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# Glucocorticoid-induced therapy resistance in solid tumors


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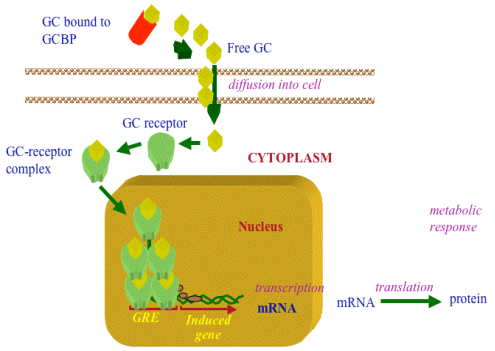
## 1 Introduction

Cortisone drugs are steroid hormones in the glucocorticoid (GC) family. These medicaments are not only used in liver transplantation to prevent graft rejection, but also widely in cancer treatment since GCs cause programmed cell death, or apoptosis, in transformed cells of the hematopoietic system. In addition, the drugs lessen side effects such as nausea and vomiting and protect against edema formation as well as allergies to specific chemotherapeutic agents. At the same time, GCs can decrease edema in normal body tissues affected by the tumor. These facts have provided a rationale for the use of steroid hormones to lessen the side effects of chemotherapy for hematologic and non-hematologic malignancies. Some reports have been associated co-medication of GCs with an increased risk resistance towards cytotoxic therapy in some cell lines of solid tumors. Our aim in this project is to evaluate whether this happens occasionally or commonly in carcinomas.

## Experimental design

Clinically used GCs derivatives were combined with various cytotoxic treatments and the effects of apoptosis and viability of carcinomas were evaluated using more than 150 fresh surgical specimens, xenografts on mice and established cell lines of a representative spectrum of human solid malignant tumors.

## 2 Glucocorticoids induce gene expression

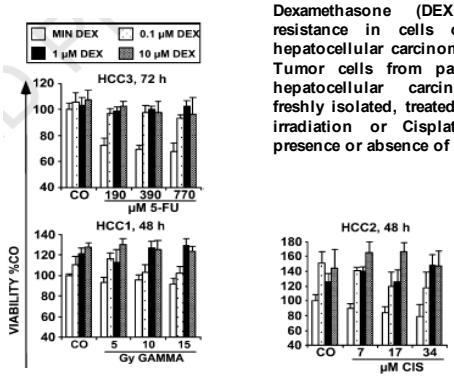



Model of glucocorticoid (GC) action. GCs are transported into the cytoplasm when bound to corticosteroid binding protein (GCBP) or by diffusion. There, they are bound to the GC-receptor and transferred into the nucleus activating gene expression.

## 3 GCs induce resistance in 95% of all examined tumors

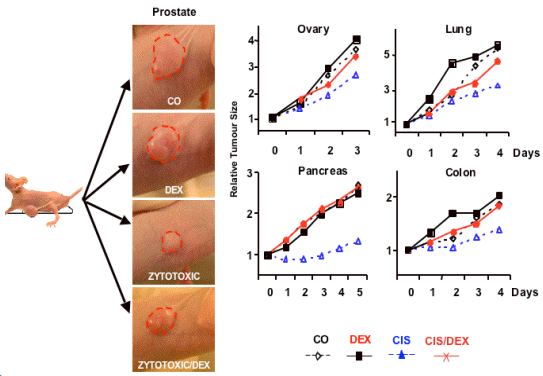
| origin of tumour/ tumour type | DEX-mediated resistance *ex vivo* (surgical specimen) | *in vitro* (established cell lines) | *in vivo* (xenografts) |
|---|---|---|---|
| bladder | n.d. | 5[a]/5[b] | n.d. |
| brain | n.d. | 5/5 | n.d. |
| breast | 2[a]/2[b] | 5/5 | n.d. |
| cervix | n.d. | 5/5 | n.d. |
| colorectal | 14/18 | 5/5 | 1[a]/1[b] |
| hepatocellular | 4/4 | 3/3 | n.d. |
| kidney | n.d. | 4/4 | n.d. |
| lung | 11/15 | n.d. | 1/1 |
| neuroblastoma | n.d. | 4/5 | n.d. |
| melanoma | n.d | 3/3 | n.d. |
| osteosarcoma | n.d. | 4/4 | n.d. |
| ovary | 7/9 | 5/5 | 1/1 |
| pancreas | 14/16 | 9/9 | 1/1 |
| prostate | 21/21 | 3/3 | 1/1 |
| Total | 75/87 (86%) | 60/61 (98%) | 5/5 (100%) |

## 4 The effect of DEX on hepatocellular carcinomas




Dexamethasone (DEX) induces resistance in cells of resected hepatocellular carcinomas *ex vivo*. Tumor cells from patients with hepatocellular carcinoma were freshly isolated, treated with 5-FU, irradiation or Cisplatin in the presence or absence of DEX.

## 5 The *in vivo* effect of DEX




## 6 Conclusion

These results raise serious questions about the routine use of Glucocorticoids (GCs) in cancer treatment and transplantation since resistance induced in solid tumors may be responsible for e.g. recurrence of HCC in transplanted liver.

## Outlook

Our work opens avenues for prospective studies in patients and for mechanistic studies to examine GC-induced cell-type specific pro- and anti-apoptotic effects in greater detail.