more glutaminolytic than the PC3 cells. This is shown by the MTT assay under growth conditions with and without glutamine (Fig. C and D).

References:

- 1) Rashid et al. Radiat Oncol 2011;6:144–156.
- 2) Gill et al. Prostate 2007;67:1641-1653.
- 3) This work is published: Canape et al. MRM 2015; 73:2296–2305.

Metabolic response to glutaminolysis

The proliferative dependency on glutamine availability supposedly correlates to activated oncogenes that influence glutamine catabolism.

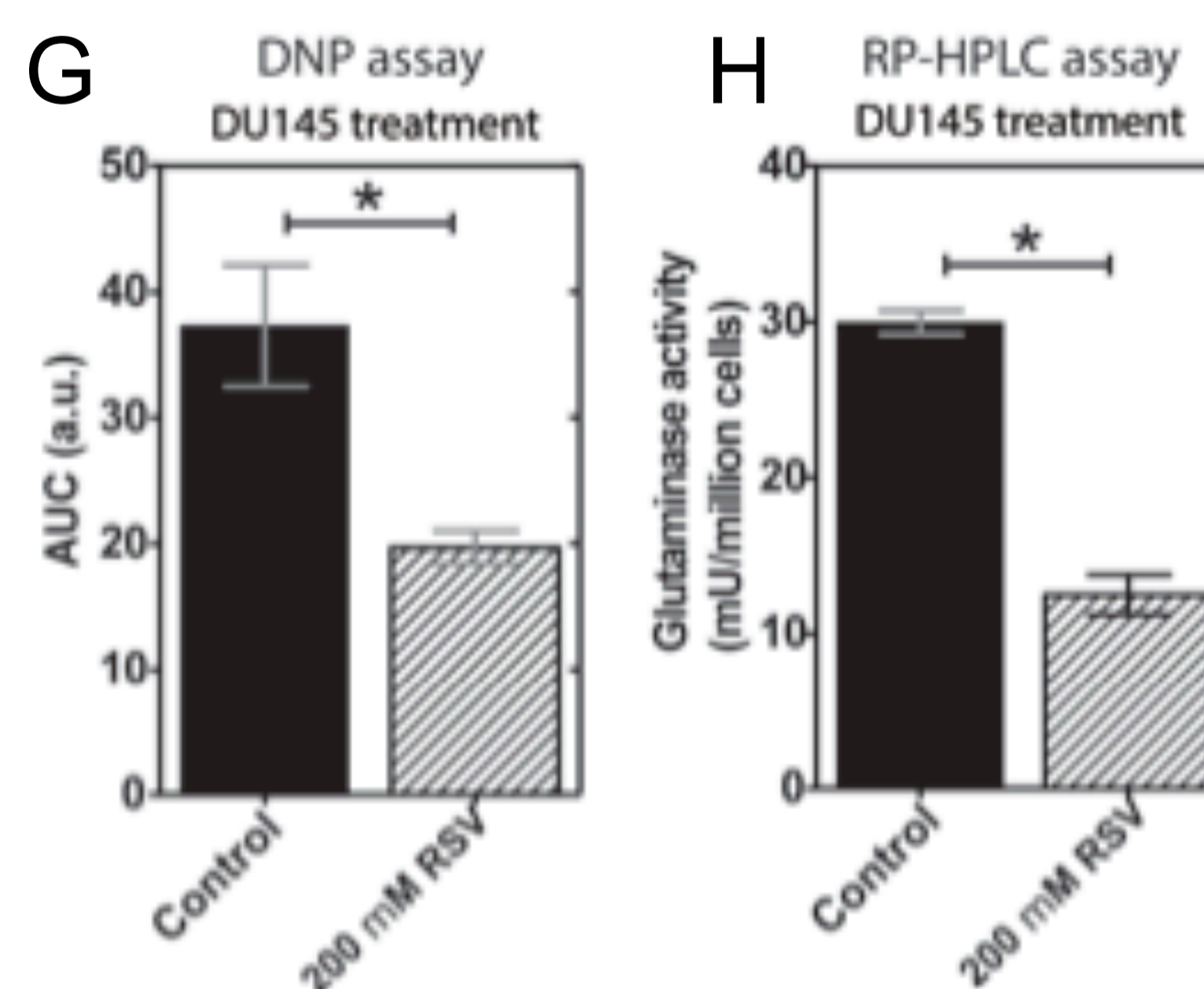


It was evaluated, if hyperpolarized [5-¹³C]glutamine metabolism is a possible biomarker for the glutamine dependence in prostate cancer cells.

Area under the curves of hyperpolarized [5-¹³C]glutamate is found to be 4 times higher in the by using hyperpolarized [5-¹³C]glutamine as a non-invasive probe (Fig. C). Invasive RP-HPLC assay determining the glutaminase activity shows similar result (Fig D).

Metabolic response to drug treatment

Resveratrol and sulforaphane are two examples of natural compounds that have attracted attention for their selective toxicity to cancer cells and their ability to sensitize cancer cells to other therapies^{1,2}.



Resveratrol and sulphoraphane have been shown to act by means of the PI3K signaling pathway. Treatment response to resveratrol is shown in Fig. E and F using hyperpolarization and RP-HPLC measurements respectively.

Glutamine metabolism is decreased after drug treatment as determined by both assays.

Hyperpolarized [5-¹³C]glutamine metabolism thus is a promising biomarker for the non-invasive detection of tumor response to treatment, as it directly monitors one of the hallmarks in cancer metabolism - glutaminolysis - in living cells³.