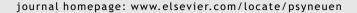


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Decrease of CD4⁺FOXP3⁺ T regulatory cells in the peripheral blood of human subjects undergoing a mental stressor

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KEYWORDS

T cells; T regulatory cells; Cell surface molecules; Acute psychological stress; Psychoneuroimmunology; Autoimmunity **Summary** We have previously shown that acute psychological stress alerts the adaptive immune response causing an increase in antigen-experienced effector T cells in the peripheral blood. Tregulatory cells (Tregs) play a central role in maintaining self-tolerance and controlling autoimmune responses. Here, we analyzed for the first time the behaviour of Tregs in the context of a stress-induced activation of the adaptive immune response.

31 healthy young males underwent a brief laboratory stressor and, in a crossover design, served as their own unstressed controls. We quantified effects of acute stress on CD4*FOXP3* T regulatory cells and other T cell subpopulations using flow cytometry. In addition, the expression of Treg-related effector molecules and stress hormone receptors were analyzed in the subjects' peripheral T cells.

We confirmed our previous observation of a stress-induced decrease in CD45RA+CCR7+ "naïve" and CD45RA-CCR7+ "central memory" T cells while CD45RA-CCR7- "memory effector" and CD45RA+CCR7- "terminally differentiated" effector T cells remained stable or increased.

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Importantly, we found acute psychological stress to cause a concomitant decrease in CD4⁺FOXP3⁺ Tregs and in CD4⁺ T cells expressing Treg-related effector molecules cytotoxic T-lymphocyte antigen-4 (CTLA-4) and latency associated peptide (LAP). Finally, we observed β_1 -adrenergic and glucorticoid α receptors to be overexpressed in Tregs, suggesting that these molecules might mediate stress-related effects on Tregs.

In conclusion, inhibiting components of the adaptive immune response, like Tregs, are down-regulated during a stress-induced activation of the adaptive immune response. In situations of chronic stress, this scenario might result in an exacerbation of inflammatory conditions such as autoimmune diseases.

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1. Introduction

The effects of acute psychological stress on the innate immune system have widely been investigated and especially the stress-induced mobilization of natural killer cells into the periphery is a repeatedly confirmed phenomenon (Segerstrom and Miller, 2004; Ader, 2007). On the other hand, the effect of an acute stressor on Tcells as key players of the acquired immune system has thus far not been examined systematically, a circumstance which seems surprising since the course of a number of T cell-mediated diseases is thought to be influenced by psychological stress. T cellrelated immune dysregulation has, for example, been associated with various autoimmune disorders (Cools et al., 2007; Yamanouchi et al., 2007; Anderson and Isaacs, 2008; Costantino et al., 2008). On the other hand, autoimmune diseases, such as multiple sclerosis, asthma, and rheumatoid arthritis, have been shown to be related to psychological stress (Sandberg et al., 2000; Mohr et al., 2004; Straub et al., 2005). However, immunological mechanisms linking the effects of psychological stress to exacerbations of autoimmune diseases have not yet successfully been delineated.

T cells can be characterized by dividing them into four distinct subsets according to their expression of the lymph node homing receptor CCR7 and CD45RA (Sallusto et al., 1999; Wills et al., 1999; Sallusto et al., 2004). CD45RA+CCR7+ "naïve" as well as the CD45RA-CCR7+ "central memory" T cells circulate between the peripheral blood and lymphoid tissue in search of antigen while CD45RA-CCR7- "memory effector" and CD45RA+CCR7- "terminally differentiated" effector T cells migrate into peripheral tissues where they exert their effector function. We have recently shown that acute psychological stress alerts the adaptive immune response causing a redistribution of these four T cell subgroups in the peripheral blood: CCR7⁺ naïve and central memory fractions decrease while CCR7- memory effector and terminally differentiated effector T cells increase (Atanackovic et al., 2006). Thus, under acute stress less mature T cells seem to be retained within lymphoid tissue awaiting exposure to antigen. Meanwhile, effector-type T cells are allocated into the blood, ready to rapidly migrate into tissues in case their effector function is needed.

While the immune system provides a large repertoire of T cells specific for foreign proteins such as microbial antigens, selection processes in the thymus largely prevent the escape of T cells directed against self-antigens into the periphery (Werlen et al., 2003). However, negative selection cannot fully guarantee the depletion of all autoreactive T cells.

Accordingly, naturally occurring Tregs, one main group of various subgroups of immunosuppressive cells, play a vital role in maintaining peripheral self-tolerance and immune homeostasis (Sakaguchi et al., 2008).

First described in 1995 by Sakaguchi et al. (1995), CD4⁺CD25⁺ Tregs have become of central research interest in the context of autoimmune disorders (Viglietta et al., 2004; Sakaguchi et al., 2006; Yamanouchi et al., 2007; Costantino et al., 2008), tumour immunity (Shimizu et al., 1999; Woo et al., 2001; Beyer and Schultze, 2006; Zou, 2006; Curiel, 2007), and infectious diseases (Belkaid and Rouse, 2005). As CD25, which constitutes the alpha chain of the IL-2 receptor, is not exclusively expressed on Tregs but also on activated conventional CD4⁺ T cells, the description of transcription factor forkhead box P3 (FOXP3), which is a specific intracellular marker and master regulator gene of naturally occurring Tregs, represented a major improvement for the proper identification of this T cell population (Fontenot et al., 2003; Hori et al., 2003). The major role of FOXP3expressing Tregs in preventing autoimmune diseases is underlined by the fact that FOXP3-deficient mice develop a lethal lymphoproliferative autoimmune syndrome and defect or loss of FOXP3 in humans leads to a severe autoimmune syndrome called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) (Bennett et al., 2001). It has been shown that Tregs actively suppress the proliferative response of CD4⁺ and CD8⁺ T cells, dendritic cells, and B lymphocytes. Tregs seem to exert these immunsuppressive functions through cell-cell contact dependent mechanisms involving various effector molecules as the glucocorticoid-induced tumor necrosis factor family-related gene (GITR), CTLA-4, lymphocyte activation gene-3 (LAG-3), as well as by secreting immunomodulating cytokines such as transforming growth factor- β (TGF- β) (Huang et al., 2004; von Boehmer, 2005).

Very little is known about the effect of acute psychological stress on peripheral Tregulatory cells. Based on our previous finding of a stress-induced mobilization of effector Tcells into the peripheral blood we hypothesized that acute stress might at the same time reduce peripheral numbers of immunosuppressive Tregs. In our present study, we analyzed for the first time the effects of acute psychological stress on human CD4⁺CD8⁻FOXP3⁺ T regulatory cells. We quantified numbers of Tregs and effector T cell subpopulations and we investigated T cellular expression of Treg-related effector molecules CTLA-4, GITR and LAP following a brief artificial stressor. Finally, we explored which hormone receptors might be responsible for possible stress-related changes in the numbers of peripheral Tregs.

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