Chapter 17
Mast Cells and Tumor Microenvironment

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Abstract Increasing evidence indicates that a unique immune cell, the mast cell, accumulates in the stroma surrounding certain tumors, especially mammary and pancreatic adenocarcinoma, as well as melanoma. Many molecules secreted by mast cells could benefit the tumor in at least four ways: (1) angiogenin, heparin and vascular endothelial growth factor (VEGF), which induce neovascularization; (2) proteases that disrupt the surrounding matrix and facilitate metastases; (3) growth factors such as, epidermal growth factor (EGF), nerve growth factor (NGF), platelet derived growth factor (PDGF) and stem cell factor (SCF); (4) histamine, IL-10 and transforming growth factor-β (TGF-β), which are immunosuppressant, along with activation of certain dendritic cells that induce immunologic anergy. These actions could only occur through the unique ability of mast cells to release certain mediators selectively without degranulation. Blocking such release of pro-tumor mediators may constitute a novel therapeutic approach.

Abbreviations

BBB	blood-brain-barrier
CRH	cortocotropin-releasing hormone
CT	tryptase and chymase mast cells
CTMC	connective tissue mast cells

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R.G. Bagley (ed.), *The Tumor Microenvironment*, Cancer Drug Discovery and Development, DOI 10.1007/978-1-4419-6615-5_17,
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DMBA	7, 12-dimethylbenz(α)anthracene
EGF	epidermal growth factor
hCBMCs	human umbilical cord blood-derived cultured mast cells
HDC	histidine decarboxylase
HMC-1	human leukemic mast cells
IFN-α	interferon-α
IFN-γ	interferon-γ
MDSCs	myeloid-derived stem cells
MMC	mucosal mast cells
MMP-9	metalloproteinase-9
NGF	nerve growth factor
NMU	nitrosomethylurea
NO	nitric oxide
NSCLC	non-small cell lung carcinomas
NT	neurotensin
PAR-1 and -2	protease-activated receptors
PDAC	pancreatic ductal adenocarcinoma
PDGF	platelet-derived growth factor
RBL-1	rat basophil leukemia cells
SCF	stem cell factor
SCLC	small cell lung carcinomas
SP	substance P
T mast cells	tryptase mast cells
TAMs	tumor-associated macrophages
TGF-β	transforming growth factor-β
TNF	tumor necrosis factor
TRAIL	TNF-related apoptosis-related ligand
TSLP	thymic stromal lymphopoietin
VEGF	vascular endothelial growth factor
VPF	vascular permeability factor

Introduction

Despite substantial resources invested in basic cancer research, mortality rates for the most frequent forms of cancer have not decreased significantly. Metastasis facilitated by stromal proteolytic enzymes (Almholt and Johnsen 2003) and chemokines (Murphy 2001) remains the chief cause of morbidity and mortality. The stroma surrounding the tumor is increasingly acquiring importance for its growth and dissemination, with infiltrating inflammatory cells actually contributing to cancer proliferation (Mantovani et al. 2002). For instance, tumor-associated macrophages (TAMs) and tumor-associated fibroblasts can be beneficial to tumor angiogenesis and growth (Silzle et al. 2003; Yu and Rak 2003) through secretion of vascular endothelial growth factor (VEGF) (Barbera-Guillem et al. 2002) and platelet-derived growth factor (PDGF) (Kataki et al. 2002). In one model of

subcutaneous melanoma, both angiogenesis and growth rate correlated with tumor infiltration by macrophages that expressed angiotensin II type 1 receptor and VEGF (Egami et al. 2003). TAMs were also significantly correlated with squamous cell carcinoma invasion (Li et al. 2002).

Mast cells are important in allergic and late phase reactions, but also in inflammation and T-cell mediated immune responses (Mekori and Metcalfe 2000; Redegeld and Nijkamp 2003; Pedotti et al. 2003). Yet, mast cells appear to be recruited by tumors and accumulate in the stroma (Theoharides 1988) (Fig. 17.1). Mast cells could be helpful to the tumor, but only if secretion of beneficial molecules could occur *selectively without degranulation* (Theoharides et al. 2007). In fact, the tumor stroma microenvironment could alter the phenotypic behavior of mast cells. For instance, acidity created by rapid cancer cell proliferation inhibits mast cell degranulation, but enhances IL-4 production (Frossi et al. 2003). Nitric oxide (NO) generated by new vessel growth inhibits mast cell degranulation (Coleman 2002), as do oxidized polyamines secreted by the tumor (Vliagoftis et al. 1992). Mast cells can promote tumor development by: (a) disturbing the normal stroma-epithelium

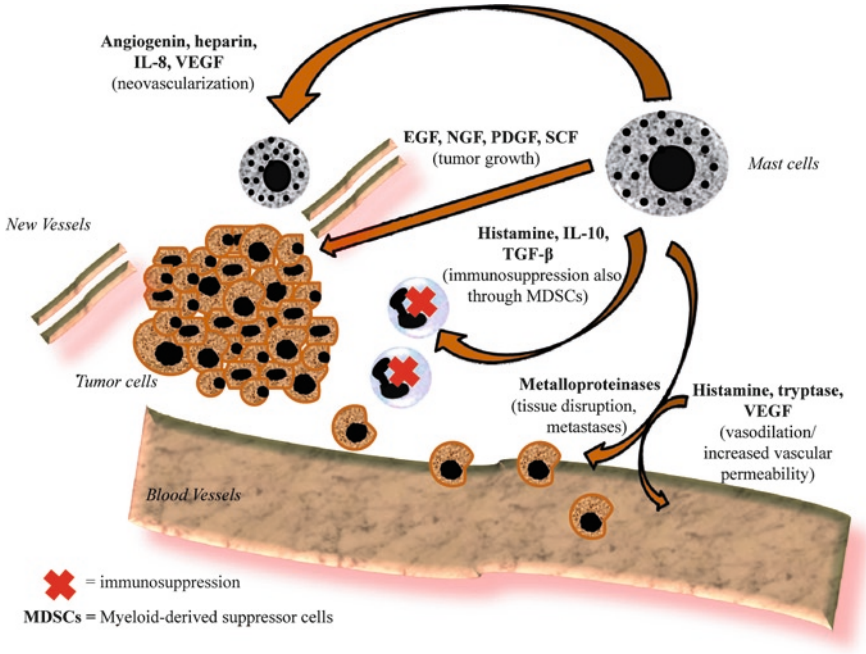

Fig. 17.1 Schematic representation of the possible role of increased number of mast cells in the stroma of certain tumors. Mast cells could be recruited by tumor-derived chemoattractants such as adrenomedullin, MCP-1, RANTES and SCF, to selectively secrete molecules beneficial to the tumor; these could include growth factors, histamine which is mitogenic (H_1) and immunosuppressant (H_2), neovascularization agents such as heparin, VEGF and IL-8, as well as proteases that could permit new blood vessel formation and metastases

communication as was shown for matrix degradation at sites of tumor invasion in rat mammary adenocarcinoma, (b) facilitating tumor angiogenesis, (c) releasing growth factors (Conti et al. 2007), and (d) inducing a state of immunosuppression. The tumor enhancing effect of mast cells has been shown repeatedly with the use of W/W^v mast cell deficient mice, which developed fewer lung metastases to subcutaneous B16-BL6 tumors (Starkey et al. 1988), and in which mice premalignant angiogenesis of squamous epithelial carcinogenesis was blocked (Coussens et al. 1999). The development of 1, 2-dimethylhydrazine-induced intestinal tumors was slowed by 60% in W/W^v mice (Wedemeyer and Galli 2005). There was also reduced microvessel formation and tumor size in W/W^v mice injected with MB49 murine bladder carcinoma (Dethelfsen et al. 1994).

Mast Cell Biology

Mast cells derive from a specific bone marrow progenitor cell, they migrate into tissues where they mature depending upon microenvironmental conditions, and they participate in allergic reactions, as well as innate and acquired immunity (Mekori and Metcalfe 2000; Galli et al. 2005a, b). Mast cells are located perivascularly close to neurons and could have a critical role in neuroinflammatory diseases (Theoharides and Cochrane 2004), as well as in stress-induced brain metastases (Theoharides et al. 2008). Mast cells vary considerably in their cytokine and proteolytic enzyme content: connective tissue mast cells (CTMC) contain tryptase and chymase (CT mast cells), while mucosal mast cells (MMC) contain only tryptase (T mast cells). However, the phenotypic expression of mast cells is not fixed, since MMC can develop into CTMC given the appropriate microenvironmental conditions (Galli et al. 2005a). Moreover, addition of IL-5 to human umbilical cord blood-derived cultured mast cells (hCBMCs) augmented IgE-induced production of distinct cytokines, such as tumor necrosis factor (TNF) and MIP-1α, but without histamine (Ochi et al. 2000).

In addition to IgE and antigen, the main trigger in allergic reactions, anaphylatoxins (C3a, C5a), cytokines (IL-1, IL-33), hormones (CRH) and neuropeptides can stimulate mast cell activation; the latter include endorphins, substance P (SP), neurotensin (NT), and nerve growth factor (NGF) leading to secretion of numerous biologically active mediators, but through different pathways (Theoharides and Kalogeromitros 2006). In addition, thymic stromal lymphopoietin (TSLP) released from epithelial cells in response to infection, trauma, and inflammation activates mast cells in the absence of IgE, but in the presence of IL-1, to release IL-5 and IL-13 (Allakhverdi et al. 2007; Al-Shami et al. 2005).

Mast cells can secrete either the content of individual granules (Theoharides and Douglas 1978) or distinct mediators selectively (Theoharides et al. 1982), possibly through regulation by specific phosphoproteins (Sieghart et al. 1978; Theoharides et al. 1980). Vascular permeability/vascular endothelial cell growth factor (VPF/VEGF) can be secreted from bone marrow-derived mouse mast cells

(Boesiger et al. 1998). In view of the fact that acute stress increased tumor size and decreased survival (Sklar and Anisman 1979; Antoni et al. 2006), we investigated if cortocotropin-releasing hormone (CRH), secreted under stress, could induce VEGF release from hCBMCs. We reported that CRH induced selective VEGF release without histamine (Cao et al. 2005). We further showed that IL-1 could induce selective secretion of IL-6 from hCBMCs without degranulation through a unique vesicular shuttle (Kandere-Grzybowska et al. 2003). IL-1 can further stimulate secretion of VEGF (Salven et al. 2002), thus promoting angiogenesis (Salven et al. 2002) and lung carcinoma growth (Saijo et al. 2002). Stem cell factor (SCF) can also induce selective release of IL-6 without histamine and without degranulation (Gagari et al. 1997). This process has been termed "differential release", "intragranular activation" or "piecemeal degranulation" (Letourneau et al. 1996). Moreover, in certain diseases such as scleroderma and interstitial cystitis (Theoharides et al. 1995), mast cells could be almost totally depleted of their granule content, without classic degranulation, rendering them undetectable by light microscopy ("phantom mast cells") (Claman et al. 1986).

Mast Cells Could Be Beneficial to the Tumor

Mast cells could accumulate at sites of tumor growth in response to numerous chemoattractants (Table 17.1) such as RANTES or MCP-1 (Conti et al. 1997), and are associated with poor prognosis (Molin et al. 2002). In addition, SCF at low doses mediates chemotaxis of mast cells, while a higher dose is necessary for release of mediators (Huang et al. 2008), such as metalloproteinase-9 (MMP-9) (Huang et al. 2008). Adrenomedullin can stimulate histamine release from rat peritoneal mast cells (Yoshida et al. 2001), but can also be released from human cultured A549 lung carcinoma cells and stimulate human leukemic mast cells (HMC-1) (Zudaire et al. 2006). Moreover, adrenomedullin is also produced by HMC-1 cells, it augments growth of lung cancer cells (Zudaire et al. 2006), and adrenomedullin-producing mast cells were shown to infiltrate human lung cancers (Zudaire et al. 2006).

Mast cells have been consistently implicated in tumor angiogenesis (Crivellato et al. 2008), along with other myeloid cells (Murdoch et al. 2008). Mast cell-deficient W/W^v mice exhibited decreased rate of tumor angiogenesis (Starkey et al. 1988). Mast cells could facilitate tumor angiogenesis through heparin-like molecules that would also permit metastases through their anti-clotting effects (Fig. 17.1). Mast cells

Table 17.1 Tumor-derived mast cell chemoattractants/triggers

• Adrenomedullin
• MCP-1
• RANTES
• SCF

also generate and secrete IL-8 which has been shown to be an angiogenesis factor, as well as a tumor cell chemotactic factor and tumor mitogen (Waugh and Wilson 2008). Mast cells secrete a number of growth factors, such as EGF, PDGF, NGF, and SCF (Galli et al. 2005b). Moreover, VPF/VEGF is secreted from mouse bone marrow-derived and human cultured mast cells (Boesiger et al. 1998), as well as from HMC-1 cells (Grutzkau et al. 1998) (Table 17.2).

Mast cells are rich in metalloproteinases, such as MMP-9, that can facilitate tumor invasiveness (Almholt and Johnsen 2003). Such enzymes can disturb the normal stroma-epithelium communication, as was shown for matrix degradation at sites of tumor invasion in rat mammary adenocarcinoma (Dabbous et al. 1986). Mast cells and stress could also disrupt the blood-brain-barrier (BBB) and promote brain metastases (Theoharides et al. 2008). Acute stress can activate mast cells and increase BBB permeability that is mast cell dependent (Esposito et al. 2002a). These findings are important in view of the fact that acute stress increases metastases in breast and other tumors (Sklar and Anisman 1979; Antoni et al. 2006), and over 30% of breast cancer patients develop brain metastases with poor associated prognosis (Schouten et al. 2002). In fact, a number of cancers express CRH receptors (Reubi et al. 2003), prompting the suggestion that CRH may affect tumor cell behavior. For instance, a human breast cancer line MCF7 expresses CRH mRNA and secrets immunoreactive CRH (Graziani et al. 2006b), prompting the possibility of autocrine or paracrine effects.

Another aspect of tumor microenvironment is immunosuppression. Histamine induces tumor cell proliferation through H1 receptors, while suppressing the immune system through H2 and possibly H4 receptors (Tiligada et al. 2009; Gutzmer et al. 2005). It was also shown that the histamine content of human breast

Table 17.2 Mast cell mediators relevant to tumor microenvironment

Mediators	Main pathophysiologic effects
Histamine	Vasodilation, mitogenesis, immunosuppression
Enzymes	
Chymase	Tissue damage
Metalloproteinases	Tissue disruption, metastases
Tryptase	Tissue damage, metastases
Growth factors	Tumor growth
EGF, GM-CSF, NGF, PDGF, SCF	
Angiogenic factors	Angiogenesis, neovascularization
Angiogenin	
Heparin	
VEGF	
Cytokines	
IL-8	Chemoattractant, tumor mitogen

EGF epidermal growth factor, *GM-CSF* granulocyte monocyte-colony stimulating factor, *NGF* nerve growth factor, *PDGF* platelet-derived growth factor, *SCF* stem cell factor, *VEGF* vascular endothelial cell growth factor

cancer tissue was much higher than adjacent normal tissue and sufficient to act as a local immunosuppressant (Reynolds et al. 1998). The H2 receptor antagonist, famotidine, given preoperatively enhanced tumor infiltrating lymphocytes and increased metastatic lymph node reactive changes in breast cancer in humans (Parshad et al. 2002). Mast cells can promote immunosuppression by also secreting the immunosuppressants transforming growth factor-β (TGF-β) and IL-10 (Conti et al. 2003). SCF-mediated mast cell infiltration of tumors further enhances immunosuppression (Huang et al. 2008). Mast cells may further contribute to tumor anergy by promoting the development/recruitment of "tolerogenic host antigen-presenting cells" (Wasiuk et al. 2009) and Treg cells (Wasiuk et al. 2009). Mast cells may also influence migration and function of dendritic cells through distinct prostaglandins (PGE_2 and PGD_2) (Wasiuk et al. 2009). In addition, mast cells could indirectly down-regulate anti-tumor immunity by influencing the functions of immune suppressive myeloid-derived stem cells (MDSCs). MDSCs also secrete VEGF (Marx 2008), but this action requires MMP-9 (Yang et al. 2004), which is produced by mast cells. Mast cell-derived IL-1b induces MDSCs in mice with transplanted mammary carcinoma or fibrosarcoma (Bunt et al. 2006).

Breast Cancer

Disruption of the normal flow of information between stroma and parenchyma could permit neoplastic progression (Barcellos-Hoff 1998). Stromal matrix metalloproteinases, rather than the target cell, were shown to promote mammary tumorigenesis (Sternlicht et al. 1999), while irradiated mammary gland stroma promoted carcinogenesis of unirradiated epithelial cells (Barcellos-Hoff and Ravani 2000). Mammary carcinogenesis in Wistar/Furth rats occurs when *only* the stroma of the mammary gland (fat pad) is exposed to the carcinogen nitrosomethylurea (NMU) (Maffini et al. 2004). The earliest effects of carcinogen administration in mammary gland carcinogenesis are manifested in the stroma with infiltration of inflammatory cells including 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). Moreover, the number of mast cells was greater in scirrhous than papillotubular carcinoma (Kashiwase et al. 2004). The histamine content of human breast cancer tissue, an index of mast cell presence, was much higher than adjacent normal tissue (Reynolds et al. 1998). Recent papers also confirmed high number of mast cells in human mammary adenocarcinoma (Rajput et al. 2007; Ribatti et al. 2007). Some of these papers suggested that the presence of mast cells may indicate a favorable prognosis (Rajput et al. 2007; Dabiri et al. 2004); however, in these instances mast cells were "identified" by staining for c-kit (Rajput et al. 2007; Dabiri et al. 2004), which is not specific, as cancer cells also express c-kit (Charpin et al. 2009). Moreover, reduction of c-kit expression was associated with malignant transformation of breast epithelium in human breast cancer (Polat 2007), and in carcinogen-induced rat mammary carcinoma (Maffini

et al. 2008). Consequently, tumor c-kit expression and not the presence of c-kit positive mast cells, appears to be associated with favorable outcomes.

An increased number of mast cells was reported in cis-hydroxyproline-induced mammary tumors in Buffalo rats (Strum et al. 1981). Similar findings were obtained in 7, 12-dimethylbenz(α)anthracene (DMBA)-induced mammary adenocarcinoma in which mast cells accumulated, but appeared to be intact and resistant to the mast cell degranulator compound 48/80 (Andersson et al. 1976). The mast cell inhibitor disodium cromoglycate increased blood clotting and hypoxia in invasive murine breast cancer (Samoszuk and Corwin 2003).

The location of mast cells in relation to tumor cells may also be important. Lymph nodes may behave differently (Munn and Mellor 2006) upon cancer cell entrapment. Tryptase-positive mast cells correlated with angiogenesis and presence of micrometastases in sentinel lymph nodes from 80 patients with breast cancer (Ribatti et al. 2007). In contrast, intermammary lymph node enlargement with mast cell infiltration was considered to be a positive prognostic sign (Quan et al. 2002).

Melanoma and Basal Cell Carcinoma

Mast cells accumulate especially around invasive melanoma (Reed et al. 1996; Dvorak et al. 1980), and their numbers correlate with increased neovascularization, mast cell overexpression of VEGF, tumor aggressiveness, and poor prognosis (Ch'ng et al. 2006). Tumor vascularity and tryptase-positive mast cells correlated with poor melanoma prognosis (Ribatti et al. 2003). Moreover, SCF splice variants were detected in melanoma (Welker et al. 2000), and could present new forms of mast cell growth factors related to melanoma growth. Mast cells have also been repeatedly noted to accumulate around basal cell carcinoma lesions and are thought to contribute to cancer growth by inducing immunosuppression (Grimbaldeston et al. 2000). Increased dermal mast cell numbers are associated with higher risk of developing basal cell carcinoma in humans possibly through UVB-induced immunosuppression (Grimbaldeston et al. 2002). Mast cells can also mediate TNF-α dependent dendritic cell migration and consequently increase skin tumor antigen presentation, but in a manner that does not elicit an immune response (Munn and Mellor 2006; Hart et al. 2002).

Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is the 4th cause of cancer-related deaths in the USA, with a prognosis of less than 6.0 months and 5-year survival of less than 5% (Welsch et al. 2007; Hezel et al. 2006). PDAC escapes early detection and resists treatment (Tuveson and Hingorani 2005). Even though PDAC had been

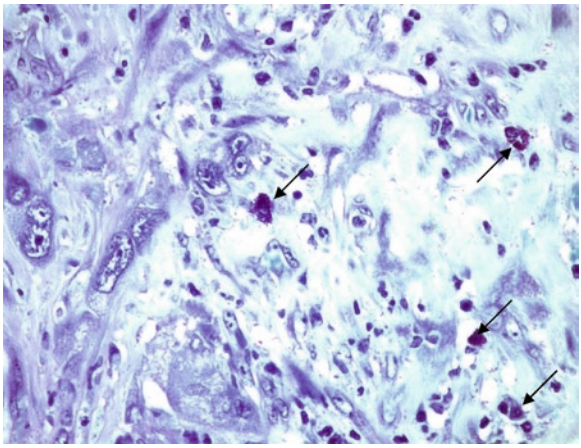

Fig. 17.2 Light photomicrograph of ductal pancreatic adenocarcinoma with a number of infiltrating intact mast cells (*solid arrows*) stained with acidified toluidine blue, magnification = 20×

thought not to be particularly vascular, it was shown to secrete VEGF (Luo et al. 2001). Adrenomedullin, discussed earlier as a mast cell trigger, is expressed by pancreatic cancer cells and increases their growth and survival (Nakamura et al. 2006; Keleg et al. 2007). Increased numbers of mast cells have also been noted in pancreatic cancer (Esposito et al. 2002b, 2004). Moreover, a recent paper reported that mast cells were an absolute requirement for angiogenesis and cancer development in Myc-activated mouse pancreatic tumors (Soucek et al. 2007). Mast cells are actually localized among ductal adenocarcinoma cells, and they appear morphologically intact (Fig. 17.2), suggesting that pro-tumor molecules may be released without degranulation.

Lung Cancer

The relevance of lung mast cells to lung cancer is intriguing, given that mast cells are well known to be increased in asthma and other inflammatory lung diseases (Krishnaswamy et al. 2007). In fact, lung mast cells are also increased in the epithelium of smokers (Lamb and Lumsden 1982), especially in the small airways (Battaglia et al. 2007). Gene profiling of disaggregated human lung mast cells from patients with interstitial diseases showed increased expression of matrix metalloproteinases (Edwards et al. 2005). The number of mast cells was increased in bronchoalveolar lavage of patients with bronchial carcinoma (Walls et al. 2007). Also, increased mast cell density using tryptase and surface CD34 immunocytochemistry was significantly correlated with tumor progression, angiogenesis and poor prognosis in human adenocarcinomas (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). This direct correlation between increased numbers of mast cells and lung cancer was apparently independent of tumor angiogenesis, as measured by the presence of endothelial cells stained with anti-human factor VIII antibody (Tomita et al. 2000). Nevertheless, increased mast cell density correlated with increased VEGF expression and poor prognosis in 33/53 cases of non-small cell lung carcinomas (NSCLC) (Imada et al. 2000). Histidine decarboxylase (HDC) immunoreactivity, an index of mast cell presence/activation, could distinguish 18/23 cases of small cell lung carcinomas (SCLC), but only 6/12 cases of NSCLC (Matsuki et al. 2003), suggesting that higher number of mast cells were infiltrating the SCLC, known to be more aggressive.

Mast Cells Could be Detrimental to the Tumor

Even though mast cells could be detrimental to tumor growth, they apparently cannot secrete such mediators as they may be inhibited from degranulation by tumor-derived blockers, such as oxidized polyamines (Vliagoftis et al. 1992), or chondroitin sulfate, which inhibits mast cell activation (Theoharides et al. 2000). It would be fascinating if one could inhibit mast cells from secreting pro-tumor mediators, but promote secretion of anti-tumor molecules. For instance, tryptase stimulates protease-activated receptors (PAR-1 and -2), also activated by thrombin and trypsin respectively, and induces widespread inflammation (D'Andrea et al. 2001). IL-4 binds to IL-4 receptors expressed by human breast carcinoma cells, and leads to apoptosis (Gooch et al. 1998). TNF-α could also induce tumor cell death (Gordon and Galli 1990). Histamine inhibited human primary melanoma cell proliferation presumably by acting through H1 receptors, an action enhanced by IL-6 (Lazar-Molnar et al. 2002). Heparan sulfate proteoglycans could block binding of heparin to the cell surface and prevent neovascularization (Fannon et al. 2003). For instance protamine, which binds to heparin and neutralizes its anticoagulant properties, induced selective thrombosis of blood vessels within mammary adenocarcinoma (Su et al. 2001). On the other hand, cancer cell-associated chondroitin sulfate accumulates in mammary gland tumors and in metastatic lesions (Hinrichs et al. 1999); in fact, tumor cells metastasize through binding of their surface chondroitin sulfate to the interstitial matrix (Kokenyesi 2001).

Interferon-α (IFN-α) or mast cell-derived interferon-γ (IFN-γ) may enhance TNF-related apoptosis-related ligand (TRAIL) gene expression and translation, leading to apoptosis of tumor cells in an autocrine and paracrine manner (Abadie et al. 2004; Wang et al. 2004). Moreover, treatment of melanoma patients with IFN-α increased TRAIL levels in serum (Tecchio et al. 2004). Receptor binding of TRAIL, in turn, activates an number of down steam events leading to regulation of the inflammatory response (Collison et al. 2009). In addition to its cytotoxic role,

TRAIL can inhibit angiogenesis indirectly by facilitating apoptosis of endothelial cells (Li et al. 2003).

Certain studies indicate that CRH may inhibit growth of endometrial (Graziani et al. 2002) and breast cancer cells (Graziani et al. 2006b) in culture. Other studies suggest that endometrial cancer not expressing CRHR-1 may be associated with a more aggressive phenotype in humans (Graziani et al. 2006a). Mast cells (Kempuraj et al. 2004) and other inflammatory cells (Karalis et al. 1997) can synthesize and release CRH. It would, therefore, be interesting if mast cells could release CRH, but at the same time be prevented from CRH inducing VEGF release in an autocrine fashion.

Conclusion

Mounting evidence indicates that mast cells accumulate in tumor stroma and can promote tumor growth and metastases. Mast cells may, therefore, serve as a new target for the adjuvant treatment of tumors (Groot et al. 2009), such as mammary adenocarcinoma or pancreatic cancer (Theoharides 2008), through the selective inhibition of tumor-promoting molecules. A possible therapeutic approach could involve the use of select flavonoids. Flavonoids are naturally occurring polyphenolic compounds present in green plants and seeds with anti-oxidant, anti-inflammatory and cancer-inhibiting properties (Middleton et al. 2000). A multiethnic epidemiological study identified an inverse relationship between flavonoid intake and pancreatic cancer (Nothlings et al. 2007). An inverse relationship has also been reported between intake of flavonoids, such as quercetin, and risk of lung cancer in general (Le Marchand et al. 2000), as well as in male smokers in particular (Hirvonen et al. 2001). The flavonoids quercetin, luteolin and epigallocatechin also decrease proliferation of pancreatic carcinoma cells in culture (Lee et al. 2002; Shankar et al. 2008; Takada et al. 2002), but the mechanism of this action is not known. We showed that these flavonoids inhibit proliferation and secretion from rat basophil leukemia (RBL-1) cells (Alexandrakis et al. 1999) and HMC-1 cells (Alexandrakis et al. 2003), as well as pro-inflammatory cytokine release from normal hCBMCs (Kempuraj et al. 2005). In fact, recent reviews have re-emphasized the potential use of select flavonoids, such as epigallocatechin, quercetin and curcumin in cancer treatment (Saif et al. 2009; Sogno et al. 2009; Jagtap et al. 2009).

Future studies should investigate any unique ability of select flavonoids with anti-cancer properties to also inhibit secretion of pro-cancer molecules, while permitting secretion of anti-cancer mediators from mast cells.

Acknowledgments Work discussed was supported in part by a "Concept Award" No. BC024430 from the United States Department of Defense to (TCT), and funds from Theta Biomedical Consulting and Development Co., Inc. (Brookline, MA). The possible therapeutic role of inhibiting mast cell-derived molecules beneficial to tumor growth is covered by patent application US 10/811,838 submitted by TCT and assigned to Theta, Inc.

Many thanks are due to Dr. Eva Karamitropoulou (Attikon General Hospital, Athens Medical School, Athens, Greece) for the pancreatic cancer photo, and to Ms. Jessica Christian for her word processing skills.

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