The non-conventional effects of glucocorticoids in cancer[†]

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[†] This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jcp.25408]

Additional Supporting Information may be found in the online version of this article.

Received 25 April 2016; Revised ; Accepted 25 April 2016
Journal of Cellular Physiology
© 2014 Wiley Periodicals, Inc.
DOI: 10.1002/jcp.25408

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Abstract

Synthetic corticosteroids are widely used for the treatment of a variety of diseases, including pre-malignant and malignant conditions. In striking contrast, recent evidence suggests that corticosteroids can bear tumour-promoting effects in solid tumours of epithelial origin. We have recently shown that epithelial tissues, including the mucosa of the oral cavity and the skin, are able to modulate the local concentration of active corticosteroids and to produce steroids *de novo*. This has important clinical and physiopathological implications, because tissue-specific regulation of glucocorticoids plays a key role in the overall effect of these molecules. In the present review of the current English literature, performed using MEDLINE / PubMed / Ovid databases, we collected published evidence to demonstrate that corticosteroids induce effects that are more complex and controversial than previously acknowledged. Published studies clearly demonstrate that this class of molecules influences pathophysiological processes that are strictly related to malignancy, providing the rationale for further investigation.

Keywords: glucocorticoids, 11 β -HSD, cancer, proliferation, apoptosis, chemotherapy

Introduction

Cortisol is an endogenous glucocorticoid (GC) hormone produced by the adrenal cortex in response to adrenocorticotrophic hormone (ACTH), and it is released in response to various stress stimuli. ACTH secretion from the pituitary gland is a result of hypothalamus activation. GCs have long been regarded as drugs that promote apoptosis and inhibit cell proliferation and wound healing (Schlossmacher et al., 2011). However, a body of evidence has mounted over the last ten

years that shows potentially harmful effects of GCs in cancer therapy. Data from laboratory, preclinical, and clinical studies suggest that glucocorticoids induce treatment resistance in solid tumours, including prostate, ovarian and breast cancer (Herr and Pfitzenmaier, 2006). Our data also support this view by demonstrating that cortisol significantly reduces the cytotoxic effects of chemotherapeutic agents in several cell lines from oral squamous cell carcinoma (OSCC) (Celentano et al, manuscript in preparation). GCs also form the mainstay of the therapeutic armamentarium of a number of diseases with malignant potential, such as oral lichen planus (OLP). Therefore, the potential pro-tumorigenic activity of GCs can have vast clinical implications and warrants urgent attention.

Recent research demonstrates that epithelial cells, including those lining the skin and oral mucosa, can metabolize glucocorticoids de novo from cholesterol or systemic steroid intermediates. It has been shown that there is an endogenous non-adrenal glucocorticoid system existing in human epidermal keratinocytes and they exhibit high levels of corticosteroid metabolising activity (Slominski et al., 2014). Keratinocytes express major enzymes involved in the synthesis and metabolism of cortisol, including; cytochrome P450 chain, 11 β -hydroxysteroid dehydrogenases (11 β -HSD1/11 β -HSD2), adrenocorticotrophic hormone receptor (ACTHR/MC2R) and glucocorticoid receptor (Cirillo and Prime, 2011). Alteration of both the Hypothalamus-Pituitary and Adrenal (HPA) axis and non-adrenal tumour-associated glucocorticoid system has been linked to carcinoma progression as it results in altered cortisol levels (Bernabé et al., 2012; Rasmuson et al., 2001). These data may have major implications for cancer pathophysiology and therapy, as GCs are routinely administered during cancer treatment. This paper primarily aimed to review the current evidence supporting the traditional (conventional) and non-conventional role of GCs in normal and malignant cells.

Effects of GCs on epithelial cells – Conventional and non-conventional effects

GCs are conventionally used to up-regulate anti-inflammatory factors and down regulate pro-inflammatory factors. In oncology, GCs have been widely used in association with other treatment for cancer patients because they have potent proapoptotic properties in lymphoid cells, can reduce nausea and acute toxic effects in healthy tissue (Herr and Pfitzenmaier, 2006). However, a number of secondary effects have been documented that influence a variety of functions such as cell migration, differentiation, apoptosis and proliferation.

Role in cell proliferation and apoptosis

The anti-inflammatory and pro-apoptotic effects of GCs (Feng et al., 2013; Sidler et al., 2011) are fundamental in their use as therapeutic agents. However, as showed on normal human epidermal keratinocytes, the cortisol can exerts both immunostimulatory and immunosuppressive activities depending on its concentration (Itoi et al., 2013).

GCs are able to alter signalling in key survival pathways and this can result in reversible growth arrest or cell death in certain cell types, which may be particularly important in the arrest of tumour cell proliferation (Schlossmacher et al., 2011). However, although GCs are conventionally used to treat cancer or as adjuvants in cancer treatment, it has been observed that they may in fact induce tumour growth and metastasis formation (Deguchi et al., 1998; Romero et al., 1992). The underlying mechanism in which GCs induce tumour growth has been explored and it has been proposed that the hyper-secretion of GCs decreases peripheral blood lymphocytes (PBLs); cells which play a central role in killing tumour cells (Deguchi et al., 1998). Alternatively, studies have focused on the fact that GCs are inhibitory to the immune system and thus may inhibit certain molecules which are known to be tumouricidal (Irwin 1991).

Whilst the phenomenon of glucocorticoid-induced apoptosis in haematological cells is well established (Olnes et al., 2016), a growing body of evidence now suggests that glucocorticoids can act as anti-apoptotic agents in epithelial cells to promote cancer progression. It has been demonstrated that elevated levels of GCs during chronic restraint stress mediate an inhibitory effect on the tumour suppressing protein p53 thereby promoting tumourigenesis (Feng et al., 2012). Moreover, extra-adrenal GCs produced by intestinal epithelium have been implicated in aiding the progression of colon carcinoma cells through an immune evading mechanism (Sidler et al., 2011). The colon carcinoma cells synthesize and release bioactive immunosuppressive GCs which in turn suppress T-cell activation (Sidler et al., 2011).

Guendisch et al. analysed the role of glucocorticoids (GCs) in the survival and proliferation of tumor cells. The non-apoptotic actions of glucocorticoids on tumour cell lines, primary tumor cells and an in vivo model along with molecular signalling studies were examined. The first important finding of this study was that dexamethasone, a commonly used glucocorticoid in cancer patients, enhances tumour cell proliferation in vitro and in vivo. Dexamethasone enhanced tumour cell proliferation in 9/17 cell lines from solid tumours from all three different germ layers (Guendisch et al., 2012). It was found that these dexamethasone-induced proliferative changes were mediated by the glucocorticoid receptor. GCs lead to an activation of intracellular signalling molecules such as N3RC1, AKT and p38-MAPK which all function in various ways to mediate dexamethasone-induced tumour cell proliferation. In terms of clinical relevance, the findings from this paper suggest that the non-use of GCs might actually improve the prognosis of patients with cancer (Guendisch et al., 2012). Moreover, Dexamethasone showed to suppress antitumor immune responses and facilitate tumor progression by enhancing PD-1, a key cell-surface receptor of CD28 superfamily that can attenuate T-cell responses and

promote T-cell tolerance, resulting in faster tumor growth and poor prognosis in the clinical setting of anti-cancer therapy (Xing et al., 2015).

A reported well-known effect of GCs is their ability to inhibit cell proliferation (Newton, 2000; Rabbitt et al., 2003; Spiegelman et al., 1997, Yuan et al., 2016). However, it has also been shown that cortisol can increase cell proliferation at certain concentrations. Cortisol concentration modulates the level of Interleukin-6 (IL-6), a cytokine that stimulates the growth of cancer cells via an autocrine mechanism (Bernabé et al., 2011). IL-6 has been associated with angiogenesis and tumour progression (Heikkilä et al., 2008, Jobe et al., 2016). In head and neck SCC it can be correlated with recurrence, lymph node recruitment, and a poor prognostic survival (Duffy et al., 2008; Nagata et al., 2003). At higher concentrations of cortisol (100 and 1000nM) there is a lower level of IL-6 mRNA expression and secretion in oral SCC. However, at cortisol concentrations that simulate physiological stress levels (10nM) there is an increase in IL-6 mRNA expression and secretion with a subsequent increase in cell proliferation (Bernabé et al., 2011).

There is also support for this increase in cell proliferation, as a result of cortisol treatment, in non-malignant situations. This has been documented in foetal cardiomyocytes and Purkinje fibres (Feng et al., 2013). Cell nuclei expressing Ki67; a marker for cell proliferation, were found in greater numbers in foetal heart tissue that were infused with cortisol. The myocyte proliferation due to exogenous GC treatment resulted in cardiac enlargement and hypertrophy leading to increased wall thickness. The proliferative effects of cortisol were blocked by the use of an antagonist to the mineralocorticoid receptor, which is a receptor of particular interest because it can be found in the epidermis of skin and interacts with the 11β -HSD enzyme (Kenouch et al., 1994). In foetal hearts it was found that there was an increase in apoptosis in

Purkinje fibres which was blocked through the use of a specific antagonist to the GR (Feng et al., 2013). In contrast, GR activation in cardiomyocytes has an anti-apoptotic effect, reflecting another non-conventional effect (Ren et al., 2012).

Studies on the transcriptional profiles of primary human keratinocytes revealed further evidence for the non-conventional anti-apoptotic effect. The treatment of keratinocytes with dexamethasone promoted anti-apoptotic gene expression and inhibited pro-apoptotic expression. As a result, the treated keratinocytes did not undergo UV-induced apoptosis (Stojadinovic et al., 2007). To explain the presence of both apoptotic and anti-apoptotic properties of GCs it has been suggested that they are not mutually exclusive and these effects may occur at different stages i.e. GCs inhibit early stages of differentiation and promote later stages of differentiation. (Stojadinovic et al., 2007). Therefore, GCs can have different effects depending upon cell type, developmental age and cellular environment (Feng et al., 2013).

Role in wound healing and anchorage independence

Delayed wound healing is a well-known effect of the therapeutic use of GCs. It has been shown that overexpression of the GR in transgenic mice slows down the skin wound healing process. This delay is attributed to the inhibition of keratinocyte proliferation, motility and migration. Furthermore, delayed wound healing is accompanied by a decrease in granulocyte and macrophage recruitment, as well as a reduction in ERK activity and the expression of TNF- α , IL- β , proangiogenic factor and vascular endothelial growth factor (Sanchis et al., 2012; Stojadinovic et al., 2007). However, conflicting results have suggested that in fact GCs may have some repair potential. In one particular experiment, mucociliated human bronchial epithelial cell (HBEC) cultures were created to imitate an asthmatic environment and the effects of therapeutic agents

such as dexamethasone were studied. As expected, it was found that dexamethasone delayed immediate wound repair of HBEC by lowering the proliferative rate of cells surrounding the injured site. However, this in turn reduced proliferative stress on epithelial stem cells and transit amplifying cells in the basal compartment of the bronchial epithelium during post-wound metaplasia. Hence, the functional lifespan of these replacement cells is enhanced leading to better long term repair potential (Wadsworth et al., 2006).

GCs have long been used as agents in the treatment and management of particular diseases. The effects of commonly used GC medications to treat pemphigus vulgaris (PV) were studied to demonstrate whether their supposed therapeutic properties in regenerating PV-like lesions could be demonstrated in vitro. Using methylprednisolone (MP) and pyridostigmine bromide (PBr) this study found that MP and PBr significantly improved the rate of keratinocyte wound regeneration associated with PV lesions. However, it was found that these drugs could not accelerate the rate of wound healing in monolayers cultured under no conditions. This suggests that MP and PBr function to specifically offset the effects of PV serum on wounded keratinocytes (Lanza et al., 2009). Other studies have explored the effects of both endogenous and exogenous corticosteroids on human keratinocyte survival and proliferation rates.

The capacity of human keratinocytes to promote the formation of anchorage-independent multicellular aggregates (MCAs) in vitro was studied using endogenously-produced and exogenously administered hydrocortisone. Benign /non-tumorigenic (I-7/HaCaT) and malignant low metastatic/high metastatic (II-3/RT-3) keratinocytes were treated with ACTH and assessed for determine the levels of cortisol being synthesized. It was found that the malignant keratinocytes secreted higher levels of endogenous hydrocortisone in response to ACTH treatment compared to benign keratinocytes (Kennedy et al., 2015). Overall, this study

demonstrates the interaction between glucocorticoids and keratinocytes during cancer progression. These findings indicate that epidermal glucocorticoid systems are associated with tumour progression which is of clinical relevance as synthetic corticosteroids are so widely used for potentially malignant conditions.

Alteration of cortisol and related enzymes in malignancy: possible role of the tumour-associated glucocorticoid system

Alteration of key molecules involved in the glucocorticoid pathway in cancer has been reported in previous literature. For instance, elevated cortisol levels have been found in cancer patients where it is believed it affects cancer prognosis by impairing the cellular and humoral immune response and by promoting tumour metastasis (Bernabé et al., 2012; Mazzoccoli et al., 2003; Rasmuson et al., 2001).

11 β -Hydroxysteroid dehydrogenase (11 β -HSD) is the main enzyme that regulates the endogenous activity of GCs and is expressed in two isoforms, type 1 and type 2. These two enzymes are involved in activation and deactivation of GCs (11 β -HSD1 and 11 β -HSD2 respectively), thus controlling cell proliferation. Expression of 11 β -HSD1 generally results in decrease in cell proliferation, whereas expression of 11 β -HSD2 is involved in increase in cell proliferation. Studies have illustrated that expression of these enzymes is altered in tumours and may create a microenvironment favourable for tumour growth. For instance, an earlier study on murine and human epidermal cells observed the involvement of 11 β -HSD1 in the natural skin ageing process (Tiganescu et al., 2013). It was found that 11 β -HSD1 expression increases in ageing skin, resulting in local GC excess and adverse effects such as: altered skin integrity, thinning and impaired wound healing. This is due to the changes in the extracellular matrix (ECM) including: collagen atrophy, collagen disorganisation, shredded appearance of collagen

structure and large inter-fibril spaces. This disordered ECM microenvironment is vital for tumour metastasis. Hence the study suggested that the local increase in 11 β -HSD1 in ageing skin may increase the risk of skin cancer.

The GC receptor (GR) also plays a key role in the glucocorticoid pathway. It is a member of the nuclear hormone receptor family normally located within the cytoplasm of cells. Upon binding with cortisol it migrates to the nucleus and functions as a transcription activator or repressor that affects gene regulation to ultimately cause decreased cell proliferation (Schlossmacher et al., 2011; Slominski et al., 2014). Mutations in GR structure, aberrant processing of GR pre-mRNA and impaired functionality have been implicated in cancer progression.

Table I lists studies that have demonstrated dysregulation of cortisol, 11 β -HSD enzymes and glucocorticoid receptor in different types of cancers.

Use of corticosteroids in malignancy and premalignant conditions

GCs have a wide array of uses and effects in premalignant and malignant conditions. As strong anti-inflammatory agents, they have the ability to regulate cell fate by inducing expression of anti-apoptotic genes while suppressing apoptotic factors (Oakley and Cidlowski, 2011; Sung et al., 2009). Additionally, GCs are used as analgesics and antiemetics by patients receiving cancer treatment (Stojadinovic et al., 2007).

There are possible mechanism-based benefits in the use of GCs in pre-malignant conditions. An example of a potentially malignant condition that has potential for transformation is oral lichen planus. Progression to oral SCC can occur in up to 5.8% of cases (Kaplan et al., 2012; Kesić et al., 2009). Lichen planus is an autoimmune condition characterized by chronic inflammation (Ismail et al., 2007). It is postulated that chronic inflammation is a factor that may lead to the

development of malignancy such as oral SCC. The powerful anti-inflammatory effects of GCs may therefore be a protective factor in this situation, and they are currently first-line treatment for this condition (Lodi et al., 2012; Scully et al., 2000; Usatine and Tinitigan, 2011). Nevertheless, the recent finding that GCs may bear cancer-promoting effects warrants further consideration in this area.

GCs are used as a monotherapy or in combination with other treatments to manage and treat many different forms of malignancy. GC monotherapy has been shown to have positive treatment outcomes in patients with breast and prostate cancer via proposed mechanisms of adrenocortical inhibition and adrenal androgen suppression respectively (Keith, 2008). In a systematic review investigating the combination therapy of chemotherapy +/- GCs, evidence supported such added treatment outcomes as decreased leukopenia, decreased thrombocytopenia and an improved tolerance for increased chemotherapy dose in the group that received GCs as an adjunct to their chemotherapy compared to the group only receiving chemotherapy (Keith, 2008). Corticosteroids are also prescribed for the treatment of hypercalcaemia associated with malignancy. Renal tubular resistance to endogenous calcitonin during treatment for hypercalcaemia in malignancy can be overcome by the addition of corticosteroids to the treatment (Hosking et al., 1990). Despite their benefits in cancer treatment, GCs have also paradoxically been implicated in cancer progression (Nakane et al., 1990; Sidler et al., 2011; Zhang et al., 2006). The postulated benefits of corticosteroids in preventing malignancy should therefore be balanced against the possible carcinogenic effects of immunosuppression warranting further research in this area.

In a study of the primary adult brain tumour, glioblastoma, the use of GCs as part of the standard treatment protocol was examined. The standard treatment protocol for primary adult tumours

included maximum surgical resection, radiation therapy and chemotherapy with about 99% of the patients also receiving perioperative corticosteroids with some patients receiving continued doses throughout the course of care (Seyfried et al., 2010). High dose GCs are generally prescribed for their anti-inflammatory mechanism to help combat radiation therapy associated brain swelling and tumour oedema (a conventional use and effect). However, GCs such as Dexamethasone that are regularly prescribed have been shown to considerably increase blood glucose levels. The blood glucose is a fuel for glycolysis-dependant tumours and also facilitates production of glutamate, a neurotransmitter linked with causing excitotoxic damage to neurons (Seyfried et al., 2010). Higher levels of blood glucose have been shown to accelerate brain tumour growth and lower treatment prognosis (Seyfried et al., 2010).

Glucocorticoid-induced resistance has been identified in cells of solid tumours when used with various anticancer drugs and with radiotherapy. Such observations were made in established carcinoma cell lines cultured in vitro, in xenografts on nude mice, and in primary cells that had been isolated from fresh surgical samples of solid tumours (Herr et al., 2003; Sui et al., 2006; Zhang et al., 2006). Tumours analysed were derived from bladder, brain, breast, cervix, colon or rectum, liver, lung, kidney, ovary, pancreas, and prostate. The finding that the tumour-associated glucocorticoid system is active in all these tumours (Cirillo et al., manuscript in preparation) adds a further level of complexity and raises the possibility that a de-regulated GC metabolism may serve as a tumour promoting mechanism in cancer (**Figure 1**).

Overall, it can be ascertained from the wide array of research on this topic that the effects and uses of GCs in malignant conditions can be both beneficial and detrimental in terms of controlling tumour growth and progression. Conventional uses of GCs have been shown to help treat malignant conditions either alone or in combination with other treatment modalities. Yet the

literature also supports the adverse effects of GCs in tumour progression and growth which are linked closely to the non-conventional effects of GCs in malignant conditions.

Conclusion

Based on preliminary data and evidence obtained from this literature review it can be suggested that in contrast to previous thought, increased levels of autocrine, paracrine and exogenous cortisol are important to tumour progression. Hence it is possible that alterations in the expression of enzymes regulating the levels of tumour-derived cortisol take place in cancers. It will be important, therefore, to assess the levels of expression of steroidogenic molecules, steroids and receptors amongst normal and malignant epithelial cells as well as the correlation of the expression levels of steroid-related molecules to the clinical-pathological parameters of cancer.

In addition to shedding light on key patho-physiological mechanisms of SCC, characterization of the tumour-associated GC systems will have salient *diagnostic, preventive and therapeutic* clinical implications. Changes in the expression levels of components of the epithelial GC pathway may aid in the selection of novel markers of cancer progression. Identification of the presence of alterations in the steroid pathway in malignant epithelial cells would open new avenues in the management of inflammatory pre-malignant conditions such as lichen planus and provide basis for a mechanism-based approach to cancer treatment.

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Table I. Dysregulation of serum cortisol, 11 β -HSDs and glucocorticoid receptor in different types of cancers.

Study	Type of Cancer	Dysregulated Molecule	Specific Findings
(Bernab� et al., 2012)	Oral squamous cell carcinoma (SCC)	Cortisol	Elevated plasma and salivary cortisol levels in SCC and also higher levels in advanced stage compared to initial stage.
(Rasmuson et al., 2001)	Renal cell carcinoma (RCC)	Cortisol	Serum cortisol levels higher in RCC and positively correlated with tumour diameter and grade. Elevated cortisol levels also had worse prognosis.
(Sephton et al., 2000)	Metastatic breast cancer	Cortisol	Flat diurnal salivary cortisol circadian rhythm where elevated cortisol levels associated with early mortality.
(Sephton et al., 2013)	Lung cancer	Cortisol	Flattening of the diurnal cortisol rhythm associated with early death.
(Terao et al., 2013)	Skin SCC, basal cell carcinoma (BCC) and seborrheic keratosis (SK)	11 β -HSD1 and 11 β -HSD2 enzyme	Reduction in 11 β -HSD1 expression with increased keratinocyte proliferation. 11 β -HSD2 expression increased in basal cell proliferating conditions such as BCC and SK.
(Parks et al., 1998b)	DMS-79 cells (cell line derived from an ACTH-producing small cell lung cancer).	11 β -HSD2 enzyme	11 β -HSD2 normally not found in healthy lung tissue, was expressed in cancerous lung tissue.
(Temkin et al., 2006)	Ovarian epithelial cancer	11 β -HSD2 enzyme	11 β -HSD2 enzyme not found in normal post-menopausal ovarian tissue was increased in cancer cells.
(Bland et al., 1999)	Osteosarcoma	11 β -HSD2 enzyme	Overexpression of 11 β -HSD2 enzyme in cancer, compared with predominant expression of 11 β -

			HSD1 enzyme in normal human osteoblast cells.
(Žbáňková et al., 2004)	Colorectal cancer	11 β -HSD2 and 11 β -HSD1 enzyme	Decrease in the abundance of 11 β -HSD2 mRNA and enzyme activity in cancer tissue. Also demonstrated increase in 11 β -HSD1 in some samples.
(Cirillo et al., 2012)	Oral squamous cell carcinoma (SCC)	11 β -HSD2 enzyme	Decrease in 11 β -HSD2 expression in cancer.
(Lu et al., 2011)	Breast cancer	11 β -HSD1 enzyme	Decrease in 11 β -HSD1 expression in cancer.
(Budunova et al., 1997)	Mouse epidermal papillomas and SCC.	Glucocorticoid receptor	In early skin papilloma GR expression is reduced but in late papilloma and in SCC, GR levels are similar or higher than normal.
(Spiegelman et al., 1997)	Mouse epidermal papillomas and SCC.	Glucocorticoid receptor	No significant changes in GR gene structure and expression in cancer but resistance to glucocorticoid fluocinolone acetonid more likely due to alterations in receptor function.
(Waters et al., 2004)	Small cell lung carcinoma (SCLC)	Glucocorticoid receptor	Normal expression of GR, however its functionality altered by subtle changes in co-factors such as Nuclear co-repressor which was overexpressed in cancer.
(Ray et al., 1996)	Small cell lung carcinoma (SCLC)	Glucocorticoid receptor	Mutations in GR gene structure lead to its impaired function.
(Parks et al., 1998a)	Small cell lung carcinoma (SCLC)	Glucocorticoid receptor	Abnormal splicing of the GR transcript causes GR resistance to GC stimulation in cancer cells.
(Kay et al., 2011)	Small cell lung carcinoma (SCLC)	Glucocorticoid receptor	Increased DNA methylation of promoter c leads to decreased GR expression.
(Li et al., 1996)	Transformed $\Delta 5$ mouse lung	Glucocorticoid receptor	Transformed cells contain functional GR but expression which

	cells		antagonises glucocorticoids.
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Legend to figures

Figure 1. Schematic representation of cancer-promoting glucocorticoid effects.

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(Rasmuson et al., 2001)	Renal cell carcinoma (RCC)	Cortisol	Serum cortisol levels higher in RCC and positively correlated with tumour diameter and grade. Elevated cortisol levels also had worse prognosis.
(Sanhron et	Metastatic	Cortisol	Flat diurnal salivary cortisol

al., 2000)	breast cancer		circadian rhythm where elevated cortisol levels associated with early mortality.
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(Kay et al., 2011)	Small cell lung carcinoma (SCLC)	Glucocorticoid receptor	Increased DNA methylation of promoter c leads to decreased GR expression.
(Li et al., 1996)	Transformed A5 mouse lung cells	Glucocorticoid receptor	Transformed cells contain functional GR but express cjun which antagonises glucocorticoids.

Figure_1 (5) .

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Title:

The Non-Conventional Effects of Glucocorticoids in Cancer

Date:

2016-11-01

Citation:

Azher, S., Azami, O., Amato, C., McCullough, M., Celentano, A. & Cirillo, N. (2016). The Non-Conventional Effects of Glucocorticoids in Cancer. JOURNAL OF CELLULAR PHYSIOLOGY, 231 (11), pp.2368-2373. <https://doi.org/10.1002/jcp.25408>.

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