



Endogenous and exogenous glucocorticoids abolish the efficacy of immune-dependent cancer therapies

Yuting Ma ^{a,b}, Heng Yang^{a,b}, and Guido Kroemer ^{a,b,c,d,e,f,g,h,i}

^aCenter for Systems Medicine, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; ^bSuzhou Institute of Systems Medicine, Suzhou, Jiangsu, China; ^cUniversité Paris Descartes, Sorbonne Paris Cité, Paris, France; ^dEquipe 11 labellisée Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers, Paris, France; ^eInstitut National de la Santé et de la Recherche Médicale, Paris, France; ^fUniversité Pierre et Marie Curie, Paris, France; ^gMetabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; ^hPôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; ⁱDepartment of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Glucocorticoids mediate potent anti-inflammatory and immunosuppressive effects. A chronic elevation of the endogenous glucocorticoid tonus subsequent to mental stress, as well as continuous treatment with exogenous glucocorticoids, activate an immunosuppressive transcription factor, TSC22D3, in dendritic cells, causing the subversion of cancer therapy-elicited antineoplastic immune responses and subsequent therapeutic failure.

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Synthetic glucocorticoids such as dexamethasone and prednisolone are widely used as anti-inflammatory and immunosuppressive agents to dampen autoimmune and inflammatory diseases. Indeed, they mimic the effects of endogenous glucocorticoids (in humans mostly cortisol) in thus far that they act on glucocorticoid receptors. Endogenous glucocorticoids play a major role in homeostatic responses to stress,¹ avoiding unwarranted autoimmunity² and suppressing potentially lethal inflammatory responses, for instance in the context of septic shock.^{2,3} In cancer immunotherapy, adverse effects due to the (re-)activation of autoimmune responses are highly frequent and even have been attributed a positive prognostic role with respect to the overall response rate. However, such adverse effects are usually managed by the administration of high-dose glucocorticoids,⁴ and this type of medication is negatively associated with prognostic feature of immunotherapy, in particular for cancers outside of the central nervous system.⁵ Although glucocorticoids can favor tumor progression through direct effects on the malignant cells *per se*,^{6,7} there are reasons to believe that they favor cancer progression and therapeutic failure through indirect immunological effects as well.

In a recently published study,⁸ we demonstrated that, in mouse models, both endogenous and exogenous glucocorticoids can inhibit anticancer immune responses, thereby subverting the oncopreventive action of anticancer vaccination with dying-tumor cell preparations, as well as abolishing the tumor growth reducing effects of immunogenic chemotherapy (such as anthracyclines and oxaliplatin) and immunotherapy with PD-1 blockade. These findings were obtained in two models to cause “mental” stress, namely a model of social defeat-induced by repeated male domination (in which

C57Bl/6 males are exposed to males from an inherently aggressive CD-1 strain) or repeated restraint stress (in which mice are confined in narrow falcon tubes). Especially in the social defeat model, mice reproducibly developed signs of anxiety and depression, coupled to a chronic elevation of glucocorticoid tonus (in mice mostly corticosterone) that were durable for at least 3.5 weeks. Indeed, administration of mifepristone, a potent glucocorticoid receptor antagonist, abolished the negative effects of mental stress on the efficacy of cancer vaccination or treatment with chemotherapy or immunotherapy. In contrast, administration of dexamethasone or prednisolone mimicked these negative impacts,⁸ echoing the clinical results obtained in humans.⁵ Indeed, treatment of human immune cells with exogenous glucocorticoids used at clinically relevant concentrations has immunosuppressive effects on the capacity of dendritic cell to present tumor antigens,⁹ as well as on T cell activation and tumor-killing activity.¹⁰

To investigate the molecular mechanism through which mental stress cause cancer therapy-relevant immunosuppression in the mouse model, we performed extensive analyses of the transcriptome of tumor-infiltrating dendritic cells (TIDCs) and the profile of soluble factors in the peripheral blood, comparing social defeat pre-conditioned mice and non-stressed control mice. These analyses revealed that mental stress caused a state of both local (within tumor micro-environment) and systemic immune suppression, as manifested by the inhibition of myeloid leukocyte differentiation, antigen signaling pathway, neutrophil chemotaxis, type I and II IFN responses. Moreover, the capacity of anthracyclines or PD-1 blockade to elicit interferon- gamma production by tumor-infiltrating T cells was suppressed upon social

defeat. Bioinformatics analyses led to the discovery that dendritic cells upregulated *Tsc22d3*, an immunosuppressive transcription factor.⁸

Although *Tsc22d3* is ubiquitously expressed by most cell types, it turned out that social defeat favored the transcription of *Tsc22d3* mostly in TIDCs, but not in other major immune cell types infiltrating the cancer, or in dendritic cells residing in the spleen or in the tumor-draining lymph node.⁸ Based on this observation, we took advantage of genetically engineered mice which either overexpress *Tsc22d3* in dendritic cells (under the control of the CD11c promoter), or lack *Tsc22d3* in dendritic cells subsequent to a conditional knockout (in which a CD11c promoter-driven Cre recombinase excises the first exon of the floxed *Tsc22d3* gene). The dendritic cell-restricted overexpression of *Tsc22d3* was sufficient to mediate immunosuppression and to abolish tumor-preventive immune responses elicited by a prophylactic vaccination or therapeutically relevant immune response elicited by cancer chemotherapy. Conversely, the dendritic cell-targeted knockout of *Tsc22d3* was able to abolish the immunosuppressive effects of exogenous glucocorticoids as well as those mediated by social defeat. Thus, the *Tsc22d3* knockout reestablished therapeutic responses to immunogenic chemotherapy and immunotherapy with PD-1 blockade in spite of mental stress. Moreover, *Tsc22d3* knockout restored the type-I interferon response, the expression of genes involved in MHC class-I or class-II-restricted antigen presentation, as well as the production of interferon-gamma by tumor-infiltrating T cells in the condition of social defeat. Thus, TSC22D3 function within dendritic cells affected the activity of other immune cells, including T lymphocytes, within the tumor bed.⁸

Altogether, these results can be condensed into a cascade linking mental stress to an elevation of endogenous glucocorticoids, TSC22D3 activation in tumor-infiltrating dendritic cells, immunosuppression and subsequent failure of immunogenic chemotherapy or immunotherapy (Figure 1). Logically, this scheme implies that cancer patients should not be exposed to iatrogenic stress (which would increase the glucocorticoid

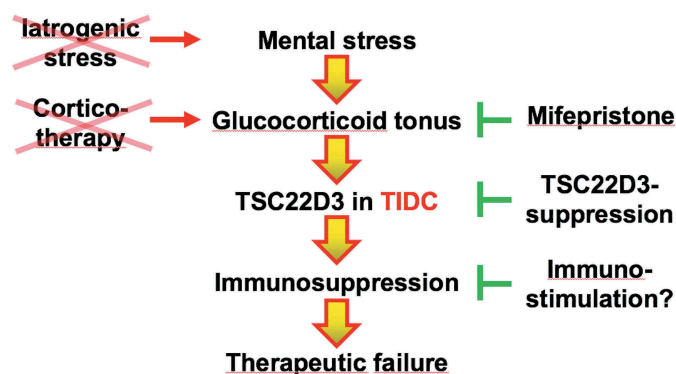


Figure 1. Cascade of events that link mental stress to the failure of anticancer therapies. Mental stress causes an elevation of the glucocorticoid tonus that stimulates TSC22D3 expression by tumor infiltrating dendritic cells (TIDC), causing local immunosuppression and therapeutic failure. Exogenous glucocorticoids (corticotherapy) have a similar immunosuppressive effect. While iatrogenic stress should be avoided, glucocorticoid receptor antagonists exemplified by mifepristone, TSC22D3 inhibition or immunostimulatory agents that bypass the pathway of immunosuppression might be used for avoiding therapeutic failure.

tonus) and rather might profit from social, psychological or psychopharmacological interventions that reduce their mental stress. Instead of administering synthetic glucocorticoids, alternative strategies for managing side effects (such as administration of tumor necrosis factor antagonists) should be considered. Glucocorticoid antagonists might be prescribed to anxious and depressed patients with elevated cortisol levels. Although, pharmacological TSC22D3 antagonists are currently not available, it might also be attempted to stimulate the antigen-presenting function of tumor-infiltrating dendritic cells by suitable immunomodulators, perhaps by means of local immunotherapy, thus bypassing the immunosuppressive effects of the glucocorticoid-TSC22D3 axis.

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ORCID

Yuting Ma <http://orcid.org/0000-0001-6267-1852>
Guido Kroemer <http://orcid.org/0000-0002-9334-4405>

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