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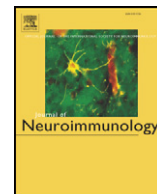
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Review

Impact of stress and mast cells on brain metastases

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ABSTRACT

Metastases continue to be the chief cause of morbidity and mortality for many tumors, including brain metastases of lung and mammary adenocarcinoma. Stress appears to increase metastases, but the mechanism is not understood. Recent evidence suggests that local inflammation is conducive for cancer growth and a unique immune cell, the mast cell, accumulates in the stroma surrounding tumors and is critically located at the blood-brain-barrier (BBB). Mast cells express receptors for and can be stimulated by corticotropin-releasing hormone (CRH), secreted under stress, to release mediators such as histamine, IL-8, tryptase and vascular endothelial growth factor (VEGF), which disrupt the BBB permitting metastases. Stress and mast cells could serve as new targets for drug development to prevent brain metastases, especially since CRH receptor antagonists and brain mast cell inhibitors have recently been developed.

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1. Introduction

The chief cause of morbidity and mortality for the most frequent forms of cancer (Gupta et al., 2005) remains metastases, including those in the brain (Lassman and DeAngelis, 2003). These are of great

importance for breast cancer patients since more than 30% of them develop brain metastases with poor associated prognosis (Nishizuka et al., 2002; Schouten et al., 2002). Stress increases metastatic spread of tumors (Ben-Eliyahu et al., 1991; Wu et al., 2001) and reduces host resistance to breast cancer recurrence (Palesh et al., 2007). Moreover, tumors in stressed animals have greater vascularization and vascular endothelial growth factor (VEGF) levels (Thaker et al., 2007). Stress may also promote cancer growth (Antoni et al., 2006; Kruk and Aboul-Enein, 2004; Nielsen and Gronbaek, 2006; Saul et al., 2005), and render breast cancer resistant to chemotherapy (Su et al., 2005). Stress

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also increased susceptibility to UV-induced squamous cell carcinoma in a mouse model (Saul et al., 2005). In a retrospective study, evaluation of the psychosocial status of 50 women (30–70 years old) with breast cancer indicated high levels of anxiety, but not depression, prior to the appearance of the disease in 68% of subjects; the loss of a loved one was the most common cause of severe anxiety (Naesse et al., 2003). Psychological distress was also found to be more severe in breast cancer patients who died than those who survived a five year observation period (Gazelius et al., 1981).

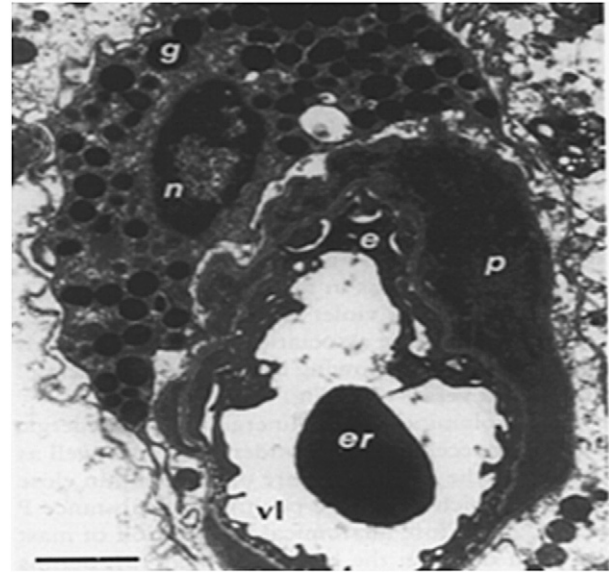
The blood-brain-barrier (BBB) is defective in metastatic tumors (Long, 1979), permitting brain metastases (Menter et al., 1995). For instance, cancer cells can penetrate the BBB in metastatic melanoma (Hasegawa et al., 1983) and mammary carcinoma (Boogerd, 1996), which can be preceded by meningeal carcinomatosis (Ornstein and Frederickson, 2000). However, how the BBB permits tumor dissemination to the brain remains unknown (Weber and Ashkar, 2000). Many AIDS patients also develop neurologic problems that do not necessarily correlate with the viral load (Perry and Marotta, 1987). One explanation may be that the HIV-1 virus does not infect peripheral neurons directly (Gelbard and Epstein, 1995), but enters the brain through increased BBB permeability (Gray et al., 2000) inside macrophages and T-cells crossing the BBB, or by accumulating in perineuronal mast cells (Sundstrom et al., 2007). Mast cells are involved in stress-induced inflammation (Theoharides and Cochrane, 2004) and could be critical not only in allowing cancer cell entry into the brain, but also in cancer growth and metastases in general (Conti et al., 1997; Rousset et al., 2006). Mast cell infiltration in Hodgkin's lymphoma was associated with poor prognosis (Molin et al., 2002). Mast cells were recently shown to be an absolute requirement for pancreatic cancer growth (Theoharides, 2008).

### 1.1. BBB, stress, mast cells and cancer metastases

The BBB is formed by a complex system of endothelial cells, astroglia, pericytes and perivascular mast cells (Wahl et al., 1988), with tight junctions that restrict passage of most circulating cells and molecules (de Boer and Breimer, 1998; Petty and Lo, 2002). However, BBB can play a dynamic role permitting certain peptides in and out of the brain (Kastin et al., 1999). BBB breakdown occurs in neuroinflammatory diseases (De Vreus et al., 1997) and precedes any pathological or clinical signs of multiple sclerosis (MS) (Kermode et al., 1990; Kwon and Prineas, 1994; Moor et al., 1994), as shown by trans-BBB leakage of albumin (Syndulko et al., 1993) and MRI-gadolinium studies (Kwon and Prineas, 1994). MS is a neurologic condition (Rodríguez, 1997; Smith and McDonald, 1999) involving brain infiltration by lymphocytes that leads to demyelination (McFarland, 1996; Raine, 1994). Even though Th1 cell involvement has been well documented in MS, recent evidence implicates also Th2 processes historically associated with allergic reactions (Pedotti et al., 2003a,b; Robbie-Ryan et al., 2003). These findings have led to a re-appraisal of the CD-Th1 model for MS suggesting that MS may be heterogeneous and not necessarily strictly autoimmune in nature (McClellan and Scott, 2003).

Mast cells encircle endothelial cells and pericytes (Fig. 1) making up the BBB and had been proposed to act as "gate keepers" of the BBB (Theoharides, 1990). Brain mast cells also have anatomical and functional connections with neurons (Rozniecki et al., 1999). Acute stress can disrupt the BBB through mast cell activation by corticotropin-releasing hormone (CRH) (Theoharides and Konstantinidou, 2007). CRH is secreted under stress and even though it activates the hypothalamic-pituitary-adrenal (HPA) axis, it can also have pro-inflammatory effects (Chrousos, 1995) through mast cell activation (Theoharides et al., 2004).

Acute stress activated rat intracranial mast cells, an action blocked by pretreatment with CRH antiserum (Theoharides et al., 1995). Acute stress also led to increased BBB permeability (Esposito et al., 2001) that was inhibited by the CRH receptor-1 antagonist, Antalarmin. Further, site injection of CRH in the rat hypothalamus induced BBB permeability that was blocked by site pretreatment with the mast cell



**Fig. 1.** Electron photomicrograph of a mast cell encircling the endothelial cell of a capillary from the thalamus of a normal rat. Note the numerous, intact secretory granules (g) Magnification:  $\times 6000$ . Notations: e = endothelial cell; er = erythrocyte; n = nucleus; p = pericyte.

stabilizer disodium cromoglylate (cromolyn); intracranial injection of CRH also did not affect the BBB in  $W/W^v$  mice (Esposito et al., 2002). CRH could be released in response to immunologic stimulation (Lyttinas et al., 2003) and lead to mast cell activation and vascular permeability (Singh et al., 1999b); these effects were also absent in  $W/W^v$  mice (Esposito et al., 2002; Singh et al., 1999a; Theoharides et al., 1998). Functional CRH-receptors (CRH-R) are expressed on human mast cells (Theoharides et al., 2004) and on brain vessels (Esposito et al., 2003). Human mast cells not only respond to, but also synthesize and secrete CRH (Kempuraj et al., 2004).

Additional evidence suggests that stress facilitates cancer metastases. For instance, social stress increased B16F10 melanoma pulmonary metastases in mice (Cuello et al., 1978). Stress experienced by subdominant male rats resulted in 10-fold lower clearance of MADB 106 tumor cells (Gallacher, 1983). Moreover, isolation stress was associated with enhanced liver invasion of colon cancer in Balb/c mice, also associated with increased TNF- $\alpha$  immunostaining in and around the metastatic cells (Adamkiewicz et al., 1978; Lehtosalo et al., 1984). This is interesting given the fact that TNF- $\alpha$  was recently shown to be associated with ulcerative colitis and colon cancer (Popivanova et al., 2008).

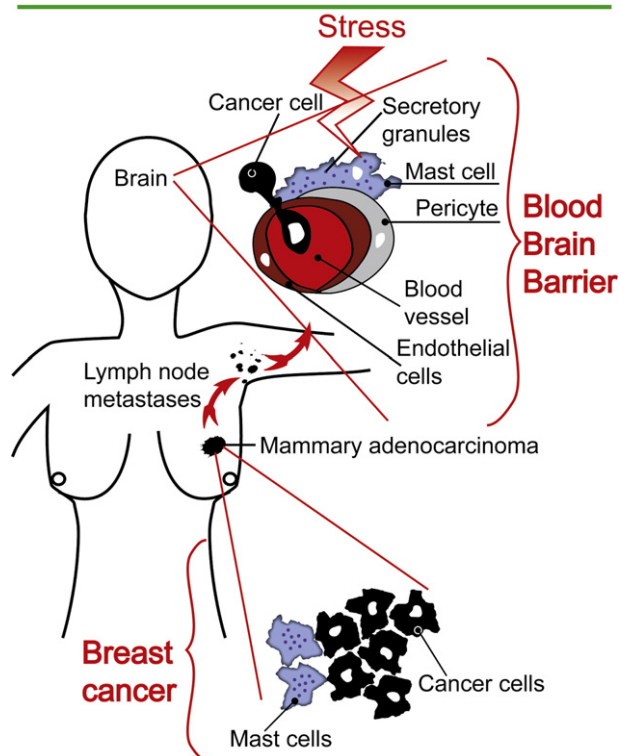
CRH-R are expressed by a number of human cancers (Reubi et al., 2003). CRH-R can function as a growth factor (Slominski et al., 2006) and could enhance migration of murine melanoma cells (Yang et al., 2006). In addition, chronic stress suppresses the immune system (Dhabhar and McEwen, 1999; Elenkov et al., 1999; Khansari et al., 1990; Kort, 1994; Rinner et al., 1992; Sheridan, 1998) and could further exacerbate cancer growth and metastases.

Cancer cells can be tagged in order to visualize metastases non-invasively. The 4T1 mammary carcinoma cell line can metastasize to tissues affected by breast cancer. This cell line was modified to facilitate visualization of tumor metastases (Tao et al., 2008). Preliminary results suggest that acute restraint stress could significantly increase brain metastases of systemically administered luciferase-tagged mouse 4T1 cells in mice (Fig. 2) (Rozniecki et al., submitted for publication).

### 1.2. Role of inflammation in cancer growth and metastases

Recent evidence suggests that local inflammation can be conducive for cancer growth (Affara and Coussens, 2007; De Marzo et al., 2007;

## Effect of stress and mast cells on breast cancer brain metastases



**Fig. 2.** Diagrammatic representation of the possible effect of stress on brain mast cell activation, blood-brain-barrier disruption, and metastases using breast cancer as a possible example.

Goldstraw et al., 2007; Lawrence, 2007; Mantovani et al., 2002; Miki et al., 2007; Pollard, 2004; Theoharides and Conti, 2004) and that stromal cells, such as fibroblasts, macrophages, and mast cells can promote carcinogenesis (Leek and Harris, 2002; Orimo and Weinberg, 2006; Parmiani, 2005; Silzle et al., 2003; Theoharides and Conti, 2004). Moreover, some genetic polymorphisms of inflammatory responses appear to be associated with increased risk of cancer (Theodoropoulos et al., 2006).

A case in point is lung carcinoma, the rate of which is increased in patients with asthma, bronchitis or emphysema (Boffett et al., 2002; Gonzalez-Perez et al., 2006; Lu et al., 2006; Samet et al., 1986; Vesterinen et al., 2007; Wang et al., 2006; Wu et al., 1995). In fact, this increased risk is present even in patients who had never smoked (Brown et al., 2005; Santillan et al., 2003) implying that lung inflammation is a distinct risk factor. The relevance of lung mast cells to lung cancer is intriguing given that mast cells are increased in asthma and other inflammatory lung diseases (Bradding et al., 2006; Krishnaswamy et al., 2007), especially in the small airways of smokers (Battaglia et al., 2006; Lamb and Lumsden, 1982). For instance, the number of mast cells was increased in bronchoalveolar lavage of patients with bronchial carcinoma (Walls et al., 2007). Moreover, mast cell density was increased in 180 human adenocarcinomas and was significantly correlated with tumor progression, angiogenesis and poor prognosis (Takanami et al., 2000). High counts of chymase-positive mast cells also correlated with worse prognosis in bronchoalveolar carcinoma (Nagata et al., 2003) and in lung adenocarcinoma (Ibaraki et al., 2005). Increased mast cell density further correlated with increased VEGF expression and poor prognosis in 33/53 non-small cell lung carcinoma (NSCLC) cases (Imada et al., 2000). Finally, histidine decarboxylase (HDC) immunoreactivity, an index of mast cell presence, could dis-

tinguish 18/23 cases of small cell lung carcinoma (SCLC), but only 6/12 NSCLC (Matsuki et al., 2003), suggesting that higher number of mast cells were infiltrating the more aggressive SCLC.

Mammary carcinogenesis in Wistar/Furth rats was shown to occur only when the stroma of the mammary gland (fat pad) was exposed to the nitrosomethylurea (NMU) and involved stroma infiltration of mast cells (Maffini et al., 2004). The number of mast cells was significantly increased in malignant, as compared to benign, lesions in human breast biopsies (Kashiwase et al., 2004). In another study, a statistically increased number of mast cells was detected around mostly hormone receptor positive human breast cancers (della Rovere et al., 2007). It was recently reported that increased stromal "mast cells", identified with immunocytochemistry for c-kit, in invasive human breast cancer may be a favorable prognostic sign. However, breast cancer cells also stain for c-kit, making this type of identification problematic. In fact, the loss of c-kit expression by breast cancer cells associated with advanced stage and poor prognosis (Roussidis et al., 2007; Tsutsui et al., 2006). It was also recently shown that the absence of c-kit permitted increased development of mammary tumors in NMU-treated  $W_s/W_s$  rats (Maffini et al., 2008).

Mast cells may be involved in cancer metastases in more ways than just regulating the BBB. Mast cell deficient mice were reported to have reduced metastases (Starkey et al., 1988). Moreover, a mast cell stabilizer inhibited growth and metastases of rat mammary adenocarcinoma (Dabbous et al., 1991). Use of mast cell deficient mice has strengthened the premise that mast cells are necessary for tumor growth. There was reduced microvessel formation and tumor size when  $W/W^v$  mice were injected with MB49 murine bladder carcinoma (Dethelsen et al., 1994). Premalignant angiogenesis in squamous epithelial carcinogenesis was blocked in mast cell deficient mice, while the development of 1, 2-dimethylhydrazine-induced intestinal tumors was slowed by 60% in  $W/W^v$  mice (Wedemeyer and Galli, 2005). It was recently shown definitively using mast cell deficient mice and the mast cell inhibitor, cromolyn, that mast cells are an absolute requirement for the development of pancreatic islet tumors (della Rovere et al., 2007).

An increased number of mast cells has been noted in rat mammary tumors when the carcinogen, cis-hydroxyproline, was used in Buffalo rats (Strum et al., 1981). Interestingly, rat mammary adenocarcinoma induced by 7, 12-dimethylbenz ( $\alpha$ ) anthracene (DMBA) also was associated with a high number of mast cells, but these cells were resistant to degranulation (Andersson et al., 1976), suggesting that the tumors were somehow preventing release of antitumor molecules such as TNF- $\alpha$  and tryptase. Such inhibition could be the result of oxidized polyamines released by tumor cells (Vliagoftis et al., 1992).

### 1.3. Mast cell pathophysiology and cancer

Mast cells derive from a bone marrow progenitor (Rodewald et al., 1996) and mature in tissues depending on microenvironmental conditions. Mast cells are important for allergic reactions (Blank and Rivera, 2004), but also in inflammation (Theoharides and Kalogeromitros, 2006), autoimmunity (Benoist and Mathis, 2002), and T-cell mediated immune responses (Galli et al., 2005; Mekori and Metcalfe, 2000; Redegeld and Nijkamp, 2003). Mature mast cells vary considerably (Tainsh and Pearce, 1992) in their cytokine content (Bradding et al., 1995) and the phenotypic expression of mast cells does not appear to be fixed (Bischoff et al., 1999). Mast cells can secrete numerous vasoactive, inflammatory and growth promoting mediators (Theoharides and Kalogeromitros, 2006). A number of these are known to disrupt the BBB and include bradykinin, CRH, prostaglandin  $D_2$ , neurotensin (NT), substance P (SP), tryptase, IL-6, IL-8, vasoactive intestinal peptide and VEGF (Table 1).

Mast cell triggers include, in addition to IgE and antigen, numerous other molecules such as anaphylatoxins, bacterial and viral super antigens, drugs, as well as many neuropeptides. The latter include SP

**Table 1**  
Mast cell-derived mediators that could disrupt the BBB<sup>a</sup>

Bradykinin
Corticotropin-releasing hormone (CRH)
Endorphin
Endothelin
Histamine
Interleukin 8
Neurotensin
Nitric oxide (NO)
Prostaglandin D <sub>2</sub> (PGD <sub>2</sub> )
Substance P (SP)
Tryptase
Tumor necrosis factor (TNF)
Vascular endothelial growth factor (VEGF)
Vasoactive intestinal peptide (VIP)
Urocortin (Ucn)

<sup>a</sup> These mediators could be released selectively, sequentially, or together.

(Ali et al., 1986), NT (Carraway et al., 1982), and nerve growth factor (NGF) (Bienenstock et al., 1987; Tal and Liberman, 1997), which is released under stress (De Simone et al., 1990). NT is also secreted by many cancer cells (Souaze et al., 2006) and can stimulate mast cells (Carraway et al., 1982).

Mast cells can also uniquely release some of their mediators selectively (Theoharides et al., 2007). For instance, SP can activate mast cells without degranulation (Janiszewski et al., 1994). IL-1 (Kandere-Grzybowska et al., 2003) and stem cell factor (SCF) (Gagari et al., 1997) induce selective release of IL-6 without degranulation, while CRH can induce selective release of VEGF (Cao et al., 2005). IL-1 can also stimulate secretion of VEGF (Salven et al., 2002), as well as promote angiogenesis and tumor growth (Salven et al., 2002).

Tumor-derived molecules can also activate mast cells. For instance, adrenomedullin is released from human lung carcinoma cells (Yoshida et al., 2001) and can stimulate leukemic mast cells (HMC-1) (Zudaire et al., 2006); however, adrenomedullin is also produced by HMC-1 cells and augments growth of lung cancer cells (Zudaire et al., 2006). Moreover, adrenomedullin producing mast cells were shown to infiltrate human lung cancers taken from archival biopsies (Zudaire et al., 2006). Similarly, endothelin 1 and 2 can be produced by cancer cells (Vural et al., 2001) and mast cells (Liu et al., 1998), but they also stimulate mast cells (Matsushima et al., 2004). Endothelin receptors are also expressed by tumor cells and their activation leads to growth and tumor invasion (Spinella et al., 2007). Mast cells can accumulate around tumors in response to tumor-derived peptides (Poole and Zetter, 1983), SCF, the ligand for the growth receptor c-kit, as well as RANTES or MCP-1 (Conti et al., 1997).

Mast cells could promote tumor development through many different ways: (a) VPF/VEGF, which is secreted by mast cells in response to allergic stimulation (Boesiger et al., 1998; Grutzkau et al., 1998), facilitates tumor angiogenesis (Nienartowicz et al., 2006; Ozdemir, 2006); (b) IL-8, can act as an angiogenesis factor, as well as a tumor cell chemotactic factor and tumor mitogen (Arenberg et al., 1996; Bailey et al., 2007; Brew et al., 2000; Kido et al., 2001; Lehrer et al., 2007; Powell and Mousa, 2007), especially since human NSLC progression was reduced in mice by neutralizing IL-8; (c) epidermal growth factor (EGF), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), SCF and NGF, as well as macrophage inhibitory factor (MIF), which was recently considered as a possible link between inflammation and cancer (Bucala and Donnelly, 2007); (d) transforming growth factor beta<sub>1</sub> (TGF-β<sub>1</sub>) (Kanbe et al., 1999), which can regulate the tumor microenvironment (Stover et al., 2007); (e) histamine, which induces tumor cell proliferation through H1 receptor activation, while suppressing the immune system through H2 receptors (Jutel et al., 2001), (f) Metalloproteinases that disturb the normal stroma-epithelium communication and permit tumor invasiveness (Almholt and Johnsen, 2003), especially in rat mammary

adenocarcinoma (Dabbous et al., 1986), since metastases appear to be regulated by stromal proteolytic enzymes (Almholt and Johnsen, 2003) and chemokines (Murphy, 2001). Finally, mast cell infiltration in response to tumor-secreted SCF can exacerbate tumor immunosuppression (Huang et al., 2008).

#### 1.4. Relevance

Metastases, especially in the brain, continue to be a major source of morbidity and mortality. Stress appears to permit brain metastases, and it also activates brain mast cells that disrupt the BBB. Preliminary results indicate that acute stress permits brain metastases of mammary adenocarcinoma in mice. Moreover, mounting evidence indicates that inflammation, including mast cells accumulating around tumors, could promote tumor growth. Stress is unavoidable in patients with cancer. In addition to attempts to reduce it with psychotropic drugs, neutralizing peripheral CRH or administering CRH receptor antagonists may not only reduce anxiety, but also inhibit mast cell activation by CRH.

Brain mast cells and CRH could serve as new targets for novel drug development against metastases especially in the brain.

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