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Effects of Social Stress on Immunomodulation and Tumor Development

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1. Introduction

Over the last 30 years, much interesting research has been carried out in the field of psychoneuroimmunology which has shown, with scientific rigor, that psychological states, including those generated by exposure to stress-inducing agents, may alter the immune balance and influence both health and illness. Psychoneuroimmunology is the convergence of various different disciplines (behavioral science, endocrinology, neuroscience and immunology) which studies the immune changes associated with behavioral change and the behavioral changes associated with immunological changes, as well as the mechanisms involved in this relationship. It is based on the reciprocal relationships which exist between the Central Nervous System (CNS) and the Immune System (IS), the two most complex systems involved in the maintenance of homeostasis. Communications between the CNS and the IS are bidirectional and involve neurotransmitters, neurohormones, neuropeptides and cytokines, which together form a complex network that is still being explored today.
Four general research areas have found evidence of the existence of afferent and efferent communication channels between the two systems. These areas are:

- Studies focusing on lesions to or stimulations of certain regions of the brain which alter the immune response (Rassnick et al., 1994).
- Studies which have revealed the extensive presence of sympathetic nervous system fibers, mainly noradrenergic in nature, innervating both the primary and secondary lymphoid organs. These nervous fibers innervate the vascular and parenchymal zones of lymphoid organs, thus providing a close anatomical link between the two systems (D. L. Felten et al., 1985).
- Studies focusing on the influence of numerous CNS neurohormones, mainly hypothalamic-pituitary in nature, which have a strong regulatory effect on the IS, as well as on the expression of numerous receptors which the immune cells have for them (Blalock et al., 1985).
- Finally, other studies have shown that products of immune cells, such as cytokines, have a neuroendocrine activity which is capable of influencing diverse brain functions, as well as providing information to the neuroendocrine system, activating inhibitory feedback circuits to ensure their own regulation (Dantzer et al., 2001).

These discoveries have given rise to a new approach to the IS. This new model, known as the "danger model", was first proposed by Polly Matzinger in 1994. The key idea of this model is that the main function of the immune system is to recognize and protect the organism from any potentially dangerous threat. According to the model, "danger" is anything capable of harming or destroying the cell or tissue. Polly Matzinger argues that in order to carry out this function, the IS has to communicate with the organism's other systems (Matzinger, 2002).

This way of conceiving the IS function has opened up a whole new field of study in diverse models in which the activation/modification of the immune response cannot be explained solely by pathogens from outside the organism. Rather, other variables are also involved, including the effect of situations of psychological stress on the development of infectious diseases, autoimmune diseases and cancer. In this chapter we aim to highlight the importance of social stress and the effects of the hormones released during stressful situations in the study of tumor development, particularly in relation to melanoma tumor progression. To this end, the chapter first outlines the basic physiological aspects of neuroimmunomodulation, which underpin the effects that stress may have on immunity and tumor development. Next, we will examine the studies carried out in relation to melanoma tumor development, and the possible therapeutic benefits of psychosocial intervention.

2. Communication pathways between the Central Nervous System and the Immune System

The recognition and integration of internal and external sensorial stimuli by the CNS triggers changes in the synthesis and release of neurotransmitters, hormones and neuropeptides. These substances reach the organs and lymphoid cells through two main descending communication pathways, which enable the CNS to control the activity of peripheral organs, including the organs of the immune system.

On the one hand, the neurovegetative communication pathway, through automatic innervation and the subsequent secretion of norepinephrine from nerve endings and epinephrine from the adrenal medulla, enables the CNS to control the activity of immune organs such as the spleen, the thymus and the lymph nodes, among others. And on the other, the neuroendocrine communication pathway refers to the synthesis and release of secretion factors by certain cells to the pituitary gland's pituitary portal system. This stimulation causes the pituitary gland to synthesize and release diverse hormones into the bloodstream, and in turn, these trigger the synthesis and secretion of new hormones capable of influencing diverse organs and peripheral cells (Fig. 1).

The activation of these two neurochemical communication pathways and the subsequent secretion of hormones and neurotransmitters may have a major effect on the immune system function. By means of receptor-ligand interaction, these endogenous substances affect diverse processes of the immune response, such as cell development and differentiation, lymphocyte activation and proliferation, cell migration, the production and release of cytokines and the expression of cytokine receptors.

Receptors for monoamines (norepinephrine, epinephrine, dopamine and serotonin), cholecystokinin, adrenocorticotropic hormone (ACTH), methionine-enkephalin, leucine-enkephalin, β-endorphin, neurotensin, substance P, vasoactive intestinal peptide (VIP), prolactin (PRL), growth hormone, thyroid-stimulating hormone (TSH), melatonin,

dynorphin, corticotropin-releasing hormone (CRH), cortisol, somatostatin and gonadal hormones have all been found in IS cells (Weigent & Blalock, 1987; Yada et al., 2004). The activation of these receptors by selective agonists triggers well-defined changes in the working of these cells, both *in vivo* and *in vitro*.

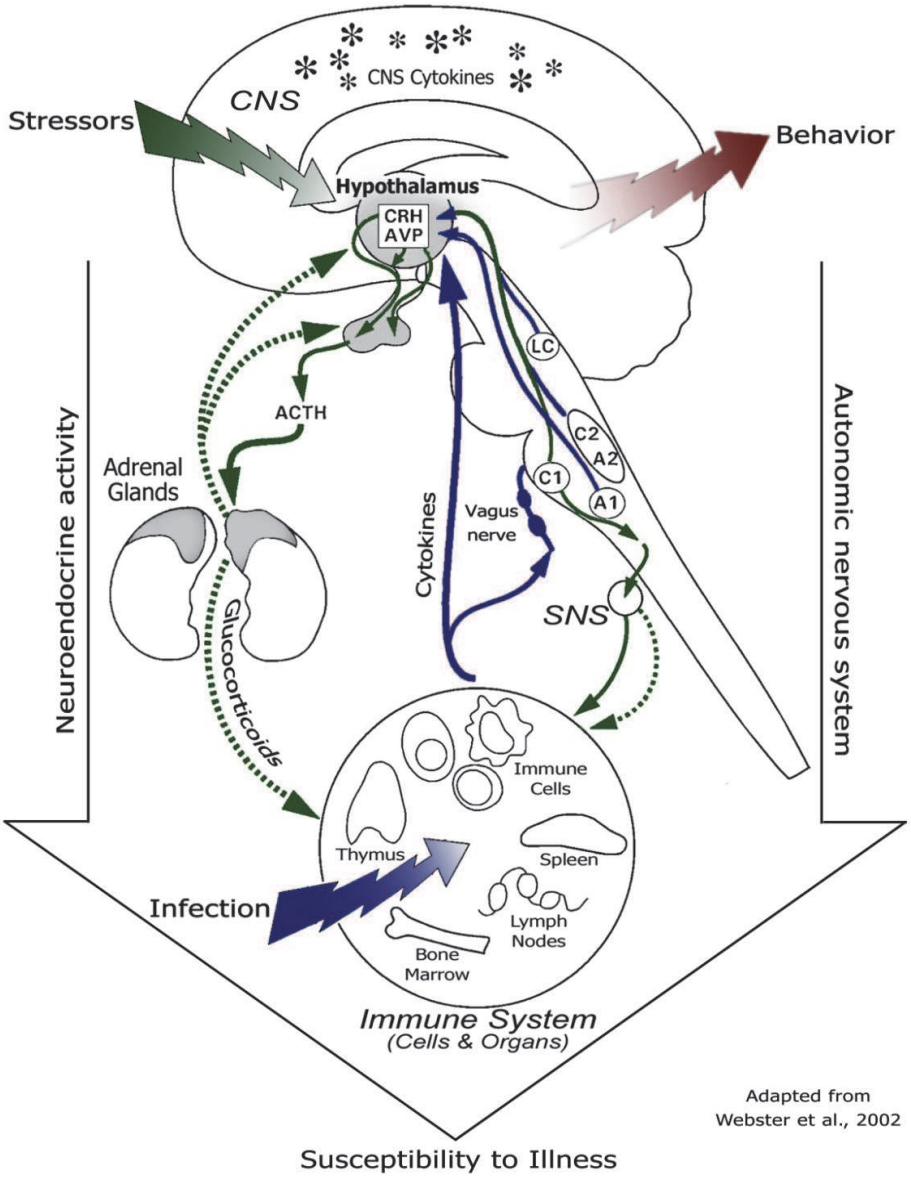

Fig. 1. Diagram of the routes of communication between the brain and immune system, including the HPA axis, sympathetic nervous system, and cytokine feedback to the brain.

Since this chapter focuses on the effects of stress on the immune response, we will pay special attention to the neuroendocrine (hypothalamic-pituitary-adrenal, or HPA axis) and vegetative (sympathetic-adreno-medullary or SAM axis) pathways through which this relationship is established.

2.1 The neuroendocrine pathway, the hypothalamic-pituitary-adrenal axis (HPA)

The hypothalamic-pituitary-adrenal (HPA) axis is constituted by three main structures: the hypothalamus, the pituitary gland and the adrenal glands. The sensorial activation signals converge in the paraventricular nucleus (PVN) of the hypothalamus, where they stimulate the synthesis and release of adrenocorticotropin-releasing hormone (CRH) and other neuropeptides. The axons of these neurons extend to the outer layer of the median eminence, where they release their neurosecretary products into the hypophyseal portal system, triggering the synthesis and release of ACTH by corticotropic cells of the anterior pituitary gland. The fast release of ACTH reaches the adrenal glands, where it stimulates the synthesis and release of glucocorticoids. The activation of the HPA axis also triggers the activation of the set of opioid peptides, which are thought to play a key immunomodulatory role, and as well as ß-endorphin, derived from pro-opiomelanocortin (POMC), whose synthesis and release is activated by CRH and which seems to affect the IS, modulating the effects of glucocorticoids in the immune function and the activation of natural killer cells (NK cells) Other peptides from the family of endogenous opioids, such as encephalins and dynorphins, are also involved in the modulation of the immune response (Carr et al., 1990).
Other pituitary hormones, such as vasopressin or the group formed by prolactin, growth hormone and somatostatin, as well as other neurotransmitters and neuropeptides, seem also to have immunomodulatory effects (Jessop, 2002)
Finally, glucocorticoids (GCs) are one of the most secreted hormones in the stress response and the object of special attention in numerous research projects which have highlighted the important role that they play in the regulation of the immune response (Besedovsky & del Rey, 2007).

2.2 The neurovegetative pathway, the sympathetic-adreno-medullary axis (SAM)

The activation of the SAM axis involves the activation of the sympathetic nervous system, which in turn triggers the secretion of norepinephrine (NE) by the sympathetic nerve endings and the secretion of epinephrine (E) and NE by the adrenal medulla.
The SAM axis innervates all the primary and secondary lymphoid organs in both animals and humans (S. Y. Felten & Felten, 1991), providing catecholamines with the physical space they require to modulate many immune parameters (Oberbeck, 2006). The local secretion of NE from nerve endings and the secretion of E and NE into the blood stream enable them to influence not only innervated organs and tissues, but also other cells of the immune system. For this reason, the SAM axis provides a regulation and integration channel between the CNS and the IS. Specifically, noradrenergic fibers have been found to exist in both primary lymphoid organs, including the thymus and bone marrow, and secondary organs, including the spleen, lymph nodes and the mucosa-associated lymphoid tissue. Evidence has also been found of the existence of adrenergic receptors in immune cells (such as T and B lymphocytes), in natural killer cells (NK cells) and in macrophages (Benschop et al., 1997). Finally, it has also been found that lymphocytes are able to synthesize catecholamines, and that these in turn may act both autocrinally and paracrinally. The effects of E and NE in target cells are mediated by receptor-ligand interactions. There are two types of receptors, as

well as catecholamines, alpha adrenergic receptors (αAR) and beta adrenergic receptors (βAR), which are expressed specifically in accordance with the tissue and which have different degrees of affinity (Biber et al., 2006).

The regulatory effect of catecholamines on the immune system cells has been widely studied. It has been shown that catecholamines inhibit the activity of those cells associated with the innate immune response, and may either increase or inhibit the activity of cells associated with the adaptive immune response. Through adrenergic receptors, mainly β2-adrenergic receptors (β2AR), NE is able to regulate the immune responses of antigens, influencing clonal expansion, the production of cytokines and/or the response capacity of certain cells, altering the expression of receptors, changing the balance between T and B cells and increasing or inhibiting the inflammation response and lymphocyte mobilization (Bellinger et al., 2008). Adrenergic agonists may modulate *in vitro* all aspects of the immune response during the initiation phase, the proliferation phase and the effector phase. Research has shown that, in addition to inhibiting mitogen-induced T cell proliferation, the stimulation of β2ARs also inhibits the differentiation of T cells in type 1 T-helper cells (Th1), thus affecting early events which are involved in the initiation of the proliferation (Sanders et al., 1997).

The sympathetic nerve endings of the bone marrow are involved in regulating hematopoiesis. These endings respond to certain stressors which increase the concentration of NE, and may therefore affect the cell formation process. Diverse studies have shown that the function of noradrenergic innervation is to suppress the proliferation of thymocytes, while at the same time increasing their differentiation. The inhibition of T lymphocyte proliferation may be explained in part by the capacity of catecholamines to inhibit the expression of the interleukin-2 receptor (IL-2) and /or the production of this cytokine by activated T lymphocytes (Sanders et al., 1997). The increase in catecholamines affects B lymphocytes also. These lymphocytes complete their development in the bone marrow and possess β-adrenergic receptors (Whisler et al., 1992).

Like glucocorticoids, catecholamines have generally been considered immunosuppressants. However, evidence has been found indicating that, under normal physiological conditions or in conditions generated during situations of stress, catecholamines may influence the immune system in a much more complex way (Elenkov et al., 2000). This new approach may help explain some of the well-known yet often contradictory effects that occur as a result of the activation of the stress response and which affect the immune function.

3. Social stress and cancer

Since the first quarter of the 20th century, many epidemiological studies have been carried out on the effects of stress and other psychological variables on tumor development and growth in humans. The results suggest that stress and the ability to cope with it are related to both the incidence of cancer and survival time. These studies have generally be classed as retrospective, quasi-prospective and prospective. The majority of studies fall into the category of retrospective analysis, and reveal that the appearance of various forms of neoplasms are often preceded by stressful life events. Cancer appears more frequently than expected in people who have been widowed or who have gone through a divorce or separation (Hemminki & Li, 2003). Some authors have found a direct relationship in women between stressful life events and breast cancer (Forsen, 1991), although other authors have failed to find any such association (Priestman et al., 1985). These apparently contradictory results may be analyzed in more detail by taking into account the coping strategies

employed in response to stress by the subjects in question. The concept of coping styles, i.e. the idea that both animals and humans adapt to adverse situations in different ways, and that the repercussions of these responses on health also differ, is an area of great scientific interest. This hypothesis has been corroborated by the results obtained in subsequent studies. Thus, an association has been found between the coping strategy adopted by breast cancer patients and the course of the disease (Lauver et al., 2007). It has also been observed that planning, positive coping and distraction are positive predictors of good health, while guilt has been found to be a negative predictor (Li & Lambert, 2007).

Quasi-prospective studies also support the idea that factors associated with life stressors are predictors of greater neoplasic development (Grossarth-Maticek et al., 1995). Cooper et al., (1989) found that although women diagnosed with breast cancer recounted fewer stressful life events, they tended to view them as more threatening (Cooper et al., 1989). Other authors have also found similar results. Price et al., (2001) observed that women who perceived a stressor as extremely threatening and who also lacked social and emotional/family support, were nine times more at risk of developing breast cancer (Price et al., 2001). These studies suggest that it is not the mere existence of life stressors in themselves that may affect our health and be associated with the development of cancer, but rather their specific impact on the individual. In accordance with these results, it has been found that individual differences in the type of coping strategy adopted may affect the health of women at serious risk from hereditary breast cancer (Pieterse et al., 2007).

Finally, in prospective studies, the effect of life stressors is fairly inconsistent. Some authors have found that the more intense the stressful life experience, the higher the recurrence rate of cancer and the shorter the survival time (Forsen, 1991); others, however, failed to find any such relationship (Surtees et al., 2010). Contradictory results have also been found in relation to cancer mortality rates in widows and widowers (Martikainen & Valkonen, 1996), as well as in connection with the relationship between social support and neoplasic progression (Maunsell et al., 1995)

In addition to life stressors, certain personality traits and, again, certain coping strategies (particularly the concept of emotional repression) have also been the subjects of much attention (Eysenck, 2000; Segerstrom, 2003). Specifically, studies involving patients with malignant melanomas indicate that personality type predicts neither recurrence nor survival time (Canada et al., 2005). However, a greater progression of the disease was found in patients who claimed to have accepted their illness or who expressed feelings of impotence/desperation (Temoshok et al., 1985) and a positive relationship was observed between the manifestation of active coping strategies and a higher survival rate (Fawzy et al., 1993).

3.1 Physiological response to stress and cancer

The biological mechanisms which underlie the effects of stress on cancer have yet to be fully explained, and their clinical significance for human diseases has yet to be clarified. A number of studies involving both humans and animals suggest that stress may influence the growth and behavior of tumor cells, either directly, through central nervous system mediators, or through the neuroendocrine regulation of the immune response to the tumor.

The former involves the effects of stress-released hormones on the tumor cells themselves or on their cellular microenvironment. Research carried out on animals has shown that stress may foster angiogenesis through the release of catecholamines, which though beta-adrenergic mechanisms trigger an increase in tumor vascularization (Tasker et al., 2006).

Hormones such as NE, which are linked to the activation of the SNS, foster angiogenesis in human tumors, increasing the levels of vascular endothelial growth factor (VEGF) through beta-adrenergic mechanisms (S. K. Lutgendorf et al., 2003). Norepinephrine also fosters various steps which are essential to tumor metastasis development, such as migration and invasion (Masur et al., 2001). Glucocorticoids regulate a wide variety of glucocorticoid-receptor-mediated cellar processes, activating or repressing target genes. Recent experimental studies carried out *in vitro* and *in vivo* have demonstrated that as well as inducing apoptosis in lymphocytes, glucocorticoid hormones also activate the survival of genes which protect cancer cells from the effects of chemotherapy (Wu et al., 2004). Glucocorticoids may also activate oncoviruses and inhibit anti-tumor and anti-viral cellular immune responses. Moreover, glucocorticoids such as cortisol may function in synergy with catecholamines to facilitate cancer growth (Nakane et al., 1990). It is therefore plausible that stressful situations characterized by increased levels of catecholamines and cortisol (such as uncontrollable stress, for example) may have a greater impact on cancer-related processes.

Stress affects the levels and expression of other hormones also, such as prolactin (which increases with stress) and oxytocin and dopamine (which decrease with stress). Prolactin may foster cell growth and survival in breast tumors and other tumor cells (Clevenger et al., 2003). Oxytocin inhibits the growth of epithelial tumor cells (such as those in the endometrium and the breast), as well as of cells of neural or medullar origin; however, this hormone has a stimulatory effect on the growth of trophoblastic and endothelial tumors (Pequeux et al., 2004). For example, endogenous oxytocin has a dose-dependent mitogenic effect on small lung cancer cell lines, which is blocked by oxytocin receptor antagonists. Dopamine, which inhibits the growth of various types of malignant tumors, blocks VEGF-induced angiogenesis both *in vitro* and *in vivo* (Basu et al., 2001). For a review of the physiological mechanisms through which stress influences angiogenesis and tumor development, see Antoni, 2006 (Antoni et al., 2006).

Another pathway through which stress may influence neoplasic processes is neuroimmunomodulation. As described above (section 1), the HPA axis and the SAM axis are the two principal pathways through which stress may alter the immune activity. The section below analyzes the data found by studies involving both humans and animals regarding the effects of social stress on different immune parameters.

3.2 Stress and the Immune System

3.2.1 Studies in humans

Studies carried out in humans have revealed that stress can strongly influence both innate (Redwine et al., 2003), and adaptive immunity (Sommerhoff et al., 2010). The studies in question also demonstrate that these effects are not always the same. Research conducted with medical students has shown that academic exams may trigger an increase in the number of neutrophils and platelets, and a decrease in the number of eosinophils, monocytes and basophils (Qureshi et al., 2002). The activation of the response to this type of stress has also been associated with a reduction in the number of natural killer (NK) cells (Isowa et al., 2004). Chronic social stress has been linked to an increase in neutrophils and a reduction in the number of B cells, cytotoxic T cells and NK cells (McKinnon et al., 1989), as well as to a drop in the cytotoxic capacity of NK cells (Irwin et al., 1988a).

It has also been found that social stressors may induce an immature phenotype of dendritic cells through the secretion of powerful neuroimmune mediators such as glucocorticoids, catecholamines and cytokines (Piemonti et al., 1999). Thus, patients receiving high doses of

corticoids have been found to have significantly lower levels of dendritic cells in the blood. Also, it has been shown *in vitro* that glucocorticoids prevent the maturing and correct functioning of dendritic cells (Rozkova et al., 2006). However, other studies have found that certain types of stress may trigger the immunostimulation of the immune response, inducing an activation of dendritic cells and an increase in their effectiveness as antigen presenter cells (Saint-Mezard et al., 2003). Stress has also been found to affect proinflammatory cytokines (Segerstrom & Miller, 2004). The stress induced by caring for dementia patients may increase interleukin-6 (IL-6) levels by up to four times (Kiecolt-Glaser et al., 2003). In a sample of homeless people, Arranz et al. (2009) found a decrease in the migratory and phagocytic capacity of neutrophils, a lower proliferative capacity of lymphocytes, lower levels of interleukin-2 and a reduced activity of NK cells (Arranz et al., 2009). It has also been observed that stress triggers changes in the balance of different types of lymphocytes. In a comparative study involving patients suffering from chronic pain, those with high levels of emotional stress were found to have a lower response of Th1 cells (Kaufmann et al., 2007). In situations of academic stress, a drop has been observed in the production of cytokines by Th1 cells, accompanied by an increase in the number of cytokines released by type 2 T helper cells (Th2) (Marshall et al., 1998).

Fifty years ago, Rudolph H. Moos proposed that the development of rheumatoid arthritis (an autoimmune disease) was related to certain personality traits, such as perfectionism, self-sacrifice and conflict denial (Moos, 1964). As stated earlier, major differences exist in the way in which individuals perceive and respond to the same external and internal environmental stimuli. Individual differences in cognition, emotion and behavior also seem to play a potentially important role in the modulation of the IS. The results of research into the relationship between personality traits and the immune function are not clear enough to enable an association to be established between one type of personality and a higher or lower level of IS activity (Segerstrom & Miller, 2004). However, what has been observed is that individual differences in the anxiety level triggered by a stressful situation correlate with a significant drop in the cytotoxic capacity of NK cells, or with a drop in the total number of monocytes (Ironson et al., 1990; Jamner et al., 1988). It has also been found that affiliative motivation, as a personality dimension, increases immunoglobulin A (IgA) levels in saliva, and that those receiving greater social support also have higher IgA levels in saliva (Jemmott et al., 1983).

3.2.2 Studies in animals

The need to understand the relationship between stress and the IS in humans has prompted much interest in the study of the impact of social stress in animals, and in the development of different models for analyzing this impact. Social adaptation and social status are determining factors for the activation of the HPA and SAM axes (Cole et al., 2003). For this reason, social stress models are currently considered the best models available for studying the causes and mechanisms involved in the development of stress-related pathologies.

The immunomodulatory effects of social stress on innate and adaptive immunity in animals are described below.

In relation to innate immunity, as with studies involving humans, divergent results have been found depending on the immune parameter measured and, above all, the type and duration of the stress model applied. Thus, it has been observed that acute social stress may trigger an increase in the infiltration capacity of leucocytes in the immune activation zone and an increase in the number of macrophages and neutrophils (Bailey et al., 2007; Viswanathan et al.,

2005), while chronic social stress decreases the number, traffic and infiltration of leucocytes (Sutherland et al., 2006). It has also been observed that the prolongation of social stress results in an increase in interleukin 1β (IL-1β) levels in the hypothalamus (Barnum et al., 2008). This effect on proinflammatory interleukins is specific to the type of brain structure studied and the type of stress applied (Plata-Salaman et al., 2000).
As regards the adaptive immune response, it has been shown, for example, that chronic stress alters the balance of Th1 and Th2 lymphocytes (Frick et al., 2009). Social stress may also trigger a decrease in the proliferative capacity of splenic T lymphocytes and the proliferative capacity of NK cells (Beitia et al., 2005; Stefanski & Ben-Eliyahu, 1996).
Diverse studies coincide in asserting that the main mediators of the effects of stress on immunity, regardless of whether those effects are positive or negative, are glucocorticoid hormones and catecholamines (Besedovsky & Del Rey, 1996). Evidence also exists of the existence of different neuroendocrine responses associated with different coping strategies, which in turn have different immune consequences (Bartolomucci et al., 2001).

4. The effect of social stress on melanoma tumor development

In order to study the mechanisms involved in the relationship between social stress and melanoma tumor development in more detail, the following section outlines some of the work which has been carried out with animal models of social stress. Using different experimental tumor development models, these studies show that social stress significantly increases the development of tumor metastases (Stefanski & Ben-Eliyahu, 1996). An increase in B16 melanoma pulmonary metastasis development has also been observed (Fig. 2) in a mouse model for human melanoma applied to socially-stressed mice (Sa-Rocha et al., 2006; Vegas et al., 2006). The relationship of dominance/subordination which is necessarily established following social interaction between male mice has enabled researchers to observe that the stress to which the defeated or subordinate animals are subject triggers a significant increase in the development of B16 melanoma pulmonary metastasis.
These results suggest that an understanding of the general neurobiology of stress and the specific alterations associated with an imbalance in the HPA and SAM axes will likely lead to a clarification of the role of stress in disease, including neoplastic processes (Armaiz-Pena et al., 2009; Kiecolt-Glaser et al., 2002b). While some studies have shown the anti-tumor effect of glucocorticoids (Banciu et al., 2008b; Bhakoo et al., 1981b; Carlson et al., 2001). Arbiser et al., (1999), using both *in vitro* and *in vivo* assays, have found that CRH is able to enhance angiogenesis and stimulate epithelial tumor growth in the skin (Arbiser et al., 1999). Evidence also exists of a possible involvement of the SAM axis in tumor development. A number of studies have shown that sympathetic ganglionic blockade, adrenal demedullation or the administration of a nonselective beta-blocker either ameliorated or attenuated tumor metastases induced by social stress (Ben-Eliyahu et al., 2000; Shakhar & Ben-Eliyahu, 1998; Stefanski & Ben-Eliyahu, 1996), and increased resistance to B16 melanoma tumor development (Hasegawa & Saiki, 2002).
Similarly, in our laboratory we have found that blocking the neuroendocrine response through the administration of antalarmin (a corticotropin-releasing factor receptor antagonist) or nadolol (a beta-adrenergic antagonist), results in fewer and smaller pulmonary metastatic foci in subjects exposed to acute social stress, confirming the involvement of both the HPA axis and the SAM axis in the effects of social stress on melanoma tumor development (Fig. 3).

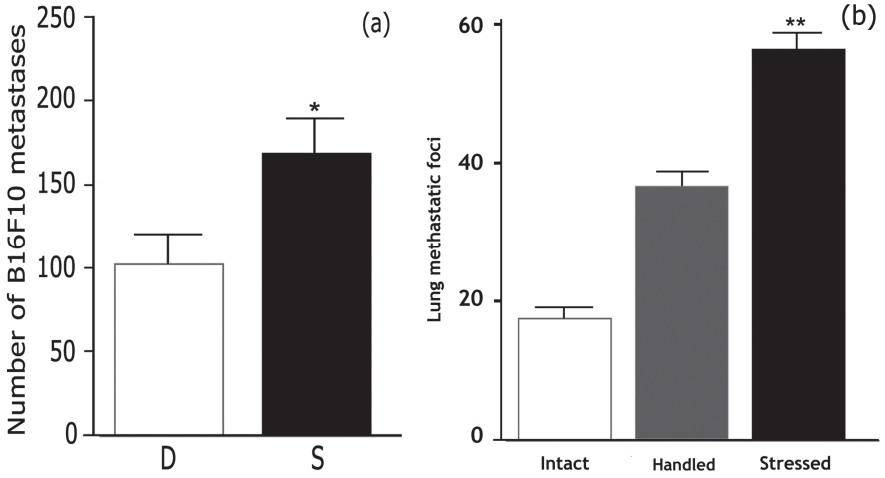

Fig. 2. (a) Effects of social stress on melanoma tumor development. (a) Number of metastasis in the lung of dominant (D) and submissive (S) mice counted 14 days after B16F10 (2×10^5) tumor cell inoculation into their tail vein (Sa-Rocha et al., 2006). (b) Mean (GSE) pulmonary metastatic foci numbers in intact, handled control and stressed mice groups, inoculated with B16F10 murine melanoma cells, 21 days after inoculation (Vegas et al., 2006). *p<0.05; **p<0.001.

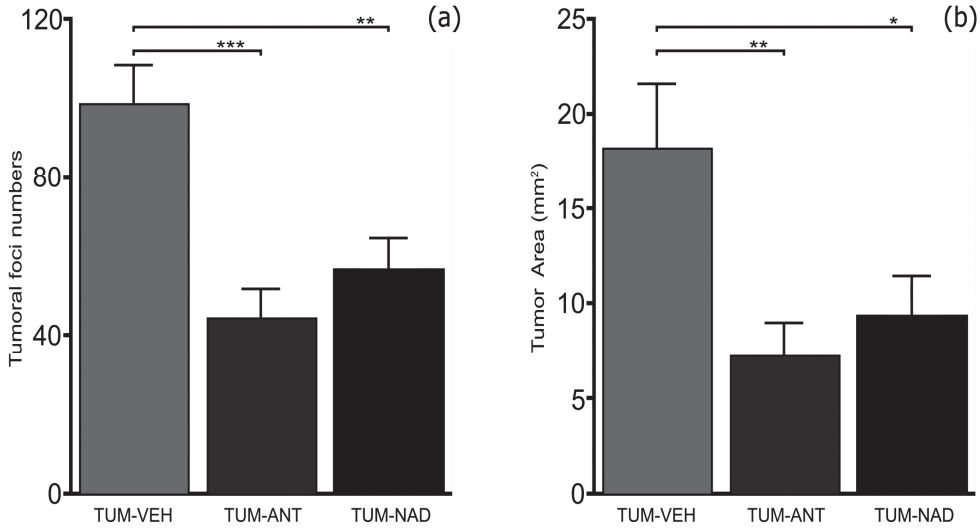

Fig. 3. Mean (±SE) tumor development (foci and area) in stressed mice inoculated with B16F10 melanoma cells, 21 days after inoculation (Vegas et al., 2009). *p < 0.05, **p < 0.01, ***p < 0.0001.

Diverse studies have shown that glucocorticoid receptors are widely expressed in normal and transformed melanocytes (Bhakoo et al., 1981a). Although some authors have found that glucocorticoid-based therapy appears to protect against melanoma incidence (Banciu et al., 2008a; Bhakoo et al., 1981b), the effect of GC on melanoma development is controversial (Arbiser et al., 1999; Chaudhuri et al., 1982). The results obtained in our laboratory do little to help clarify this point, since we observed a similar reduction in pulmonary metastatic development in both animals with lower levels of corticosterone (Antalarmin Group) and in animals with high levels of this hormone (Nadolol Group). However, it is possible that glucocorticoids may affect tumor development indirectly, through other mechanisms, or that the activation of the HPA axis may affect melanoma tumor development through mechanisms that are independent from the release of glucocorticoids.

Moreover, melanoma cells also express adrenergic receptors (alpha and beta) which may be activated by the catecholamines secreted in response to social stress. In this sense, Yang et al. (2009) found that the catecholamine stress hormone, norepinephrine, may influence tumor progression by modulating the expression of factors implicated in angiogenesis and metastasis (Yang et al., 2009).

Our results also indicate a clear involvement of the sympathetic pathway in melanoma tumor development, since blocking beta-adrenergic receptors resulted in a reduction of pulmonary metastases, as found also by other authors (Hasegawa & Saiki, 2002; Melamed et al., 2005; Stefanski & Ben-Eliyahu, 1996). The results of this study also suggest that the lower level of tumor development observed after blocking the HPA axis may also be due to indirect action on the sympathetic pathway, as other authors also point out (Gold & Chrousos, 2002), and that blocking CRH receptors may decrease the activity of both axes (Habib et al., 2000).

Different studies have indicated that the effects of neuroendocrine stress mediators on tumor development may be produced through their effects on the immune activity. There is a broad consensus regarding the idea that psychosocial stress affects parameters of the immune activity involved in tumor processes (Kiecolt-Glaser et al., 2002a, 2002b), and that the catecholamines released in response to stress act as important efferent immune modulators, often acting in concert with the activation of the HPA axis (Cunnick et al., 1990). Studies in animals have revealed that the intraventricular administration of CRH results in a suppression of NK activity which may be attenuated through peripheral adrenergic blocking (Irwin et al., 1988b; Tasker et al., 2006). The administration of Z-100, an immunomodulating agent, increases interferon *gamma* levels and reduces the development of B16F10 melanoma tumor metastases via the suppression of glucocorticoid-genesis (Oka et al., 2002). Nevertheless, a negative effect of stress on NK cell activity and tumor development has also been observed; this effect is independent of the reactivity of the HPA axis (Ben-Eliyahu & Shakhar, 2001). The increase of the aggressive potential of melanoma tumor cells observed by Yang et al. (2009) after the administration of NE is partly due at least to the fact that this catecholamine stimulates the production of VEGF, IL-8 and IL-6 (Yang et al., 2009). In this sense, the results obtained in our laboratory have shown that social stress reduces diverse parameters of the immune activity (proliferative response to Con-A, IL-2 and IL-12), and that this immunosuppression is accompanied by greater tumor development (Vegas et al., 2006). The data presented so far suggest that the course of melanoma tumor development may be affected by the hormones released during the stress response, either through the intervention of this response in the immune balance, or through other mechanisms capable of regulating the complex process of neoplastic development.

In the study of the possible effects of social stress on tumor development, it is important to bear in mind that the same adverse stimulus may not pose the same threat to all individuals, and that individuals respond to threats differently, from both a behavioral and physiological perspective. It has been observed that the neuroendocrine and immune changes produced by social stress in defeated subjects depend on the behavioral characteristics shown during social interactions (Sa-Rocha et al., 2006). Subjects which adopt different coping strategies (active or passive coping strategies) have different HPA and SAM activation patterns (Koolhaas et al., 2007). Previous studies in our laboratory show that social stress increases the pulmonary metastatic development of B16 melanoma, and point to a greater degree of tumor development in subjects which employ a more passive coping strategy in response to stress (Vegas et al., 2006). The coping strategies for social stress were obtained from an exhaustive analysis of the complete mouse ethogram developed by Brain et al. (1989), which covers 51 behavioral elements grouped into 11 broad categories: attack, threat, non-social exploration, social investigation, exploration from a distance, digging, body care, avoidance/flee, defense submission, sexual behavior and immobility.

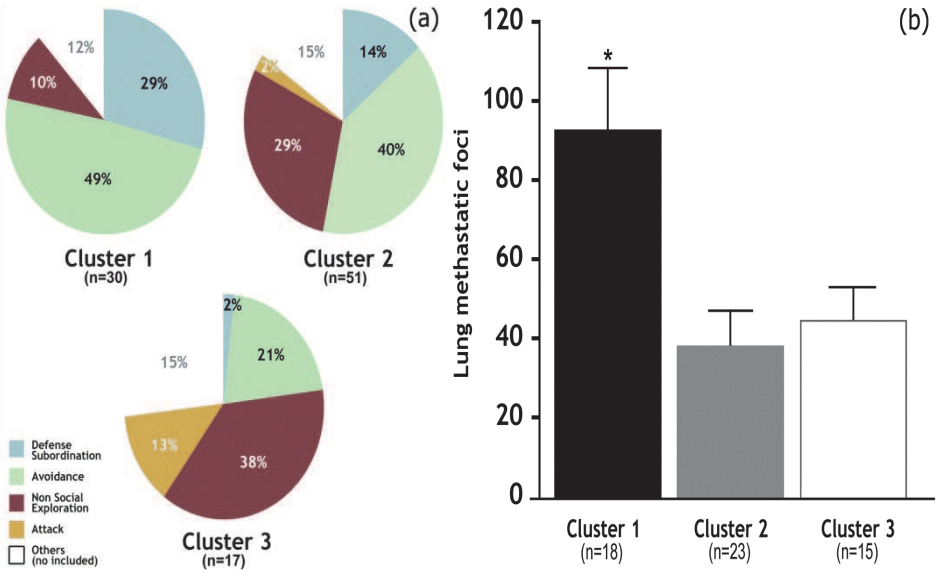

Fig. 4. (a) Mean percentages of the time allocated by mice inoculated with melanoma cells and subjected to the sensory contact stress protocol, to the behavioral categories that the discriminant analysis revealed to be most relevant in defining each cluster, namely: attack, defense/subordination, avoidance and non-social exploration. (b) Mean (GSE) pulmonary metastatic foci numbers in mice subjected to social stress and inoculated with B16F10 murine melanoma cells, belonging to each of the three clusters derived from the final cluster analysis, 21 days after inoculation (Vegas et al., 2006). *P<0.05.

Furthermore, these differences in HPA and SAM activation patterns have been shown to occur in conjunction with differences in the activation of monoaminergic pathways (Overli et al., 2001; Salome et al., 2006). One of the most interesting aspects of the impact of stress on the immune system or tumor development is the possible relevance of the individual

behavioral characteristics exhibited by subjects in such situations (i.e. coping strategies). These differences in the physiological and behavioral coping styles adopted in response to stress may underlie differences in vulnerability to disease, including malignant melanoma (Azpiroz et al., 2008; Sajti et al., 2004; Stefanski & Ben-Eliyahu, 1996; Vegas et al., 2006). In this sense, recently in our laboratory we have demonstrated that individual differences in behavioral coping strategies are associated with unique alterations in the activation of the HPA and SAM axes and monoaminergic pathways. Thus, subjects from the active group had a lower level of HPA axis activity and a higher level of SAM axis activity, while subjects from the passive group were found to have a greater activation of the HPA axis and a lower activation of the SAM axis. Similarly, different coping strategies were observed to be associated with different levels of mRNA expression for serotonergic and dopaminergic synthetic enzymes (De Miguel et al., 2011). Taken together, these studies provide new evidence in favor of the idea that coping styles in response to social stress are involved in the determination of individual vulnerability to stress-related illnesses, such as malignant melanoma.

These studies, carried out in animals, indicate that social stress and coping strategies may have an effect on melanoma development, although the mechanisms involved in this relationship have yet to be determined. In humans, there are no studies to date which demonstrate this relationship. Nevertheless, later on is an outline of various studies focusing on the benefits of social intervention in cancer patients, particularly those suffering from melanoma.

5. The neurochemical and behavioral effects produced by melanoma tumor development

Since this relationship is bi-directional, the IS also sends messages to the CNS; this communication is carried out by proinflammatory cytokines, which are substances secreted by the peripheral immune cells (monocytes and macrophages) in response to infection or injury. The action of cytokines on the CNS affects both diverse physiological parameters and behavior (for a review see (Dantzer et al., 2001)). The series of behavioral changes associated with infection or injury are considered unspecific and are known as sickness behavior. They generally manifest themselves through a reduction in activity, a decrease in appetite, a loss of interest in social activities and an increase in tiredness. A number of different studies involving the peripheral or central administration of these cytokines have shown that mainly interleukin 1 (IL-1α and IL-1β), but also interleukin 6 (IL-6) and the tumor necrosis factor (TNF-α), are responsible (either directly or indirectly) for sickness behavior (Bluthe et al., 1994). In addition to behavioral changes, the immune response also provokes changes in the metabolism of the brain monoamines and the activation of the HPA axis. The result is an increase in the noradrenaline metabolism (NE) in different areas of the brain, particularly in the hypothalamus, as well as an increase in the serotonin metabolism (5HT) and, in some cases, the dopamine metabolism (DA) also (Dunn, 1992). The majority of the data regarding this type of behavioral and physiological changes have been obtained by means of virus inoculation, the administration of lipopolysaccharide endotoxins (LPS) or the central administration of IL-1, IL-2, IL-6, and TNF-α (Zalcman et al., 1994). Some studies have observed changes in the brain neurotransmitters produced in mice bearing tumors, that have been associated with hyperammonemia and reduced food intake (Chance et al., 2003). Chuluyan et al. (Chuluyan et al., 2000) found changes in the monoaminergic activity in different areas of the brain in mice inoculated with murine lymphoma cells, neoplasic line

cells that do not induce an immune response. Few studies have focused on the behavioral and neurochemical effects produced by the activation of the immune system in situations of social stress. Cirulli et al. (Cirulli et al., 1998) found modifications in the agonistic behavior of young mice exposed to situations of conflict with adult mice following the peripheral administration of IL-1. We have studied the behavioral and neurochemical effects produced during the early phases of melanoma tumor development, under the most natural circumstances possible, i.e.. territorial aggression between male mice of the same species. Besides, the effects on the brain metabolism were analyzed in relation to the hypothalamus, by assessing the activity of 5HT and DA, and in relation to the striatum (SRT) by measuring the density of dopaminergic D2-receptors.

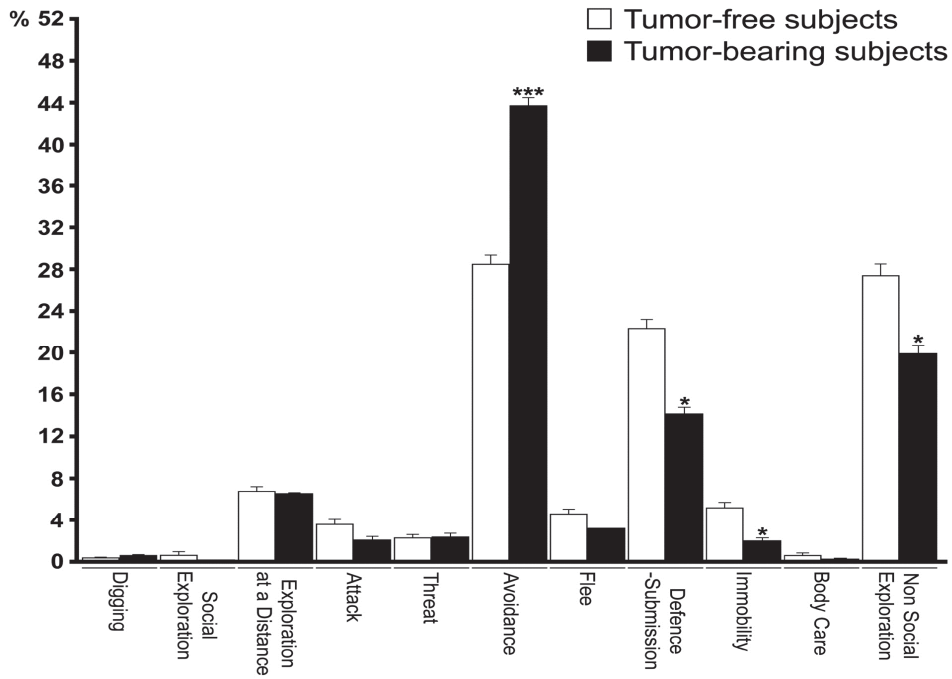

Fig. 5. Percentage of time (mean ±S.E.M.) dedicated to each of the behavioral categories, in male OF1 mice subjected to social stress, without tumoral inoculation (n = 28) and with tumoral inoculation (n = 28). (*) Tumor-bearing subjects vs. tumor-free control subjects (Vegas et al., 2004). * $P < 0.05$; *** $P < 0.001$.

After analyzing the behavioral data, we observed an effect of social stress in both inoculated and non-inoculated animals, in relation to 3 of the 11 behavioral categories analyzed (Fig. 5). We found that after a prior experience of defeat, a second confrontation with the dominant opponent resulted in a significant reduction in threat and non-social exploration behaviors, accompanied by an increase in fleeing. These results correspond with those found in other studies in which social stress was found to provoke a reduction in aggressive behavior and an increase in defensive and submissive behaviors (Albonetti & Farabollini, 1994). Although social stress was also found to have an effect on avoidance behavior, this was only true for

non-inoculated animals. The fact that inoculated subjects demonstrated high levels of fleeing in the first confrontation (something which is a major characteristic of the behavior of these subjects and is discussed later on), may be the reason for our failure to observe a reduction in fleeing among the subjects in this group. To continue with the analysis of the behavioral results we observed that animals inoculated with B16 tumor cells demonstrated the same repertoire of behavior as untreated subjects submitted to social stress. Nevertheless, clear differences were found as regards the time dedicated to each of these behaviors, and an important change was observed in the confrontation strategy used. A significant increase was observed in avoidance behavior, coupled with a decrease in non-social exploration, defense-submission and immobility in inoculated subjects.

Assays	Tumor-free subjects		Tumor-bearing subjects	
	Non-stressed	Stressed	Non-stressed	Stressed
Catecholamines				
DA†	0.242 ± 0.008	0.256 ± 0.012	0.247 ± 0.008	0.287 ± 0.016
DOPAC***	0.103 ± 0.005	0.124 ± 0.006	0.413 ± 0.112	0.287 ± 0.048
DOPAC/DA ratio***	0.433 ± 0.031	0.485 ± 0.017	1.669 ± 0.464	1.002 ± 0.160
5HT***	2.425 ± 0.037	2.406 ± 0.065	1.656 ± 0.182	2.166 ± 0.151
5HIAA	0.588 ± 0.007	0.672 ± 0.020	0.644 ± 0.024	0.647 ± 0.032
5HIAA/5HT ratio**	0.243 ± 0.002	0.282 ± 0.012	0.479 ± 0.097	0.319 ± 0.030
Cell proliferation				
Con-A proliferation***	1.162 ± 0.112	1.192 ± 0.068	2.372 ± 0.197	2.360 ± 0.179
PHA proliferation**	1.456 ± 0.061	1.302 ± 0.030	1.512 ± 0.066	1.496 ± 0.049
D_2-receptors*	201.58 ± 27.63	161.35 ± 20.41	248.91 ± 26.34	241.64 ± 28.19

Table 1. Effects of tumoral inoculation and social stress on the physiological variables analyzed. Data are expressed as mean ± S.E.M. The interaction between these two factors was not significant in none of the analyzed variables. (Vegas et al., 2004); *tumor-bearing subjects vs. tumor-free subjects (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$); †non-stressed vs. stressed (†$P < 0.05$. * $P < 0.05$; *** $P < 0.001$).

Although sickness behavior is characterized by a drop in activity and a lack of interest in the subject's environment due to the effect of proinflammatory cytokines on the nervous system (Dantzer & Kelley, 1989), the behavior observed in this study failed to coincide exactly with this definition. The results revealed a drop in non-social exploration similar to that observed by other authors studying exploratory behavior in response to a new environment after the central or peripheral (Cirulli et al., 1998; Dunn, 1992; Spadaro & Dunn, 1990) administration of LPS, IL-1α, or IL-1β. However, has been postulated that sickness behavior should also be considered as the expression of an organized strategy that is vital for the survival of the organism; in this case, the sick individual will be capable of reorganizing his/her behavior depending on the consequences and internal and external circumstances to which he/she is exposed. This is similar to the way in which Zalcman et al. (Zalcman et al., 1998) interpret the behavioral activation observed in mice after the administration of IL-2 and IL-6. In the context of aggressive confrontation between rodents after the administration of IL-1, Cirulli et al. (Cirulli et al., 1998) observed a decrease in the aggressive components of agonistic behavior, although defensive elements such as upright submissive posture, crouching, or fleeing were not affected. Nevertheless, we should bear in mind that in our study, we observed a passive defensive behavior: avoidance. This behavior increased significantly in inoculated subjects and

may form part of a defensive strategy against attack by opponents, characterized by lower energy expenditure and a reduced receipt of injury. These changes in the behavioral strategy of inoculated animals may be related to the increase in the density of D2-receptors in the striatum. The "up regulation" of these receptors indicates a decrease in the dopaminergic activity in this structure, which may be the cause of the reduced motor activity observed (Boehme & Ciaranello, 1981; Isovich et al., 2001). In light of these data, we can hypothesize that the behavioral effects observed in inoculated animals may be caused by an increase in the secretion of cytokines. This increase may in turn be the result of the activation of the immune system in response to the B16 melanoma tumoral antigens, which are recognized by the T lymphocytes (Houghton et al., 2001), or by cytokines produced by the tumor itself. The B16 melanoma tumor produces growth factors and cytokines (IL-1α, IL-6, TGF-β, OSM, TNF, and IFN) during the early phases of tumor development (Lazar-Molnar et al., 2000). Although we did not measure the interleukins, we did find evidence of immune activation upon observing a significant increase in the proliferative capacity of spleen monocytes in animals inoculated with tumor cells, in comparison with their non-inoculated counterparts (Table 1). The changes produced by the development of the B16 melanoma both in the hypothalamic monoaminergic activity and in the density of D2-receptors in the striatum may also be caused by the action of cytokines. Uomoto et al. (Uomoto et al., 1998) found a decrease in the DA turnover in the striatum, along with a decrease in the locomotive activity and a significant increase in plasmatic IL-6 levels in mice bearing colon-26 tumor cells. Although the effects of IL-2 on behavior have yet to be fully investigated, some studies point to a possible involvement of this cytokine in behavior modulated by the dopaminergic activity of the forebrain (Petitto et al., 1997). Furthermore, a significant increase was found in the turnover of both 5HT and DA in inoculated animals, both control subjects and those exposed to social stress. These results coincide with the increase in the 5HT and DA activity found in the hypothalamus of mice after various days of inoculation with lymphoma tumor cells (Chuluyan et al., 2000). Although it has been found that an acute defeat experience may produce an increase in the serotonergic activity in different areas of the brain, including the hypothalamus (Blanchard et al., 1993), in our study, social stress only produced a significant increase in the DA content, with the turnover of this catecholamine remaining unchanged. The administration of diverse interleukins provokes changes in the monoaminergic activity in mice in different areas of the brain. A number of studies using rodents have shown that the peripheral administration of diverse interleukins produces alterations in the 5HT, DA and NE activity in different areas of the brain (Connor et al., 1998). As regards the hypothalamus, various studies have found increases in the noradrenergic activity following the peripheral administration of IL-1 and IL-2 (Zalcman et al., 1994). In relation to the 5HT and DA activity, a number of authors have found an increase in the turnover of these two monoamines following the peripheral administration of IL-1 (Dunn, 1992), and in the PNV paraventricular nucleus following the peripheral administration of IL-1 and TNF-α (Brebner et al., 2000), might be in line with our results. Similarly, following the administration of IL-1 in the front hypothalamus in rats, Shintani et al. (Shintani et al., 1993) found that this interleukin acted directly on the hypothalamus in a dosage-dependent manner, increasing the release of NE, DA, and 5HT, as well as their metabolites. In light of all these data, we can conclude that tumor development produces behavioral changes, manifested mainly in a change in defensive strategy, and neurochemical changes when subjects are exposed to situations of intense social stress. These changes may be mediated by an increase in secretion of interleukins provoked by tumor development.

6. Psychosocial intervention and cancer progression

Over recent years, many researchers have tried to establish a link between psychosocial intervention and improvements in the condition of cancer patients. Although the psychological benefits of these interventions have been well documented, evidence exists both in favor of and against the assertion that they influence the course of the disease itself. Lutgendorf et al. (2010) analyzed this relationship by reviewing over 300 intervention studies carried out over the last 50 years (S.K. Lutgendorf et al., 2010). The majority of these studies involved breast cancer patients. The review analyzes the data obtained from studies which found a beneficial effect of different forms of psychosocial intervention (including relaxation and coping techniques) on patients' quality of life (Coyne et al., 2007; Spiegel, 2002). In this sense, the review highlights the ability of psychosocial interventions to alleviate pain and anxiety in metastatic breast cancer patients with the most severe symptoms (Goodwin et al., 2001) and to improve the quality of life, depressed mood, distress and social disorders of cancer patients (Andersen et al., 2007; Antoni et al., 2006).

More controversial is the question of whether psychosocial interventions can affect the progression of cancer and patients' chances of survival. In this sense, the studies conducted (all with powerful and rigorous methodologies) offer contradictory results. In three studies with varied methodologies focusing on psychosocial interventions with breast cancer patients, the authors found that either a reduced risk of disease recurrence or the survival rate increased (Andersen et al., 2008; Coyne et al., 2007). However, in two other studies, also involving women with metastatic breast cancer, here receiving expressive therapy, the authors failed to find any increase in survival (Kissane et al., 2007; Spiegel et al., 2007). Possible explanations for this divergence include differences in the status of the disease between patient populations and differences in the physiological effects produced by the various interventions (Andersen et al., 2004; Stefanek et al., 2009). It has also been suggested that the optimization of the neuroendocrine and immune status may require both psychological and pharmacological interventions, in order to fully mitigate the deleterious effects of the biology of stress on tumor growth and progression.

The most common psychological interventions in cancer cases include, among others, training in stress coping skills. The idea that this type of intervention may have a positive effect on psychological adaptation is becoming increasingly widely accepted. Aspects of this positive effect include neuroendocrine and immune changes, a drop in cortisol levels and an increase in lymphocyte proliferation, as well as an increase in cytokines (IL-1β, IL-2, etc.) (McGregor & Antoni, 2009). Other beneficial effects of psychological therapy on health should also be taken into consideration in the effort to halt the progression of the disease. It has been shown that psychological interventions trigger changes in health behavior, improve adherence to pharmacological treatment and may reduce the incidence of opportunistic infection both during and after a surgical procedure or adjuvant therapy (Andersen et al., 2004; Coyne et al., 2007; Pereira et al., 2003).

Studies carried out in this respect with malignant melanoma patients seem to support this theory (Fawzy et al., 2003; Fawzy et al., 1990; Fawzy & Fawzy, 1994; Fawzy et al., 1993).). In these studies, recurrence and survival rate were studied in a group of 68 patients who had either been recently diagnosed or undergone a surgical procedure. Half of the sample group participated six times a week in group sessions which focused on social interaction, health education, stress management and coping skills. It was a randomized controlled experimental study. The Cox proportion hazards regression model was used to quantify the relationship between treatment and the outcomes adjusted by the covariates: age, sex,

Breslow depth, tumor site, baseline profile of Mood States Total Mood Disturbance, baseline active-behavioral coping, baseline natural killer cell activity and treatment. The stepwise procedure was used for covariate selection.
At six months, those patients who had participated in the support groups were found to be less depressed and more vigorous, and had developed better coping skills. They also had an increase in the number and function of NK lymphocytes in the blood, in comparison with their counterparts from the control group (Fawzy et al., 1990). Six years after the intervention, the same patients were studied again in relation to recurrence and death rates. Those patients who had participated in the intervention showed a trend towards a longer recurrence-free state and a statistically significant lower death rate. Finally, baseline affective distress and coping baseline were predictors for recurrence and survival (Fawzy et al., 1993).
The same authors then studied the effects of the intervention on the course of the disease in the same patients, 10 years after the treatment. In this univariate analysis, the survival and recurrence distributions for the intervention and control groups were estimated using the Kaplan-Meier method, and were tested for equality by the log-rank test. The multivariate analysis used the Cox proportional hazards regression model with the following prognostic factors: age, sex, Breslow depth, tumor size, and treatment status (i.e. intervention group vs control group). When analyzed as single covariates, the results obtained revealed that the differences between the intervention and control groups were not significant at the 10-year follow-up. However, being male and having a greater Breslow depth were predictive of poorer outcome. An analysis of multiple covariates also revealed that sex and Breslow depth were significant for survival. Furthermore, participation in the intervention was significant for survival. After adjusting for sex and Breslow depth, participation in the intervention remained significant for survival. The authors conclude that these results suggest that while the survival benefit of intervention weakens after the 5-to-6 year follow-up, participation in the intervention remains predictive of survival when the effects of other known prognosis indicators are statistically controlled (Fawzy et al., 2003).

7. Conclusion

Although the mechanisms through which psychosocial factors may affect the disease remain uncertain, and it is important to wait for the results of future replication studies, the results obtained to date suggest that this type of approach may be highly effective for exploring psychosocial influences on melanoma progression and highlight the urgent need to supplement both traditional and new medical therapies with a greater effort to ensure the psychosocial wellbeing of cancer patients.

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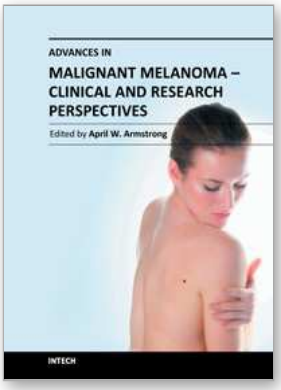

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This book titled Advances in Malignant Melanoma - Clinical and Research Perspectives represents an international effort to highlight advances in our understanding of malignant melanoma from both clinical and research perspectives. The authors for this book consist of an international group of recognized leaders in melanoma research and patient care, and they share their unique perspectives regarding melanoma epidemiology, risk factors, diagnostic and prognostic tools, phenotypes, treatment, and future research directions. The book is divide into four sections: (1) Epidemiology and Risk Factors of Melanoma, (2) Clinical Phenotypes of Melanoma, (3) Investigational Treatments for Melanoma and Pigmentary Disorders, and (4) Advances in Melanoma Translational Research. This book does not attempt to exhaustively cover all aspects of the aforementioned topics. Rather, it is a compilation of our authorsâ€™ pearls and unique perspectives on the relevant advances in melanoma during the recent years.

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