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The antiproliferative effect of glucocorticoids: is it related to induction of TGF-β?

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Introduction

Glucocorticoids (GCs) are used in treating disorders of heightened immunity such as transplant rejection, owing to their capacity to prevent T cell activation by a multitude of mechanisms, including induction of the expression of the immunosuppressive cytokine, transforming growth factor (TGF)-β. Similar to GCs, TGF-β is a pleiotropic mediator that modulates several aspects of the inflammatory response, and is a potent suppressor of T cell activation and cytokine expression. Because of their similar scope of action, it is of interest to examine the available evidence to resolve the issue

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whether GCs mediate their effects, at least in part, via TGF-β.

Mode of action of glucocorticoids

Despite their wide-spread use, the mechanism by which GCs exert their anti-inflammatory and immunosuppressive effects is not completely understood. It is well appreciated that these effects involve both direct and indirect events [1]. In this regard, GCs reportedly act directly by: (i) blocking proximal events of T cell receptor (TcR) signal transduction; (ii) inhibiting the expression of leukocyte adhesion molecules and; (iii) suppressing cytokine production and action [1,2]. In addition to these direct effects, GCs act indirectly by: (i) inducing synthesis of lipocortin which inhibits phospholipase A2 activity, and hence the release of arachidonic acid from membrane-bound stores and the ensuing production of eicosanoids, (ii) promoting a Th2 cell activity through preferential blockade of Th1 cytokines, thus precipitating a long-lasting state of tolerance and, (iii) inducing the expression of TGF-β, an immunosuppressant cytokine which blocks cytokine synthesis and hence T cell activation [1,3]. Depending on the target cell and the specific conditions of activation, GCs may utilize more than one of the aforementioned mechanisms in exerting their effects.

TGF-β as an immunosuppressant

TGF-β is a highly conserved 25 kDa protein produced by mitogen-activated T cells, B cells, monocytes, and fibroblasts [3], and exerts predominantly immunosuppressive effects on the growth and function of T cells, B cells, and other mononuclear leukocytes [4]. Its production by activated T cells was suggested as one mechanism by which T cells limit their response to a particular stimulation [5].

Although the mechanism by which TGF-β exerts its immunosuppressive effects remains elusive, recent evidence suggests that the site of action of TGFβ is distal to IL-2 production [5], involving inhibition of the expression of high-affinity cytokine receptors and signalling through cytokine receptors largely as a result of blockade of Jak-Stat signal transduction pathway [5]. Furthermore, by preferentially suppressing Th1 but not Th2 cytokine production and stimulating IL-10 accumulation [4], TGFβ converts the immune response from a Th1- to a Th2-like phenotype [4], hence alleviating Th1-mediated disorders such as allograft rejection and autoimmunity. It remains to be determined whether promotion of Th2 activity by TGF-β is the resultant of its co-expression with Th2 cytokines (and hence its mis-classification as a Th2 cytokine), as was suggested, or due to frank transcriptional repression of Th1 cytokines.

Mediation of the effects of glucocorticoids by TGF-β: supporting views

In view of the inducibility of TGF-β expression by GCs, and the similarities between GCs inhibitory effects on cytokine expression and T cell activation and those induced by TGF-β, it was speculated that GCs indirectly mediate their anti-proliferative effect by inducing TGF-β expression [3,6,7]. This conclusion was based on the findings that: (i) the synthetic GC, dexamethasone (DEX), up-regulated TGF-β mRNA expression in non-stimulated [3] and mitogen-activated T cells [3], fibroblasts [8], osteoblasts [9], macrophages [1], and other cells [6,7] in a concentration and time dependent manner and, (ii) GCs anti-proliferative effect was abrogated by neutralizing anti-TGF-β antibodies [3,7].

GCs upregulation of TGF-β expression was a rapid event, being detected as early as 1 h after GCs addition, peaking at 4–6 h, and persisting for up to 24 h post-GCs addition. Induction of TGF-β expression by GCs occurred at the transcriptional [7,8] and post-transcriptional [6,9] levels; the latter involving stabilization of TGF-β mRNA, largely as a result of antagonism of TGF-β specific RNases [3]. In addition, upregulation of TGF-β expression potentiated GCs transcriptional repression at the level of GCs receptor complex interaction with the GCs responsive elements (GRE) DNA sites, thereby constituting a feedback system between TGF-β and GCs and resulting in profound immunosuppression.

Mediation of the effects of glucocorticoids by TGF-β: opposing views

In spite of evidence implicating induction of TGF-β as a mechanism by which GCs mediate their anti-proliferative effects, other reports provided arguments against direct involvement of TGF-β in GCs anti-proliferative effects. This was based on the findings that GCs did not upregulate TGF-β mRNA expression or protein secretion [1], but rather suppressed its expression. In addition, GCs reportedly antagonized a number of TGF-β effects, such as induction of prostaglandin synthesis and expression of the procollagen gene [10]. Furthermore, the mechanism of action of GCs was distinct from that of TGF-β, as revealed by the opposing effect of TGF-β and GCs (DEX) on induced nitric oxide synthetase mRNA expression stimulated by IL-1 [11], procollagen synthesis (inhibited by GCs but stimulated with TGF-β) [12] and EGF-induced c-fos mRNA expression (inhibited by GCs but resistant to TGF-β). It is noteworthy that, while GCs anti-proliferative effect required continued GCs presence since removal of GCs results in enhanced cytokine secretion and augmented T cell proliferation, that induced by TGF-β did not require its continued presence, as removal of TGF-β did not restore T cell proliferation. Thus, induction of TGF-β by GCs and,

accordingly, any role TGF-β play in mediating GCs effects must be addressed in the context of the cell type studied, stimulation conditions, and biological readout system utilized.

Conclusion

Both TGF-β and GCs are pleiotropic mediators that affect many aspects of cell growth, differentiation, and function. It is clear that the effects of GCs on TGF-β are not uniform, and that induction, suppression, or lack of effect of GCs on TGF-β transcription are dependent on the tissue studied and the state of cellular activation. Furthermore, conclusions drawn on GCs effect on TGF-β expression were largely based on *in vitro* studies, thereby questioning the physiological role of TGF-β in mediating GCs effects, since TGF-β may act as anti-inflammatory or pro-inflammatory cytokine depending on the micro-environment and its local tissue concentration. It remains to be determined whether induction of TGF-β expression is the principal or just a secondary mechanism by which GCs exert their anti-proliferative effects.

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Renal biopsy in lupus nephritis—what for, when and how often?

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Introduction

Renal biopsy is being used extensively in systemic lupus erythematosus (SLE). However, there is not complete agreement about the need for renal biopsy at presentation. Some physicians argue that the clinical diagnosis of lupus nephritis is easy and that the prognosis and treatment may be assessed without the support of histological features. Even more controversial are the indications to repeat biopsy in patients with established lupus nephritis.

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The diagnostic utility of biopsy

There are few doubts that the clinical and biological data are generally sufficient for diagnosing SLE nephritis. However, renal biopsy is the only tool that permits the correct classification of lupus nephritis. An SLE patient with haematuria, proteinuria and normal or subnormal renal function may have any class of underlying glomerular lesions and unpredictable severity of histological lesions. This may imply a different prognosis and different therapeutic approaches. Moreover, there are instances in which the diagnosis can be difficult. A few patients may present initially with renal disease and only exhibit systemic and biologic manifestations of SLE later in their course. This is relatively frequent for patients with an underlying