Characterization of the tumor micro-environment after administration of glucocorticoids to understand their radiosensitization effect

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Introduction:

We hypothesized that glucocorticoids may enhance tumor radiosensitivity by increasing tumor oxygenation (pO_2) via inhibition of mitochondrial respiration as we previously described such effect with nonsteroidal anti-inflammatory drugs (1). This phenomenon is in accordance with the literature and is a direct effect of glucocorticoids on cytochrome c-oxidase (2-3).

Materials and Methods:

Two types of tumors were used in this study: FSaII and TLT tumors implanted in the gastrocnemius muscle of mice. Glucocorticoids were administered by IP injection. Hydrocortisone at a dose of 7.7 mg/kg, Dexamethasone at a dose of 5 mg/kg and Prednisolone at a dose of 75 mg/kg.

Oxygen pressure (measured by EPR oximetry with a 1.2 GHz spectrometer) and blood flow (monitored with DCE MRI at 4.7 Tesla) were monitored in the tumor before and after treatment.Oxygen consumption by tumor cells was measured ex-vivo using X-Band EPR spectroscopy. To assessed the potential benefit of the oxygen effect, tumors were irradiated to 25 Gy using an RX irradiator . The effect of hydrocortisone on FSaII cells was evaluated by a clonogenic cell survival assay.

Results:

All glucocorticoids tested induced an increase in tumor pO_2. Fig 1 shows the increase in tumor pO2 after hydrocortisone administration in two tumor models. DCE MRI studies carried out after hydrocortisone indicated that the increase in tumor oxygenation is not due to an increase in tumor perfusion. At the time of maximal reoxygenation, we found that the percentage of perfused tumor area (region were the contrast agent could flow characterized by significant values for Ktrans and/or vp) was decreased (Fig 2). These results are in accordance with other perfusion measurements performed with the patent blue technique. The treatment by hydrococrtisone induced a significant decrease in oxygen consumption by tumor cells (Fig 3). Finally, we observed a longer regrowth delay when irradiation was performed 30 min after injection of hydrocortisone compared with radiation alone (table). This effect is not due to a direct radiosensitization effect of hydrocortisone on the cell as evaluated by survival clonogenic assay (Fig 4).

Discussion

Our results show that glucocorticoids induce an increase in tumor oxygenation. Since this increase was not related to an increase in blood supply, it is likely that an effect on oxygen consumption is involved. At the time of increase in pO2, there was an increase in the regrowth delay after irradiation, suggesting that the radiosensitization is likely due to an oxygen effect.

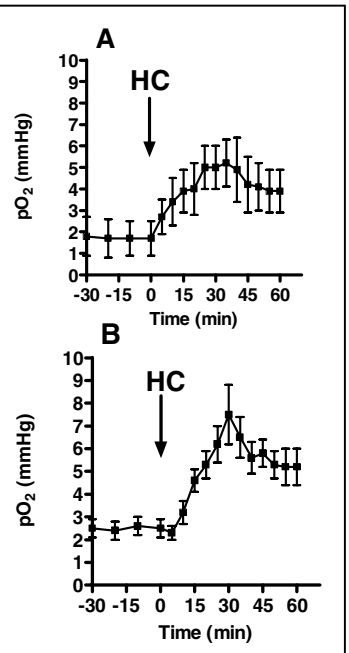

Figure 1: pO_2 (mmHg) (Mean +/- SEM) measured by EPR oximetry before and after hydrocortisone (HC) treatment. n=5/group
A : TLT tumors
B : FSaII tumors

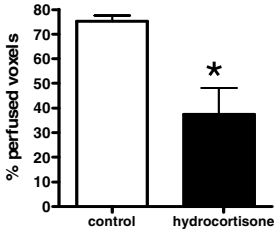

Figure 2: Perfusion of control versus HC treated FSaII group.
A : Percentage of perfused voxels measured by DCE-MRI (n=6/group) Statistic analysis : student t-test $p<0.05$

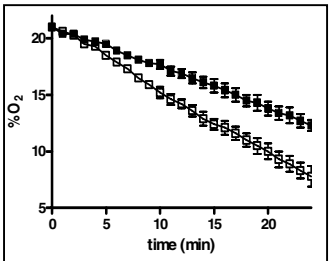

Figure 3: Oxygen consumption measured ex-vivo by X-band EPR. n=4/group
□ = control ■ = hydrocortisone

Groups	Time to 12 mm (days)	Regrowth delay (days)
saline	3.83 ± 0.45	
hydrocortisone	4.00 ± 0.13	
saline + 25 Gy	8.66 ± 0.88	4.84 ± 0.95 ***
hydrocortisone + 25 Gy	**12.46 ± 0.51**	**8.46 ± 0.53** ***

Table : Regrowth delay of 4 groups of FSaII tumor groups.
Saline (n=7), HC (n=7), saline + 25 Gy (n=6) and HC + 25 Gy (n=5)
Statistical analysis : One way Anova Tukey's Multiple Comparison test
(*** $p<0.001$).

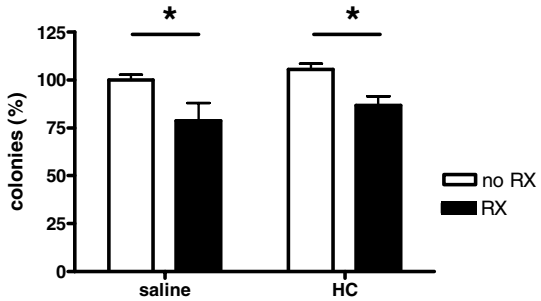

Fig 4 : Effect of hydrocortisone (HC) on FSaII tumor cells evaluated by clonogenic cell survival assay. 2 Gy irradiation induced a decrease in the number of colonies ($p<0.05$, 2 way anova) which was not enhanced by hydrocortisone. n=4/group.

References:

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