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Invited Minireview

The influence of glucocorticoid signaling on tumor progression

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ABSTRACT

The diagnosis of cancer elicits a broad range of well-characterized stress-related biobehavioral responses. Recent studies also suggest that an individual's neuroendocrine stress response can influence tumor biology. One of the major physiological pathways altered by the response to unrelenting social stressors is the hypothalamic–pituitary–adrenal or HPA axis. Initially following acute stress exposure, an increased glucocorticoid response is observed; eventually, chronic stress exposure can lead to a blunting of the normal diurnal cortisol pattern. Interestingly, recent evidence also links high primary tumor glucocorticoid receptor expression (and associated increased glucocorticoid-mediated gene expression) to more rapid estrogen-independent breast cancer progression. Furthermore, animal models of human breast cancer suggest that glucocorticoids inhibit tumor cell apoptosis. These findings provide a conceptual basis for understanding the molecular mechanisms underlying the influence of the individual's stress response, and specifically glucocorticoid action, on breast cancer and other solid tumor biology. How this increased glucocorticoid signaling might contribute to cancer progression is the subject of this review.

1. Introduction

The human biobehavioral response to stressors includes physiological changes that are initiated through an individual's interaction with the social environment. In response to these environmental stressors, including social stressors, well-defined physiological changes occur at the organismal level. These changes can be buffered by social support networks, thereby mitigating the deleterious effects of the stress response. However, when life's stressors are unrelenting and social support or other resources (e.g. financial resources) are insufficient, neuroendocrine pathways can become deregulated. It is this deregulation of physiological pathways that underlies the mechanisms whereby psychosocial stressors are hypothesized to influence the biology of chronic disease.

Cardiovascular and immune-related diseases have long served as examples of the stress response-disease relationship (Black and Garbutt, 2002; Stojanovich and Marisavljevich, 2008). More recent studies have begun to explore connections between psychosocial factors and cancer biology. Indeed, recent clinical, epidemiological, and animal-based studies suggest there is a biobehavioral influence on tumor progression (Armaiz-Pena et al., 2009; Costanzo et al., 2011). However, evidence for the impact of psychosocial factors on cancer initiation (rather than progression) has been less consistent (Costanzo et al., 2011). Nevertheless, it is well-established that neuroendocrine hormones (e.g. glucocorticoids and noradrenaline) can and do influence cancer biology (Armaiz-Pena et al., 2009). Thus, the fact that significant stress exposure can lead to deregulation of the neuroendocrine axis has led to further investigation into the effects of psychosocial factors on cancer biology as outlined below.

There are several neuroendocrine cell signaling mechanisms, executed downstream of both the adrenal and sympathetic systems, which could contribute to cancer growth. Recent reviews have outlined some neuroendocrine–cancer relationships and have extensively outlined neuroendocrine influences on the immune system (Armaiz-Pena et al., 2009; Costanzo et al., 2011). The immune system has well-established and important roles in the progression of some cancer types (e.g. melanoma and renal cell carcinoma); however, its role in other cancers is less well understood. The overall impact of the immune system on cancer biology [reviewed in (Grivennikov et al., 2010)] and specifically, the social stress-induced modulation of immunity are reviewed extensively elsewhere (Armaiz-Pena et al., 2009; Costanzo et al., 2011).

This review instead focuses specifically on glucocorticoids (GCs), steroid hormones that are either secreted from the adrenal gland during exposure to acute and chronic stressors or administered pharmacologically to reduce inflammation, and the role of GC signaling in epithelial cancer biology. We discuss potential mechanisms through which endogenous GCs (cortisol in humans and corticosterone in rodents) may influence cancer progression. These data suggest that the routine pharmacological use of synthetic GCs in some cancer treatment may not be optimal.

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Furthermore, we explore how psychosocial mechanisms might intersect with both systemic and tumor microenvironmental GC action to increase tumor progression.

2. Stress signaling: cortisol and the glucocorticoid receptor

2.1. Cortisol

The active GC in humans, cortisol, is produced and secreted by the adrenal cortex. Cortisol release into the circulation has important systemic roles in modulating metabolic and immune processes; cortisol also elicits cell-type-specific effects, some of which are discussed in detail below. Release of cortisol from the adrenal gland is regulated by the hypothalamic–pituitary–adrenal (HPA) axis, a biological circuit capable of integrating human experience with physiological signaling. In the stress response, specific neurons within the hypothalamus secrete corticotrophin-releasing hormone (CRH). In turn, CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which subsequently acts on the adrenal cortex to promote cortisol release. A negative feedback loop completes the HPA circuit resulting in cortisol suppressing the production of CRH and ACTH through feedback to the hypothalamus and pituitary. The HPA axis is further linked to the Circadian clock thereby resulting in regulation of GC levels in a diurnal pattern (Chung et al., 2011).

The biological effects of cortisol are in part mediated by the average concentration of circulating cortisol over a certain time period; however, cortisol levels within specific tissues also play an important role in its cell- and tissue-specific effects (Draper and Stewart, 2005). Two isozymes are responsible for regulating local cortisol levels within specific tissues, 11β-Hydroxysteroid dehydrogenase (11β-HSD) type I, which converts inactive cortisone to active cortisol, and 11β-HSD type II, which is responsible for the reverse reaction that inactivates cortisol. Accurately measuring tissue and intracellular concentrations of human cortisol remains challenging. However, transgenic mice with adipose tissue-specific overexpression of the gene encoding 11β-HSDI exhibit increased local corticosterone production and develop the metabolic syndrome, clearly demonstrating that a tissue-specific (rather than systemic) increase in active GCs can dramatically affect whole animal physiology (Masuzaki et al., 2001).

2.2. The glucocorticoid receptor

The most important determinant of cortisol action is its cognate binding protein, the glucocorticoid receptor (GR), which is a member of the nuclear receptor family. The GR's primary action is as a ligand-dependent transcription factor regulating gene expression. Prior to cortisol binding, the GR is cytoplasmic, where it exists in a complex with heat-shock protein 90 (Hsp90) and several immunophilins (Lewis-Tuffin and Cidlowski, 2006). Ligand binding by GC results in dissociation of the GR-Hsp90 complex, GR homodimerization, and nuclear translocation of the dimer (Lewis-Tuffin and Cidlowski, 2006). Within the nucleus, the GR regulates the expression of target genes, either directly through interacting with glucocorticoid response elements (GREs) or indirectly through interacting with other transcription factors that in turn bind to DNA.

Through GR activation, cortisol regulates numerous biological processes including metabolism, behavior, growth and cellular apoptosis. As mentioned previously, the specific response to GR activation is often dependent on the target cell or tissue type. How a single hormone-receptor interaction can result in such divergent effects in different cell types is still under active investigation and is likely to involve multiple mechanisms. For example, the GR exists as multiple transcriptional and translational isoforms (Oakley and Cidlowski, 2011). In addition, isoforms of the GR are each subject to post-translational modifications including ubiquitination, SUMOylation, acetylation, and methylation that have been shown to modulate the stability and/or function of the receptor (Duma et al., 2006; Oakley and Cidlowski, 2011). The GR can also undergo ligand-dependent phosphorylation at several serine residues, events that regulate its transcriptional activity (Duma et al., 2006). Notably, in rats subjected to the chronic stressor of social isolation, phosphorylation of the GR in the brain may regulate GR's transcriptional activity independently of elevated serum corticosterone levels (Adzic et al., 2009). Thus, the diverse effects of glucocorticoids in particular cellular contexts are likely due to the presence and proportion of specific GR isoforms and their post-translational modifications, as well as to the concentration of active GCs (Oakley and Cidlowski, 2011).

3. Pharmacological glucocorticoids and the role of GR activation in cancer

The potential for divergent GR activity in different cell types is striking when comparing GC effects on lymphocytic malignancies versus epithelial cell-derived cancers. In the former case, synthetic GCs, such as dexamethasone (DEX), are routinely used to induce apoptotic cell death in malignant lymphoid cells (e.g. lymphoma). Conversely, in epithelial (i.e. "solid") tumors, several reports suggest that GCs have the opposite effect: GCs stimulate anti-apoptotic gene expression and antagonize the ability of cancer cytotoxics to effectively induce cell death (Zhang et al., 2007). Despite mounting evidence in tumor models suggesting GC-mediated antagonism of therapy-induced tumor cell apoptosis, GCs are routinely administered before, during, and after epithelial cell tumor-chemotherapy to mitigate nausea and allergic reactions. This section will provide a brief historical perspective, focusing on the relatively recent data suggesting GCs antagonize the effectiveness of cancer cytotoxic therapy and will then highlight studies that have begun to identify the molecular mechanisms through which GCs (either endogenous or pharmacologically administered) influence solid tumor biology. Finally, we will discuss data that suggest careful reconsideration of GC use in cancer patients and underscore the potential negative impact of increased endogenous stress-induced GCs on effective cancer treatment.

3.1. Laboratory studies and model systems

One of the earliest reports of the cell survival effect by GCs was observed in immortalized human mammary epithelial cells (Moran et al., 2000). Using serum-free media and specific growth factor supplementation, Moran et al. identified novel antiapoptotic pathways in the breast epithelial MCF10A cell line and its derivative line, MCF10A-Myc. When plated under serum-free conditions, both cell lines displayed high levels of cell death. Upon addition of the GC hydrocortisone, cells were protected from apoptosis independently of activating the antiapoptotic PI3-K and Akt signaling pathways (Moran et al., 2000). In an extension to this study, GR activation in a panel of several breast cancer cell lines protected from serum deprivation-induced apoptosis (Mikosz et al., 2001). GR activation was associated with the rapid induction of the serum and glucocorticoid-regulated kinase-1 (SGK1), a protein kinase encoded by a direct GR target gene. This induction of *SGK1* expression was required for much of the GR-mediated protection from cell death usually induced by serum withdrawal (Mikosz et al., 2001; Wu et al., 2004).

In concurrent studies, another group of investigators attempted to define mechanisms by which paclitaxel (an anti-mitotic chemo-

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