

# Mechanism Linking Aggression Stress through Inflammation to Cancer

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## Abstract

Accumulating evidence shows that the central nervous system (CNS) regulates the activity of the immune system. Concerning the role of immune system in cancer, psychosocial influences on immune function provide a mechanism of association between psychosocial factors (like interpersonal aggression) and cancer prognosis. Social conflicts between males, involving high aggression stress and threat (psychosocial conflicts) produce both an allostatic state and allostatic load. The costs for aggressors (Hawks) and victims (losers) tested under semi laboratory conditions are quite different. Testosterone does not cause aggression, only exaggerates the pre-existing pattern and response to environmental triggers of aggression. The individual's personality type (authoritarian Hawk or Dove) has major impact on psychoneuroimmune mechanisms linking aggression stress through inflammation to cancer. Due to the latest connotations we propose this personality phenomenon label as "the Strauss-Kahn syndrome".

**Keywords:** Aggression stress; The allostatic load; Testosterone; DHEA; Type A personality; HPG-axis; Inflammation; NF  $\kappa$  B; IL-6; Stat3; Carcinogenesis

## Introduction

Clinical studies indicates that stress increases the immune cell apoptosis, decreases the spleen and thymus cell content, similarly the natural killer (NK) activity in the spleen, and it compromises the antitumor immune response in mice [1]. Examples of stressors associated with alterations in the autonomic nervous system (ANS) and in the hypothalamic-pituitary-adrenal (HPA) axis include aggression and post-traumatic stress disorder (PTSD) [2,3]. It can lead to chronic alterations in neuroendocrine dynamics and also alter multiple physiological processes involved in tumor pathogenesis [4,5]. Complex cell interactions in the tumor and its microenvironment play an important role in tumorigenesis and cancer progression. Cooperation between oncogenic genetic lesions is required for tumor development. Interaction between *Ras*<sup>V12</sup> and *scribble* involves JNK signaling propagations and JNK-induced upregulation of JAK/STAT-activating cytokines, a compensatory growth mechanism for tissue damage, a stress condition that activates JNK signaling. Similar cooperative mechanisms play a role in the development of other human cancers [6]. Stress events suppress a broad spectrum of immunological responses. The stress decreased the potential of the spleen cells to turn into antitumor cytotoxic T lymphocytes (CTLs) after *in vitro* restimulation. Stress significantly impairs the antitumor T cell responses through its suppressive effect on Th1-type CD4<sup>+</sup> T cells. [7,8]. Social confrontation, aggression and hypothermia resulted in increased (lung) metastasis from injected breast cancer cells [9]. Swim stress and social confrontation caused a 2-to 5-fold increase in the number of rat MADB106 breast tumor metastases in lung. Cellular and molecular events that promote cancer growth are also affected by stress: might compromise DNA repair mechanisms. Stress can also influence the expression of viral oncogenes and replication of tumorigenic viruses [10]. Tumor production of vascular endothelial growth factor (VEGF), indicate that stress might promote tumor growth by facilitating development of blood supply [11]. VEGF also interferes with the development of T cells and the functional maturation of dendritic cells, with possible effects on anti-tumor immune responses [12].

## Materials and Methods

### Subjects

Our data were collected during years 2009-2010 as part of research project of AXON on depression and it's possible relation to cancer among mostly men and women at high risk for mood disorders. Subjects were recruited from the community of Sturovo, Levice, Komarno in South Slovakia (Central Europe). Eligibility criteria were age of 15-60 years old, Slovak and Hungarian language, free of acute medical conditions, without lifetime history of psychiatric disorders, and at a high risk of developing an initial episode of depression. Subjects' medical histories were followed by detailed interview's and laboratory testing. Psychiatric backgrounds were evaluated with the Structured Clinical Interview for Diagnostic and Statistical Manual of mental Disorders, 4<sup>th</sup> Edition (DSM-IV) Non-Patient Edition. High-risk was defined as having a first-degree relative with a history of affective disorder, and scoring in the top quartile of the population distribution on one of two indices of cognitive vulnerability to depression, the Dysfunctional Attitudes scale or the Adolescent Cognitive style Questionnaire. This article focuses on 40 subjects assessed at study entry, and 6 months later.

### Interpersonal signals

Social ties can also have detrimental influences on health, especially if they are marked by conflict, mistrust and instability. Among patients recovering from a mood disorder, family tensions, tensions in workplace relations, conflicts in relations of a friendships double the odds of a relapse occurring. Interpersonal difficulties are also associated with heightened susceptibility to infections, delayed healing of wounds, accelerated emergence of the metabolic syndrome, increased morbidity

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and mortality from disease due inflammation until cancer. Underlying mechanisms may involve chronically abrasive relationships fostering low-grade systemic inflammation, contributing to the evolution and expression of psychiatric, infectious, metabolic and carcinogenic diseases.

### Chronic interpersonal stress

To assess the extent of chronic interpersonal stress in subject's lives, we administered the UCLA Life Stress Interview Version at study entry. This semistructured instrument probes stressors in multiple domains of life. In each domain, the interviewer asks a series of open-ended questions and uses the data to rate the degree of chronic stress over the last 6 months. For this paper, we averaged ratings across the interview's three social domains: friendship, working and family relationships. Scores on the final index could range from 1-5, with lower values reflecting warm, intimate and supportive relationships, and higher values suggesting conflict, mistrust and instability.

### GR, NF $\kappa$ B, and I $\kappa$ B

Expression of pro-and anti-inflammatory signaling molecules was quantified through real-time reverse transcription polymerase chain reaction (RT-PCR) at study entry and 6 months later. Total RNA was extracted from leucocytes using PAXgene Blood RNA kits. For NF  $\kappa$  B and I  $\kappa$  B, commercially available assays were used (#HS00765730\_m1 and #HS00153283\_m1, Applied Biosystems). Results are expressed as relative quantities of each target, calculated by subtracting each patient's delta C in the distribution. Thus, higher relative quantities indicate greater expression of target genes.

### Systemic inflammation and cytokine production

Systemic inflammation was assessed, using levels of CRP and IL-6, at study entry and 6 months later. CRP was measured using a high-sensitivity chemiluminescence technique (Immulin 2000), and IL-6 was measured using commercially available high-sensitivity enzyme-linked immunosorbent assays (ELISAs) with a minimum detection threshold of 0.039 pg/ml.

### Potential confounders

For determination of behavioral and biomedical characteristics as confounders we collected information regarding age, ethnicity, socioeconomic status, smoking history and physical activity. Each of these factors has been linked to interpersonal difficulties and/or immune functions. Socioeconomic status was assessed with the MacArthur Scale of Subjective Social Status. Because depressive symptoms can arise from chronic interpersonal difficulties, and themselves bring systemic inflammation, we also administered the Beck Depression Inventory at the 6-month visit.

### Statistical analyses

To evaluate the study's hypotheses, we estimated a series of partial correlations between chronic interpersonal stress at baseline and inflammation parameters 6 months later. Each analysis controlled for the potential confounding influences of age, ethnicity, socioeconomic status, as well as the outcome variable at baseline. Thus, significant associations indicate that chronic interpersonal difficulties at study entry presage changes in biological outcomes over the next 6 months, and do so in fashion that is independent of the demographic and behavioral covariates in the model.

In this our study evident that social conflicts including interpersonal difficulties can also have detrimental influences on

health. Chronic conflictual interactions foster low-grade systemic inflammation contributes to evolution of psychiatric, infectious, metabolic and cancer [13-15]. Those who expressed greater hostility showed in the laboratory higher levels of the inflammatory cytokines interleukin (IL-6) [16,17] and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [18]. Quality of interpersonal relations relates to two major biomarkers of systemic inflammation: C-reactive protein (CRP) and interleukin IL-6 [17,19,20]. In the molecular signaling pathways is important the expression of messenger ribonucleic acid (mRNA) for the chief proinflammatory transcription factor, nuclear factor  $\kappa$  B (NF  $\kappa$  B) and the glucocorticoid receptor (GR) [13,21]. GR is mediating induction of inhibitor of  $\kappa$  B (NF  $\kappa$  B), a molecule that sequesters NF  $\kappa$  B in the cytosol and prevents it from switching on proinflammatory genes [22]. Social difficulties provoke cortisol abnormalities, which over time foster resistance to glucocorticoids and expression of inflammatory mediators [15]. Corticosteroids coordinate the expression of genes in cell metabolism and synaptic transmission [23]. Signaling in limbic neurons can be regulated also through interaction of glucocorticoid (GR) with transcription factors, such as nuclear factor  $\kappa$  B (NF  $\kappa$  B) and activator protein 1 (AP1). Stress-related changes leading to expression of the inflammatory cytokines can have profound influences on social behavior [24-28].

### Results

Our study associates with growing evidence about mechanisms converting aggression stress into cellular dysfunction. Various genes up-regulated by psychosocial stress are controlled by the transcription factor nuclear factor NF  $\kappa$  B. In volunteers NF  $\kappa$  B activity was tested in peripheral blood mononuclear cells (PBMC) [29,18]. NF  $\kappa$  B was rapidly induced during stress exposure in parallel with catecholamines and cortisol. Noradrenaline resulted in a dose-dependent induction of NF  $\kappa$  B and NF  $\kappa$  B-dependent gene expression. It depended on pertussis-toxin-sensitive G protein mediated phosphatidylinositol 3-kinase, Ras/Raf, and mitogen-activated protein kinase activation. Thus, noradrenalin-dependent adrenergic stimulation results in activation of NF  $\kappa$  B *in vitro* and *in vivo*. Activation of NF  $\kappa$  B represents a downstream effector for neuroendocrine response to stressful aggression events and links changes in the activity of the neuroendocrine axis to cellular response. Our results confirm that downstream signals converting aggression stress into cellular dysfunction. Further this mechanism lead to the induction of inflammatory reactions and simultaneous decrease in anti-inflammatory reactions producing cytokine release and monocytic cell activation. Increased NF  $\kappa$  B activation was finding in blood lymphocytes of women stressed by an aggressive life-threatening stress situation characterized by anxiety and desperation. Increase in NF  $\kappa$  B-binding activity was functionally significant because NA induced a dose-dependent increase in NF  $\kappa$  B regulated IL-6 transcription in these cells. Activation of NF  $\kappa$  B observed in PBMC after exposure to aggression stress, thus linking psychosocial stress to mononuclear cell activation and subsequent changes in the immune system. PBMC circulating cells playing an important role in diseases as inflammation, and immune response. In chronic diseases, in which RAGE ligands are expressed, psychosocial stress-induced NF  $\kappa$  B activation may be amplified and converted to a constant threat.

In evolutionary terms different organisms adopt different behavioral strategies [30] to cope with stress. For our conceptual framework of the aggression stress is central the strategy of authoritarian Hawks, showing that inefficient management of allostasis mediators may lead to violent behavior, development of impulse control disorders and inflammation [31].

In a competitive situation the Hawk shows aggressive behavior, stopping only if injured or when the opponent submits. The Hawk generally wins the entire resources. If the Hawk is unsuccessful, may have lower fitness because of energy loss, wounds, blood loss and infection, which can lead to the inflammation. This can be also a consequence for the victims of the aggression stress [32,29].

Authoritarian Hawks show a fight-flight response during which an activation of the hypothalamic-pituitary-gonadal (HPG) axis is increasing the plasma level of the testosterone. Testosterone increases the likelihood of aggression by stimulating vasopressin synthesis. Higher impulsivity may be a consequence of lowered activity of the tonic 5-HT neurotransmitter system.

There is accumulating evidence that Hawks adopting the fight-flight response are characterized by a shift to sympathetic dominance. The risk of being wounded is greater in Hawks because they are more aggressive and bolder than Doves. Sympathetic noradrenergic nerve fibers innervate the vasculature and parenchymal fields of lymphocytes and associated cells in several lymphoid organs, including the thymus, spleen, lymph nodes, gut-associated lymphoid tissue and bone marrow of mammalian species.

Additionally glucocorticoids produce a Thelper1/Thelper2 (Th1/Th2) shift, from cellular towards humoral immunity because Th1-related cytokines (IL-2) stimulate cellular immunity, Th-2-related cytokines (IL-4) enhance humoral immunity. The Th1 response protects against infections and tumors. Due to their different behavioral strategies Hawks and Doves are confronted with different pathogens. Hawks are at greater risk of wounding because of their aggressiveness and boldness. Increase in the levels of catecholamines in Hawks result in elevated leukocyte numbers in the blood. Catecholamines recruit the body's soldiers, especially NK cells and granulocytes. A shift from Th1 to Th2 may counter the tissue-damaging effects of macrophages and Th1 cells. Peripherally released cytokines act on the brain via fast transmission pathway involving primary afferent nerves innervating the bodily site of inflammation and a slow transmission pathway involving cytokines originating from the choroids plexus and circumventricular organs and diffusing into the brain parenchyma by volume transmission. Immune overstimulation can be prevented through the vagus nerve pathway named cholinergic anti-inflammatory pathway. Via this route rapid inhibition of release of the macrophage, TNF, IL-1beta, IL-6 and IL-18 takes place [33,14,23].

Increased sympathoadrenal activation can be observed in dominant males when they housed in unstable social groups. These subjects suffer more extensive atherosclerosis than subordinates. Sympathetic activation induced endothelial injury. Authoritarian Hawks with their high sympathetic reactivity are more vulnerable to developing tachyarrhythmias than Doves. Shift of autonomic balance toward sympathetic dominance makes Hawks vulnerable to sudden death once apoptosis has developed in the heart. Sympathetic system hyperactivity affects not only the cardiovascular system but also the immune system. A growing number of animal findings strongly suggest that a hyporeactive HPA axis may be pathologically significant through a shift to Th1 cytokines that increases susceptibility to chronic inflammation [34]. Hawks have an increased risk of wound [35] and infections because they are more aggressive and bolder than Doves. Th1 dominated cellular immune response in Hawks is very adaptive against infections. But this hyperimmune state together with a blunted HPA axis activity incurs costs such as the risk of inflammation and autoimmune disease. The lower parasympathetic reactivity of Hawks shows that they are less well equipped to inhibit the release

of macrophage cytokines via the vagal parasympathetic route. The increased release of cytokines can contribute to the costs of allostatic load [23].

The tumor promoting effect of inflammation is now widely recognized and better understood. Immune cells often infiltrate tumors and preneoplastic lesions produce a variety of cytokines and chemokines that propagate a localized inflammatory response and also enhance the growth and survival of premalignant cells by activating transcription factors like NF- $\kappa$ B. NF- $\kappa$ B-dependent cytokines IL-6 and TNF- $\alpha$  cross-regulate each other during colitis-associated cancer (CAC) development to enhance chronic inflammation and tumorigenesis [36,20,37]. The cytoprotective and protumorigenic effects of IL-6 are due to Stat-3 activation. By regulating the differentiation and survival of pathogenic T helper (Th) cells, IL-6 perpetuate chronic inflammation [16] and ensure the continuous production of cytokines and growth factors required for malignant cell survival and growth [17]. IL-6 production is triggered by proinflammatory stimuli [14,20,15,37]. In chronic sensory contact with an aggressive opponent for 25 days induced a decrease in hippocampal gene-expression in conserved helix-loop-helix-ubiquitous kinase (CHUK) in the dentate gyrus (DG) of non-aggressive mice. CHUK is a kinase that is involved in the translocation of NF- $\kappa$ B to the nucleus [38,39]. Several genes belonging to ras-family members and members of the Bel-2 family and consequently NF- $\kappa$ B are downregulated in these non-aggressive mice. NF- $\kappa$ B plays a crucial role in neuronal survival and synaptic plasticity. Non-aggressive Doves are more responsive to threats, which in turn have deleterious consequences, including decreased hippocampal NF- $\kappa$ B signaling and increase in neuronal vulnerability.

### NF- $\kappa$ B and Stat3 integrate interpersonal stress signals

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) and Stat3 proteins are transcriptional factors [40,19,41], which integrate stress signals and orchestrate immune responses also linked to carcinogenesis. Cancer development include: self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion of apoptosis, limitless replicative potential, tissue invasion, metastasis and sustained angiogenesis. NF- $\kappa$ B signaling is involved in all these hallmarks. Recent experimental studies showing the mechanistic pathways by which NF- $\kappa$ B signaling contributes to carcinogenesis. Inflammation promotes carcinogenesis, NF- $\kappa$ B and Stat3 signaling integrate interpersonal stress signals during this process [31,42,43]. NF- $\kappa$ B and Stat3 control the expression of anti-apoptotic, pro-proliferative and immune response genes. These genes overlap and show transcriptional cooperation and inhibition between the two factors. Activation and interaction between NF- $\kappa$ B and Stat3 plays a key role in control of the dialog between the malignant cell and its microenvironment, with inflammatory/immune cells that infiltrate tumors [44,45,46]. Cytokines induced in response to NF- $\kappa$ B in immune cells of the tumor microenvironment lead to Stat3 activation in both malignant and immune cells. Within malignant and pre-malignant cells Stat3 activates oncogenic functions, within inflammatory cells it may also suppress tumor promotion through its anti-inflammatory effects. An unstable hierarchy produces robust changes in allostatic state depending on the social status of the primates. Subordinate males sometimes die within 2 weeks exposed to an unstable social system [47]. This suggests that repeated stress during recurrent depressive episodes result in cumulative hippocampal injury as reflected in volume loss. In primates hippocampal degeneration can be observed after sustained social conflict, with consequent ulceration and hyperplastic adrenal cortices indicative of sustained glucocorticoid release. Chronic activation of GRs in hippocampus can damage hippocampal neurons, may lead to severe hypercortisolism.



Than question is: what triggers the transition from adaptive plasticity to permanent damage. It is well accepted that in animals and humans social conflict not only affect mood and brain functioning but also food intake. In socially defeated individuals high levels of glucocorticoids inhibits food intake and evokes body weight loss probably via increased hypothalamic CRF levels [48]. A relationship exists between stress-related diseases and one's behavioral strategy. It was observed that humans with type A personality are more aggressive and hostile, extremely competitive, impatient and always in a hurry. Authoritarian personality type A closely resembles the Hawk type.

## Conclusions

Psychoneuroimmune interactions could be one of the biologic mechanism underlying correlations between psychologic factors and cancer. A possible mechanism suggested by recent studies are factors secreted by leucocytes (cytokines) which can influence both immune and CNS processes. The evidence for physiologic pathways linking the CNS and the immune system suggests that "hardwiring" is in place for regulation of the immune system by the CNS. The association between times of psychologic distress (aggression) and reductions in proliferative response of lymphocytes cultured with mitogens, are mitogens that activate T-cells. This *in vitro* measure of lymphocytes activation, sensitive to psychosocial influences is linked to any disease outcome. There are studies that have explored the relationships between psychosocial variables and natural killer (NK) cell activity. This studies support the link between psychosocial factors (aggression) and alterations in immune function.

Psychosocial influences on immune function providing a biologic mechanism that account for reported association between psychosocial factors and cancer. Three general categories of psychosocial variables appear to be related to cancer: history of psychologic distress (aggression), social support, and personality variables. The determination of causal links between psychosocial factors and the incidence of cancer is obscured by the long delay between the initiation of malignancy and the detection of neoplastic disease. Tumors can be induced by a number of different mechanisms, including DNA tumor viruses, retrovirus insertion near a cellular oncogene, and cellular oncogene activation occurring spontaneously or as a result of carcinogen exposure. There is evidence that the immune system can enhance the growth of some tumors as well as inhibit it. In the light of the independent evidence for a relationship between psychosocial factors and cancer, the evidence that the immune system plays a role in cancer raises the possibility that psychoneuroimmune interactions may play a role in cancer.

In conclusion, the research related to possible psychoneuroimmunologic processes in cancer provides support for the following hypotheses: (1) the outcome of some cancers can be influenced by psychosocial factors, (2) the activities of the immune system can influence the outcome of some cancers, (3) immune responses such NK-cell activity play role in defenses against cancer, appears be influenced by psychosocial factors (aggression). Alterations in immune defenses can be investigated as a possible mechanism by which psychosocial factors could influence cancer. Chronic inflammation promotes tumor development and is not the one response but instead represents a dynamic, continuously changing microenvironmental process with various effects at subsequent stages of tumorigenesis. Multiple factors in both the host and the malignant cells, the malignancy has impact on the inflammatory response and vice versa. There is evidence that testosterone 'organizes' aggression during development [23].

After a social challenge, activation of the HPA axis, testosterone secretion is significantly lowered in the psychologically defeated human patients and primates. Decrease in testosterone concentrations is responsible for a general decrease in activity and motivation, often associated with lowered self-esteem. Once the locus coeruleus (LC) become hyperactive due a positive correlation between hypercortisolism and increased cerebrospinalfluid (norepinephrine - NE), this core system may enter a vicious circle, because the LC can inhibit the prefrontal cortex.

In dominant male monkeys is observed an increased sympathoadrenal activation if housed in unstable social groups. In rabbits was shown that sympathetic activation induced endothelial injury. Shift of autonomic balance toward sympathetic dominance may cause injuries leading to civilizational diseases in social environment of the Hawks. This allostatic load may be in their microenvironment pathologically significant through a shift to Th1 cytokines and increasing susceptibility to chronic inflammation, which can on the long term trigger various forms of cancer in humans.

Most of tumors contain inflammatory and immune cells macrophages and lymphocytes, which produce cytokines and other factors that promote tumor growth and survival. Tumor-promoting role of immune cells is manifested in inflammation-associated cancers, where tumors arise and grow at sites of chronic inflammation [20]. Lymphocytes, IL-6, NF $\kappa$  B may be part of the translational entry points into the neural circuit regulating immune changes induced by environmental stress, leading to development of cancer [20,49]. The stressor significantly increased circulating levels of IL-6 and MCP-1, significantly correlated with stressor-induced changes to three bacterial genera: *Cproccoccus*, *Pseudobutyrvibrio*, and *Dorea* [50,51].

Social conflicts caused by the interpersonal aggression mediated by authoritarian type A personality of males is involving complicated immune network of the psychosocial threat of cancer as the end stage of inflammation. It has been shown in a population of mice, that males with high testosterone outnumbered those with lower levels, but the presence of too many aggressive individuals resulted in a crisis of the population. This extends into humans a large corpus of animal research, suggesting that an organism's physiology is intimately regulated by the interpersonal context in which s/he resides. Due to the latest connotations we propose this personality phenomenon label as "the Strauss-Kahn syndrome".

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