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**Role of tissue-specific steroid metabolism in oral disease: is there any
clinical implication?**

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Running Title: Local glucocorticoid system in oral disease

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ABSTRACT

The discovery of an oral glucocorticoid system has provided novel conceptual frameworks for understanding the effects of endogenous and exogenous corticosteroids in the oral cavity. For example, liquorice derivatives have long been used in the treatment of aphthous stomatitis and it is now known that the chief constituent of liquorice root, glycyrrhetic acid, inhibits 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 2 thus increasing local cortisol levels. Hence, targeting the local inter-conversion between inactive cortisone and active cortisol by 11 β -HSD inhibitors/activators offers potentially

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advantageous strategies for the treatment of oral inflammatory and autoimmune conditions. The recent characterisation of a cancer-associated glucocorticoid system has further extended the implications of cortisol metabolism in oral disease. New evidence now questions the use of synthetic corticosteroids in cancer patients and, possibly, in oral potentially malignant disorders. For example, cortisol production by cancer cells has been shown to inhibit tumour-specific CD8⁺ T cells, to promote migration and invasion, and to induce chemoresistance *in vitro*. This viewpoint briefly summarises the recent evidence for a role of the local steroid metabolism in oral oncology and immunology and its potential clinical implications.

Keywords: cancer, oral immunology, cortisol, 11 β -HSDs, keratinocytes

Introduction

Glucocorticoids (GC) are lipid hormones that are involved in the regulation of stress responses, metabolism and immune homeostasis (Sapolsky *et al.*, 2000). Whilst the adrenal glands are the major source of GC, it is now recognized that GC synthesis occurs at other sites (Noti *et al.*, 2009), including skin (Slominski and Wortsman, 2000; Hannen *et al.*, 2011; Cirillo and Prime, 2011) and oral mucosa (Cirillo *et al.*, 2012). In the skin, steroidogenesis is involved in the modulation of a variety of physiological functions (Slominski *et al.*, 2000; Vukelic *et al.*, 2011; Kennedy *et al.*, 2015). Tissue-specific

activation of cortisol occurs via 11 β -hydroxysteroid dehydrogenase (HSD) 1 (*HSD11B1* gene; Tomlinson *et al.*, 2004) whereas the reverse, cortisol to cortisone, involves 11 β -HSD2 (*HSD11B2* gene; Ma *et al.*, 2011). 11 β -HSDs, therefore, are key enzymes in the tissue-specific regulation of glucocorticoids and current thinking suggests that their deregulation is associated with a variety of pathological processes of squamous epithelia, including the oral mucosa.

A few years ago we characterised the oral glucocorticoid system and showed that the local concentration of active cortisol in normal keratinocytes had the capacity to modulate disease progression in conditions where steroids are used routinely as a treatment modality, such as autoimmune blistering disease (Cirillo *et al.*, 2012). More recently, we described for the first time the cancer-associated glucocorticoid system and showed that *de novo* synthesis of immunomodulatory cortisol was a common feature of a broad spectrum of cancers, including squamous cell carcinomas (Cirillo *et al.*, 2017). These findings raise the possibility that cancer-associated steroidogenesis and local cortisol metabolism play a role in carcinogenesis.

Gaining more insight into the molecular basis of local cortisol metabolism has salient clinical implications: not only will this offer novel therapeutic strategies for inflammatory and autoimmune diseases but, also, components of the steroid biosynthetic pathways can be used as cancer biomarkers. Finally, elucidation of the role of cortisol in oncogenesis could drastically change current practices for the use of synthetic steroids in the management of malignant and potentially malignant disorders. This viewpoint discusses the recent advances in this field.

Potential role of glucocorticoids in the development and progression of oral cancer

Long-term use of synthetic glucocorticoids causes immune suppression and there is considerable clinical evidence that immune cell functions play important roles in preventing the growth and spread of cancers. Immunocompromised patients show an increase in the incidence of malignancy and the similarity of the pattern of increased risk of cancer in HIV-positive and organ transplant patients suggests that it is immune

deficiency, rather than other risk factors for cancer, that is responsible for the increased risk (Grulich et al., 2007). Recent data suggest that post-transplant cancer risk is related to an exceptionally high and accelerating risk of SCC (Krynitz et al., 2013). Interestingly, cutaneous SCC occurrence organ transplant recipients is associated with 1.44-fold increased risk for developing later malignancies, particularly those of the oral cavity/pharynx (Zamoiski et al., 2017). OSCC have been widely described in immunosuppressed renal transplant patients (King et al., 1995) and the induction of oral cavity cancers is second to that of liver cancer in patients after bone marrow transplantation (Bhatia et al., 2001). Overall, evidence suggests that squamous epithelia, including the oral mucosa, are particularly prone to developing cancer following immune suppression.

GCs are routinely used in the management of blood malignancies but are also employed in the treatment of solid tumours (Haidar and Jeha, 2011). However, it has been suggested that systemic GCs can enhance energy metabolism, which may increase the ability of cancer cells to survive during radiation therapy and chemotherapy *in vitro* and *in vivo* (Zhang et al., 2006; Seyfried et al., 2010; Azher et al., 2016). In fact recent evidence shows that adjuvant dexamethasone administration compromises survival of cancer patients (Shields et al., 2015; Pitter et al., 2016). GCs have also been linked to apoptotic resistance in malignant tumour cells, increasing their proliferative capacity, and promoting metastasis (Herr and Pfizenmaier, 2006; Guendisch et al., 2012). Finally, constitutive expression of cancer-derived corticosteroids results in local immune suppression, potentially favouring immune escape of tumour cells (Sidler et al., 2011; Cirillo et al., 2017). In particular, we found a strong correlation between basal cortisol production from several malignant cell lines and inhibition of tumour-specific CD8⁺ lymphocyte proliferation (Cirillo et al., 2017). Taken together, published evidence strongly questions the use of adjuvant corticosteroids in cancer patients.

There is little clinical information about the effect of corticosteroids on the behaviour of OSCC. Experimental data demonstrate that stress hormones, including

cortisol, increase proliferation of OSCC cells (Bernabé et al., 2011). Interestingly, both plasma and salivary cortisol levels are significantly higher in patients with OSCC compared with controls and patients with advanced-stage OSCC show significantly higher levels of cortisol than those in an initial clinical stage (Bernabé et al., 2012). Whether increased cortisol levels occur as cause or consequence of cancer progression, however, has not been understood to date. Our own preliminary observations show that both exogenous and cancer-derived cortisol significantly increase the resistance of OSCC cells to 5-fluorouracil and doxorubicin *in vitro* (Celentano et al., 2016). Finally, we found a significantly reduced expression of the cortisol-deactivating enzyme 11 β -HSD2 in OSCC and this predicts higher levels of cortisol in the cancer microenvironment (Cirillo et al., 2017). We hypothesize that, while corticosteroids do not induce OSCC, these have a central role in promoting the progression of cancer, for example by regulating invasion, metastatic spread, and response to chemotherapy. The view that cortisol would not induce cancerisation of oral potentially malignant disorders (OPMD) is in agreement with the data that malignant transformation of oral lichen planus (OLP) is independent of steroid therapy (Gandolfo et al., 2004). It would be interesting to investigate the biological behaviour of OSCC in relation to cumulative steroid dosage in patients with transformed OLP.

Notwithstanding the paucity of clinical data available to date, corticosteroid usage in OSCC patients warrants further investigation because of the established link between cortisol and cancer progression.

Modulation of local cortisol levels in the treatment of oral inflammatory and autoimmune diseases

Generation of mice with glucocorticoid receptor (GR) inactivation restricted to keratinocytes (GR epidermal knockout or GREKO mice) has allowed demonstration that tissue-specific GC action is of paramount importance for epidermal homeostasis (Sevilla et al., 2013). Epidermal loss of GR provokes cutaneous inflammation and alteration in the

localized de novo GC synthesis in skin has been shown to be a key pathogenic mechanism of psoriasis (Hannen et al., 2017).

Synthetic GCs are the mainstay of treatment of immune-mediated oral mucosal diseases, however this class of drugs has serious side effects that limit their long-term use. The discovery of the importance of a local cortisol metabolism in the oral mucosa may now open new avenues for the development of non-steroidal drugs in the management of oral inflammatory conditions. For example, pharmacological targeting of steroid-converting enzymes shows promise as a potentially effective steroid-sparing treatment of the autoimmune disease pemphigus vulgaris (PV). In one study, blocking of endogenous cortisol catabolism in keratinocytes with the 11β -HSD2 inhibitor 18β -glycyrrhetic acid (GA) mimicked the effect of exogenous administration of hydrocortisone and partially prevented the detrimental effects induced by PV sera (Cirillo et al., 2012).

GA is obtained from the hydrolysis of glycyrrhizin - the chief component of licorice - and inhibits 11β -hydroxysteroid dehydrogenase (11β -HSD) type 2, thus increasing local cortisol levels. In one study, glycyrrhizin given intravenously resulted in a marked clinical improvement of OLP patients (Da Nagao et al., 1996). The GA derivative carbenoxolone (CBX) has long been used for the treatment of recurrent oral ulcerative conditions such as aphthous stomatitis (Worner et al., 1974) and periadenitis mucosa necrotica recurrens (Samuel, 1967). Licorice and licorice constituents have been shown to exert beneficial effects on both the oral microbial pathogens and the host immune response involved in common oral diseases such as dental caries, periodontitis, candidiasis, and recurrent aphthous ulcers (Messier et al., 2012). Taken together, current literature suggests that pharmacological manipulation of the local oral GC system could be used for the therapeutic benefit of patients with oral inflammatory and autoimmune diseases.

Periodontal disease: possible role of local steroid metabolism

Long term use of high dose synthetic corticosteroids is known to cause bone resorption and osteoporosis in a dose-dependent manner (Schulz et al., 2016). In the oral cavity, GCs can induce alveolar bone loss in long-term treated animals (Bouvard et al., 2013).

Chronic stress, which is associated with abnormal cortisol levels, is a significant risk indicator for periodontal attachment loss in humans (Ng and Keung Leung, 2006).

However, there is no evidence that low or intermittent steroid use is detrimental to periodontal health and in fact cortisol may exert beneficial effects for the periodontium. Bone mineral density is not significantly reduced in adult patients on low-dose glucocorticoids (Koetz et al., 2012). Interestingly, changes of local steroid metabolism that lead to increased cortisol levels in the microenvironment seem to reduce periodontal bone resorption. In one example, it has been shown that 18β -GA, administered either prophylactically or therapeutically, induces a dramatic reduction in bone loss using a mouse model of periodontitis (Sasaki *et al.*, 2010). The authors suggested that this effect was independent of glucocorticoids because a down-regulation of 11β -HSD2 mRNA was not seen. 18β -GA, however, is known to impair 11β -HSD2 function by blocking enzymatic activity, not by inducing down-regulation at the transcriptional level (Kratschmar *et al.* 2011). The hypothesis that inhibition of cortisol degradation can improve periodontitis was corroborated by more recent study showing that 18β -GA inhibited lipopolysaccharide-induced vascular permeability induced by *Porphyromonas gingivalis*, a major periodontopathogen that is central to the pathogenesis of periodontal disease (Kim et al., 2013). When analysing the above data in light of our findings (Cirillo et al., 2012), it is reasonable to speculate that 18β -GA reduces tissue inflammation and limits the bone loss that occurs in periodontal disease by increasing local cortisol levels.

Conclusion

Recent advances in the characterisation of tissue-specific steroid metabolism have established the importance of local cortisol in epithelial pathophysiology. We suggest that components of the steroid biosynthetic pathway can be used as biomarkers and will be exploited therapeutically to regulate local tissue concentrations of cortisol in oral diseases, particularly autoimmune and neoplastic conditions. Finally, a better understanding of the effects of corticosteroids in cancer biology will lead to a safer and more rational clinical management of solid tumours.

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