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REVIEW

Carcinogenesis: the cancer cell–mast cell connection

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Abstract

Background In mammals, inflammation is required for wound repair and tumorigenesis. However, the events that lead to inflammation, particularly in non-healing wounds and cancer, are only partly understood.

Findings Mast cells, due to their great plasticity, could orchestrate the inflammatory responses inducing the expression of extraembryonic programs of normal and pathological tissue formation. This heterogeneity of mast cells could allow a microenvironment to be recreated similar to the extraembryonic structures, i.e., amnion and yolk sac, which are needed for embryonic development. Mast cells could provide a framework for understanding the connection between inflammation and tumor growth, invasion and metastasis. In this way, the mast cells could express inflammatory phenotypes, which would enable the cancer stem cells to develop. Thus, the cancer cell uses mast cells to express the extraembryonic functions that are needed to allow the cancer stem cell to proliferate and invade. If so, then by using this appropriate inflammatory interstitial microenvironment, a cancer stem cell can reach maximum levels of growth and invasion inside the host.

Conclusion Therefore, the comparison of tumors with wounds that do not heal would be supported since both pathological processes use extraembryonic mechanisms by mast cells. The adoption of these mechanisms warrants tumor survival in an embryonic-like state.

Keywords Amniotic · Cancer · Chronic inflammation · Ischemia–reperfusion · Mast cell · Vitelline

Abbreviations

ACTH	Adrenocorticotrophic hormone
EMT	Epithelial–mesenchymal transition
FGF	Fibroblast growth factor
HIF	Hypoxia-inducible transcription factor
MCP	Monocyte chemoattractant protein
MET	Mesenchymal to epithelial transition
MIP-1	Macrophage inflammatory protein one
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol-3-kinase
PHD	Prolyl hydrolase
Treg cells	Regulatory T cells
SCF	Stem cell factor
TLR	Toll-like receptors
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor-alpha
VEGF	Vascular endothelial growth factor

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Introduction

In mammals, inflammation is required for both wound repair and tumorigenesis [1, 2]. Moreover, the chronic inflammatory microenvironment of the non-healing wound could be a risk factor for malignant transformation [1, 3]. Considerable progress has been made in understanding the cellular and molecular events that are involved in the acute inflammatory response to infection and tissue injury [4]. However, the events that lead to localized chronic inflammation,

particularly non-healing wounds [1, 5] and tumorigenesis [6–8], are only partly understood.

Impaired wound healing and tumor growth share, in addition to multiple inflammatory mechanisms [1, 9, 10], the infiltration by a cell with an enormous plasticity, the mast cell is shown [5, 11–13]. Infiltrating mast cells are commonly seen in pathological wound healing [5, 10] and in cancer [11, 13, 14], and pro- and anti-inflammatory phenotypes have been alternatively attributed to them. In particular, the relevance of infiltrating mast cells in various tumors could be related to their fundamental role in orchestrating the chronic inflammatory response that is necessary for tumor growth and invasion [14, 15].

Because of their great plasticity, mast cells could drive the chronic inflammatory response inducing the expression of embryonic programs of tissue formation [5]. This hypothetical role of mast cells could provide a logical framework for understanding the connection between the chronic inflammatory response and tumor growth, invasion and metastasis. The functional heterogeneity of mast cells could allow a microenvironment to be recreated similar to the extraembryonic structures, i.e., amnion and yolk sac, so as to reproduce embryonic development. Thus, by using this appropriate microenvironment for development, a cancer stem cell can reach maximum levels of growth and invasion inside the host.

The interstitial microenvironment in the acute inflammatory response: mast cells as mediators

The interstitial space is the field where the battle of the acute inflammatory response takes place. The interstitial space in injured tissues and organs is successively occupied by molecules, inflammatory cells and bacteria and, finally, by a mesenchymal-derived tissue, the granulation tissue. The great functional heterogeneity of mast cells enables them to be efficient mediators in all the phases of this progressive inflammatory occupation of the interstitial tissue space [16–18].

In acute inflammation, whether local or systemic, the response could be viewed as a series of three overlapping successive phases with increasingly complex trophic functional systems for using oxygen [19, 20]. The first or immediate phase has been referred to as the nervous phase, because sensory (stress pain and analgesia) and motor (contraction and relaxation) alterations, including vasomotor changes, respond to the injury [19]. This early pathological activity of the body's nociceptor pathways is associated with stress mediated through the hypothalamic–pituitary–adrenal and sympathetic–adrenal medullary axes, the sympathetic nervous system and the renin–angiotensin–aldosterone system [21, 22]. This initial phase presents ischemia–reoxygenation, oxidative and nitrosative stress and interstitial edema with selective interstitial infiltration by mediators of the stress response such as catecholamines, adrenocorticotrophic hormone (ACTH), glucocorticoids, and angiotensin, as well as glucose, amino acids and lipids, all of them derived from earlier metabolic alterations, including hyperglycemia, protein catabolism and lipolysis [23]. In addition, interstitial edema favors nutrition by diffusion through the injured tissue and activation of the lymphatic circulation (circulatory switch) [20].

In the succeeding immune or intermediate phase of the acute inflammatory response, the tissues and organs that have suffered ischemia–reperfusion are infiltrated by inflammatory cells and sometimes by bacteria [5]. This phase presents enzymatic stress, with migration of macrophages and dendritic cells to lymph nodes, where they activate T and B cells, i.e., innate and adaptive immune responses [24]. Interstitial invasion by leukocytes would create a new trophic axis based on enzymatic digestion [5].

In the last endocrine phase of the acute inflammatory response, nutrition mediated by the blood capillaries is established. Through initial and excessive proliferation, the endothelial cells could play a key role in the previous phases as antioxidant and antienzymatic cells, including induction of the acute phase response, considered as the humoral arm of innate immunity [25]. Angiogenesis is closely associated to granulation tissue formation and remodeling. In mammals, fibroblasts form a heterogeneous collection of mesenchymal cells and they are the principal constituents of connective tissue, including granulation tissue [5, 24]. Although remodeling by fibrosis begins 2–3 weeks after injury, it lasts for a year or more [20, 26].

Mast cells are ubiquitous in the interstitial spaces of the body and normally reside in the connective tissue close to blood vessels, lymphatic capillaries, nerves and epithelia [27, 28].

Mast cells could be recruited to the inflammatory interstitium by macrophage inflammatory protein (MIP)-1 and stem cell factor (SCF). This last factor is, in turn, the most important cytokine supporting their growth, also termed mast cell growth or Kit ligand, and it is produced by fibroblasts and endothelial cells [27–30]. Binding of SCF induces autophosphorylation of its receptor Kit and subsequently activation of several signaling molecules, including phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinases [31]. The activated mast cells could selectively secrete pro- and anti-inflammatory molecules, and their phenotypes probably change in accordance with microenvironmental conditions [17, 32, 33].

In the first or immediate phase of the inflammatory response, interstitial hydro-electrolytic alterations mediated by mast cells stand out. Many mast cells mediators have

been shown to increase capillary permeability, including histamine, prostacyclin, substance P and vascular endothelial growth factor (VEGF) [33]. The existence of intensive bidirectional cross-talk between mast cells and sensory nerves suggests that mast cells and sensory nerves may be viewed as a functional unit, which could be of crucial importance in the induction of neuroimmunological inflammatory pathways [34, 35]. During the inflammatory response, the activation of the neuroendocrine system and the peripheral sensory nerves leads to the release of mediators such as neuropeptides, corticotrophin-releasing hormone and melanocyte-stimulating hormone, which are capable of activating mast cells [36]. In addition, the mast cell mediators released, i.e., histamine, tryptase and nerve growth factor, can excite and stimulate surrounding sensory C-nerve fibers resulting in a feed-forward loop, thus potentiating neurogenic inflammation [36]. In particular, sensory neurons could upon stimulation release substance P and other neuropeptides that in turn activate neurokinin-1 receptors, leading to plasma extravasation from post-capillary venules. Also, substance P can induce VEGF secretion from mast cells [37] (Fig. 1).

In the intermediate or immune phase, mast cells can function as immunoregulatory cells that influence both innate and adaptive immunity [32, 33]. Mast cells comprise an important effector arm of innate immune cells along with neutrophils, macrophages and natural killer cells. Besides expressing toll-like receptors (TLR), that can be activated by different types of TLR ligands, including multiple bacterial molecules [27], mast cells also regulate the migration, maturation and function of other innate immune cells, i.e., neutrophils and dendritic cells [16, 33]. Mast cells have also been shown to play a very important role in adaptive immunity [38, 39]. Besides their role as antigen-presenting cells, mast cells promote migration of T cells and growth and differentiation of B cells [39, 40]. In particular, it is considered that the existence of cross-talk between mast cells and regulatory T cells (Treg cells) is essential for maintaining T cell-dependent peripheral tolerance [40, 41]. Mast cells and Treg cells increase in number in tolerant allografts and may be crucial in sustaining allograft survival [41].

Finally, mast cell granules contain cytokines and chemokines that can change the microenvironment of the injured area by regulating fibrogenesis and angiogenesis with progenitor cell recruitment and extracellular matrix reposition [42]. Mast cells are also producers of many factors involved in fibroblast proliferation and angiogenesis, including transforming growth factor (TGF)-β, VEGF, platelet-derived growth factor (PDGF), heparin and fibroblast growth factor (FGF) [30, 33].

Mast cells can change their phenotype depending on the local microenvironment, the underlying disease and other factors [16, 28, 43]. Therefore, the phenotypic heterogeneity of mast cells during the evolution of the inflammatory

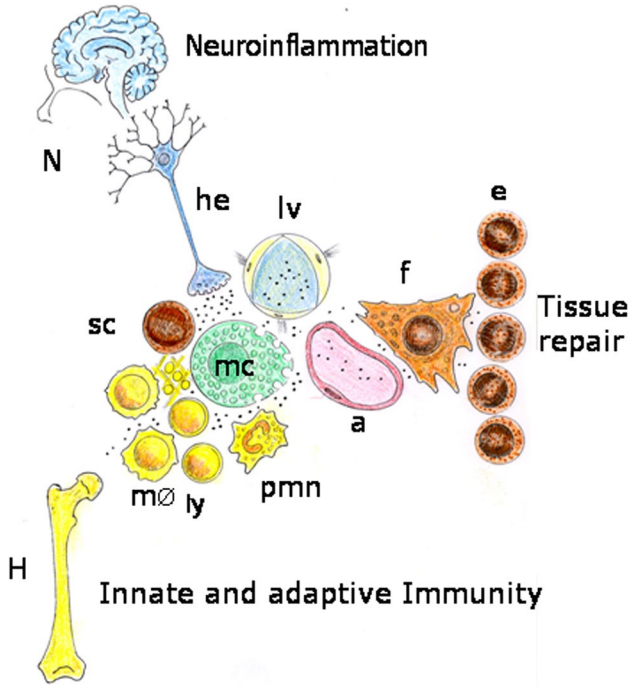

Fig. 1 Schematic drawing of the mast cell-mediated acute inflammatory response. In the first or immediate phase, interstitial hydroelectrolytic alterations associated with activation of the peripheral sensory nerves stand out. During the second or intermediate phase, the innate and adaptive immune responses play a very important role. Lastly, in the third or late phase, fibrogenesis and angiogenesis achieve tissue repair. *a* angiogenesis, *e* epithelium, *f* fibrogenesis, *H* hematopoiesis, *he* hydroelectrolytic alterations, *l* lymphatic capillary, *ly* lymphocyte, *mc* mast cell, *mØ* macrophage, *N* neurogenic axis, *pmn* polymorphonuclear neutrophil, *sc* stem cell

response could depend on the inflammatory microenvironmental characteristics in each one of the proposed phases. However, because of their plasticity, they may also influence interstitial microenvironmental changes during the different evolutive phases of acute inflammation [5]. In particular, they could play a protective role during the successive and overlapping phases of the acute inflammatory response based on the changes produced in the interstitial inflammatory microenvironment that successively favor progenitor cell viability, immunotolerance, fibrogenesis and angiogenesis [5, 42] (Fig. 1).

Mast cell phenotypes related to chronic inflammation

Mast cells could also participate in the chronicity of the inflammatory response when a noxious factor is associated [17, 44]. Chronic inflammation related to mast cells underlies many diseases including allergic diseases such as asthma, atopic dermatitis and food allergies [31, 45–49],

cardiovascular diseases, e.g., atherosclerosis [24] and metabolic diseases, e.g., metabolic syndrome [49].

Under conditions of long-lasting inflammation, the tissue interstitium is associated with oxidative stress, edema, enzymatic stress, persistent leukocyte stimulation, lymphangiogenesis, angiogenesis and fibrosis [5, 50–52]. Mast cell-derived mediators can drive chronic inflammation. It has been considered that if the insult is sustained, i.e., there is a chronic inflammatory response, mast cells can synthesize additional pro-inflammatory mediators and cytokines to recruit and activate a wide variety of leukocytes, including macrophages and lymphocytes, which can contribute to further tissue destruction and inflammation [53]. In this way, non-healing pressure ulcers are locked into a state of chronic inflammation characterized by abundant neutrophil infiltration with associated reactive oxygen species and destructive enzymes [50]. However, prolonged inflammation in wounds contributes to the development of fibroproliferative scars, in other words keloids and hypertrophic scars, both with increased mast cell density [54]. Moreover, in autoimmune diseases, persistent antigenic stimulation recruits endogenous mesenchymal stem cells to the site of the lesion and this contributes to the evolution of fibrosis [52].

Chronic inflammation and fibrotic lesions are often associated with increased densities of mast cells [50, 54]. Thus, the association of mast cells with fibroblasts/adipocytes is commonly observed in the orbital tissue in biopsies of thyroid eye disease patients. Current evidence suggests that activation of orbital fibroblasts by infiltrating inflammatory cells, particularly T cells and mast cells, plays an important role in their pathogenesis [55]. Therefore, it could be proposed that the interactions between mast cells and fibroblasts are paramount in the genesis of fibrosis [5]. Indeed, it has been shown that mast cells within airway smooth muscle, a key feature of asthma, commonly express fibroblast markers. This differentiation toward a fibroblastoid phenotype is mediated by airway smooth muscle-derived extracellular matrix protein [56]. In addition, fibroblastoid mast cells have increased chymase expression and activation with histamine release [56].

Moreover, mast cells could be associated with regional or systemic low-degree inflammation that induces fibrogenesis. Nonetheless, this process can be aggravated by an acute noxious stimulus (acute-on-chronic inflammation), which would favor the induction of phenotypic acute inflammatory changes associated with oxidative and/or enzymatic stress, which in turn would cause impaired tissue repair [57].

Mast cells and the chronic inflammatory cancer cell

Nowadays, the causal relationship between inflammation and cancer is widely accepted [2, 58–61]. In particular, chronic inflammation is a major cause of cancer [62–67]. Tumor-infiltrating mast cells can directly influence tumor cell proliferation and invasion, but also help tumors indirectly by organizing their microenvironment and modulating immune responses to tumor cells [14, 68] (Table 1).

Given the plasticity of cancer stem cells it should be kept in mind that while a malignant tumor develops, it can express phenotypes that also share the inflammatory response, such as an ischemia–reoxygenation (hypoxia) phenotype with oxidative stress, interstitial edema and lymphangiogenesis (circulatory switch); the adoption of an immune phenotype with expression of innate and acquired immune responses and migration to the regional lymph nodes; and the induction of an endocrine phenotype with granulation tissue development and tumor and metastatic growth [6, 69]. Essentially, all the elements that constitute the mast cell-mediated inflammatory response could participate in the cancer cell inflammatory response [70]. In turn, epigenetic modifications in response to environmental changes induced by the inflammatory response could contribute to cancer development [71, 72]. As a result, cancer cells can use the chronic inflammatory response mediated by mast cells to invade the

Table 1 Comparative analysis between non-healing wounds and malignant tumors. The mast cells drive the phenomena that make up both conditions through the expression of successive phenotypes

Non-healing wounds	Mast cells	Malignant tumors
Stem-like cells	Ischemia–reoxygenation cell phenotype	Cancer stem cell
Microorganisms		
Hypoxia		Hypoxia
Ischemia–reperfusion		Oxidative and nitrosative stress
Interstitial–lymphatic axis	Immune cell phenotype	Interstitial–lymphatic tumoral axis
Innate and acquired immunotolerance		Tumor-associated macrophages
Lymphangiogenesis		Lymphatic metastasis
Enzymatic stress		Matrix metalloproteinases
Friable granulation tissue	Endocrine cell phenotype	Cancer-associated fibroblasts
Fibrogenesis		Angiogenesis

host [14, 67]. Moreover, while chronic inflammation might promote tumor formation, acute inflammation might well hamper the process and is indeed used therapeutically to inhibit tumor formation [73] (Fig. 2).

The hypoxic cancer cell phenotype

During the initial avascular stages of tumor growth, when the tumor diameter is less than 0.5 cm [74], the cells seem to adopt an anoxic–hypoxic phenotype [75]. Experimental evidence indicates that the mechanism by which the cells adapt to hypoxia relies on the prolyl hydrolase (PHD)–hypoxia-inducible transcription factor (HIF) system. The distribution of the PHD–HIF system within the inflamed tumor is involved in its growth [76]. In this way, cancer cells could adopt a hypoxic metabolism to survive. Most cancer cells rely on aerobic glycolysis, a phenomenon termed "the Warburg effect". Thus, cancer cells can convert glucose and glutamine into biomass most efficiently and will proliferate more rapidly [77, 78]. Moreover, through the induction of a hyperglycolytic state, malignant cells could escape the apoptotic cascade and survive during limited glucose and oxygen availability [79]. Also, glutamine metabolism has important "non-anabolic" functions, including the regulation of oxidative stress, signal transduction and autophagy [80].

Mast cells are stable in hypoxia; however, they may have an important function in tumor growth. Hypoxia per se does not induce mast cell degranulation, but alters gene expression and releases IL-6. In turn, autocrine-produced IL-6 could promote mast cell survival [81]. Therefore, the reactivity of mast cells under conditions of low oxygen pressure would be essential in tumor progression [81]. However,

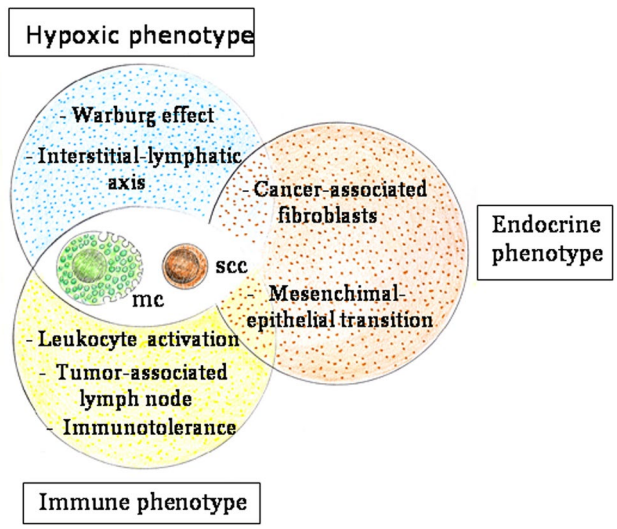

Fig. 2 The interaction between the cancer stem cell and the mast cell induces an inflammatory response formed by three phenotypes: hypoxic, immune and endocrine. mc: mast cell; scc: cancer stem cell

during inflammation-related cancer, recruited mast cells could lead to a "respiratory burst" with reactive oxygen species production [82].

In recent years, considerable evidence has demonstrated that reactive oxygen species are involved in the link between chronic inflammation and cancer [65, 66, 83]. However, recent studies have revealed that in addition to inducing genomic instability, reactive oxygen species can specifically activate certain signaling pathways and thus contribute to tumor development through the regulation of cellular proliferation. Moreover, cancer cells have up-regulated antioxidant mechanisms, i.e., glutathione, superoxide dismutase and catalase, which will protect them against reactive oxygen species [84].

Cancer cells at this stage can over-express matrix metalloproteinases [85]. In many instances, therefore, the extensive alterations produced by matrix metalloproteinases in the stromal microenvironment could induce interstitial edema [86] and promote tumor progression [2, 87, 88]. In addition, mast cell proteases enable these cells to act as important collaborators in the production of interstitial edema [89].

There is increasing evidence that conditions characterized by an inflammatory response are associated with alterations in cellular membrane potential, with subsequent depolarization and abnormal ion transport. Moreover, disturbances in ion transport are associated with intracellular as well as interstitial edema [90]. Interstitial fluid flow is elevated in tumors, thus favoring the diffusion of solutes and proteins, including mast cell effector molecules, and inducing a substantial influence on cancer cells [91, 92]. It has been suggested that tumor interstitial fluid is a rich source for the discovery of biomarkers [93]. It represents the early microenvironment of the tumor cells [86, 91]. One may therefore envisage that access to the tumor interstitial fluid bathing cancer cells is of considerable importance for understanding how tumors develop and progress [86, 91].

It could be suspected that during this early phase of the inflammatory cancer cell response, during the progression of edema, the lymphatic circulation is simultaneously activated and this circulatory switch establishes an interstitial–lymphatic tumoral axis by which lymph can reach the systemic blood circulation [92]. In this way, lymphatic tumoral vessels are transformed into routes for trafficking through the body, exploited not only by immune cells, but also by cancer cells [94]. Lymphatic vessels play a crucial role in a variety of human cancers, and invasion of lymphatic vessels by tumor cells and subsequent development of lymph node metastases significantly influence the prognosis of cancer patients [95]. The formation of new lymphatic vessels, termed lymphangiogenesis, is often observed around or within the tumors [96]. With tumor progression, cancer cells secrete lymphangiogenic cytokines and growth factors, which result in the formation of new lymphatic vessels [10,

97]. Nevertheless, the interstitial tumoral fluid flow associated with edema can have important effects on tumoral tissue morphogenesis and function, cancer cell migration and differentiation and matrix remodeling, among other processes [98].

The immune cancer cell phenotype

Cancer cells could use mast cell functions to modulate the innate and acquired immune responses [14, 70, 99, 100]. Mast cells are components of the innate immune system, together with neutrophils, macrophages and dendritic cells, but they also participate in the development of acquired immune responses [27]. Activation of mast cells causes transcription and translation of several different cytokine/chemokines, such as tumor necrosis factor-alpha (TNF-α), macrophage inflammatory protein-1 (MIP-1) and monocyte chemoattractant protein (MCP), a potent attractant of monocytes under inflammatory conditions [101, 102]. Neutrophils have now emerged as important players in cancer-related inflammation [10, 103]. However, tumor-associated macrophages have served as a paradigm for the pro-tumor activity of inflammatory cells and their mediators. In addition to promoting carcinogenesis, tumor-associated macrophages and their released factors, i.e., cytokines, have long been known to support all steps of invasion and metastasis [62, 103].

Mast cells are also antigen-presenting cells. They promote the migration, maturation and function of dendritic cells, and interact with T and B cells [14]. The infiltration of the tumor by T cells, particularly Th1 and cytotoxic types, could be a prognostic factor in terms of overall survival at all stages of clinical disease [104]. In addition, mast cells could function as intermediaries in Treg-induced tolerance, or could modify or reverse Treg-suppressive properties [14, 105].

In this way, mast cells are fated to exhibit either positive or negative regulation of immune responses [17]. Most tumors contain inflammatory cells including mast cells, which can have either an enhancing or a depressing effect on tumors. Therefore, the role of mast cells may differ depending on the tumor type, but also according to its phase of development [14, 17]. Moreover, mast cells should not be considered to remain static throughout the development of a tumor [12]. Nowadays, it is accepted that different subsets of mast cells infiltrate tumors at different stages of tumor progression [12, 14].

Mast cells are a source of TGF-β [106]. In addition to its systemic effects, TGF-β regulates the infiltration of inflammatory/immune cells into the tumor microenvironment [103, 107]. It is considered that TGF-β mediates growth inhibition in early tumor development and probably contributes to the tumor-promoting effect in later progression. Thus, TGF-β switches from tumor suppressor in the premalignant stages of tumorigenesis to tumor promotion in later stages of the disease, leading to metastasis [103].

Given the enormous plasticity of mast cells, it is not surprising that they can facilitate inflammation or tolerance during tumor development [89, 108, 109]. However, it has been speculated that very early events mediated by mast cells could influence the adaptive immune response to induce tumor tolerance [109]. In particular, tumor-infiltrating mast cells could alter Treg properties and change their phenotype from anti-inflammatory to pro-inflammatory, leading to chronic inflammation and carcinogenesis [14]. It has been suggested that any tumor that continues to grow is probably being continuously and immunologically stimulated by a low level of immunity. Thus, it appears that growth of a tumor is possible because it produces some tolerance in the host [110].

Through the lymphatic system, the tumor cell can also modulate host immunity, using its own antigen production. Tumoral antigens in the interstitial fluid are collected into open-ended lymphatic capillaries, which can form a mesh-like network by lymphangiogenesis, and thereafter could be transported to the lymph nodes [111]. However, tumoral antigens in prenodal lymph, before entering the node and once inside, could be filtered by dendritic cells and nodal antigen-presenting cells, respectively [111]. Thus, lymph-borne tumoral antigens might have particular relevance for the induction and maintenance of peripheral tolerance to cancer cells.

The functional plasticity of mast cells could also enable the adaptive immune system to mount functionally distinct types of responses, as has been described for dendritic cells [112], including the immunological tolerance that could contribute to tumor development [109, 112, 113]. In this way, it is accepted that dendritic cell vaccines will be offered to patients with either early- or late-stage disease to elicit strong and long-lived antigen-specific T cell immunity [114] (Fig. 2).

The endocrine cancer cell phenotype

Angiogenesis characterizes a phenotype of cancer that permits numerous substances, including oxygen and hormones, to be transported by the blood [115]. Angiogenesis requires the migration of endothelial cells into the interstitial space with subsequent proliferation and differentiation into capillaries [6, 7]. However, tumor-angiogenesis produces a tumor-associated vasculature that is chaotic in structure and function [116], and the tumoral tissue is hypoxic [117].

Mast cells have been described in the tumoral stroma and could play an important role in the angiogenesis switch during tumor growth [118, 119]. They release a range of proangiogenic molecules, including VEGF, angiopoietin-1, heparin, TNF and FGF [99, 120]. Association between mast

cells and new vessel formation has been reported in many tumors, including breast cancer, colorectal cancer, pancreatic carcinoma, colorectal cancer and uterine cervix cancer [89, 120–123]. Moreover, it has been shown that the number of tumor-infiltrating mast cells correlates with increased intratumoral microvessel density, enhanced tumor growth and tumor invasion, and poor clinical outcome [120, 121].

Mast cell subtypes have also been demonstrated in developing colorectal polyps. In particular, the connective tissue mast cell subtype is more prevalent in the stroma during later stages of invasive tumor development [120]. In recent years, the tumor stroma has become the focus of intense research and should be considered as a therapeutic target in malignant transformation and tumor growth and metastasis [1, 124]. In particular, fibroblasts, a heterogeneous collection of mesenchymal cells, are among the most abundant cell types in the microenvironment of solid tumors [61]. Cancer-associated fibroblasts, through the release of cytokines and growth factors, could modulate the cancer stem cell phenotype and also could lead to enhanced angiogenesis [61, 125, 126]. It has been suggested that cancer-associated fibroblasts may be derived from tumor cells that undergo an epithelial–mesenchymal transition (EMT) [127]. One characteristic of cancer-associated fibroblasts is their heterogeneity, which is also expressed through the formation in solid tumors with very different profiles of extracellular matrix proteins [61].

In neurofibromas, mast cells and fibroblasts interact directly to contribute to the tumor phenotype. In response to TGF-β, fibroblasts from human neurofibromas proliferate and synthesize excessive collagen, a hallmark of neurofibromas [128]. In addition, TGF-β signaling in stromal cells, i.e., fibroblasts, exerts significant effects on tumor development and growth. It has been shown that TGF-β, an important tumor suppressor, also regulates infiltration of immune cells as well as fibroblasts in the tumor microenvironment and promotes tumor progression [103]. Fibroblasts could also produce c-Kit ligand, the most important mast cell growth factor, while mast cells have an important effect on fibroblasts [129].

There is evidence that cancer-associated fibroblasts have a cancer-promoting phenotype [130]. If so, cancer-associated fibroblasts could produce significant extracellular matrix remodeling during tumor progression mediated by tumor-specific extracellular matrix proteins and matrix metalloproteinase isoforms [61].

Finally, it could be considered that both processes, angiogenesis and fibrogenesis, characterizing the expression of the endocrine tumoral phenotype, turn the cancer cells into cancerous tissues/organs. Therefore, the comparison of tumors with wounds that do not heal [131] includes, among other characteristics, the development of a stroma formed by a kind of granulation tissue similar to the stroma of a chronic wound [1] (Fig. 2).

Mast cells may induce extraembryonic functions to support cancer development

Mast cells might be derived from a common mast cell/basophil ancestor. Early mast cells probably appeared in the last common ancestor we shared with hagfish, lamprey and sharks about 450–500 million years ago [132]. Mast cell activation mechanisms appear highly conserved during invertebrate and vertebrate evolution. Indeed, modern mast cells are involved in the cross-talk between inflammatory and tissue repair reactions [132].

In particular, they could orchestrate the inflammatory response inducing the expression of embryonic programs of tissue formation. In this way, we have recently proposed that the inflammatory response could represent in the adult body the expression of extraembryonic functions, namely, amniotic-related functions [5]. The up-regulation of signaling pathways during gastrulation, in which the extraembryonic functions, i.e., amniotic and vitelline, would be internalized, could help explain the meaning of the diverse and complex mechanisms expressed by the mature organism in response to injury [5, 19, 20]. Gastrulation is a developmental phase that delineates the three embryogenic germ layers, ectoderm, endoderm and mesoderm [133]. The nascent mesoderm generated during gastrulation could involve internalization of extraembryonic, i.e., amniotic and vitelline, functions [127] (Fig. 3).

The amnion is an embryonic functional axis with strong neural potential [134, 135]. In addition, experimental and clinical studies have demonstrated that amniotic membrane transplantation has important biological effects, including anti-inflammatory, anti-microbial, anti-fibrosis and anti-scarring, as well as low immunogenicity [136, 137]. Amnion-derived multipotent progenitor cells secrete a unique combination of cytokines and growth factors, known as the "amnion-derived cellular cytokine solution", which establishes a communication network between mesenchymal and epithelial cells during embryo development [138]. If so, the amniotic fluid is an essential component for fetal development. Nevertheless, the amniotic fluid that surrounds the fetus may be considered an extension of the extracellular space of the fetal tissues [139] (Fig. 3).

The yolk sac in mammals is composed of two layers: the visceral endoderm, which is active in endocytosis/digestion and has larger lysosomes, and the underlying mesoderm layer, in which "blood islands" develop supporting hematopoiesis and angiogenesis [140]. Also, a major function of the yolk sac is the accumulation of carbohydrates, proteins and lipids for embryo nutrition (*vitellum*) [141]. It is accepted that the yolk sac plays a vital role in providing lipids and lipid-soluble nutrients to embryos during the early phases of development [141] (Fig. 3).

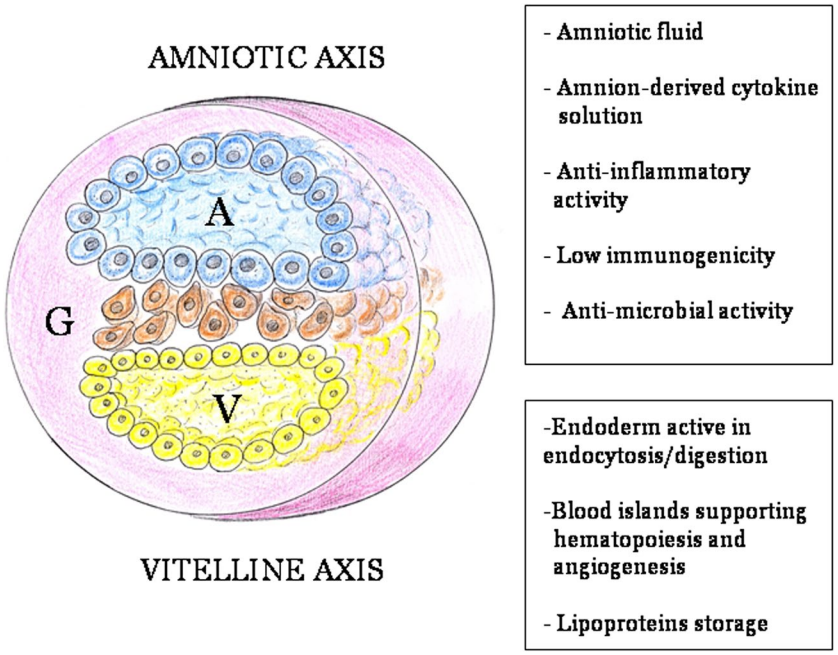

Fig. 3 Gastrulation is produced during the early phases of embryonic development. In this process, the interaction between the amniotic (A) and vitelline (V) functional axes could induce gastrulation (G), with the creation of the three primitive embryonic layers: ectoderm, mesoderm and endoderm. In particular, the mesoderm could involve an internalization of extraembryonic, i.e., amniotic and vitelline, functions

Recent studies suggest that extraembryonically derived functions and cells make an increasingly significant and possibly exclusive contribution to embryonic development [140, 142]. Thus, the molecular and cellular contribution made by both extraembryonic structures, i.e., the amnion and the yolk sac, to the interstitial space located between them, namely the mesoderm, are essential for organogenesis. The re-expression of extraembryonic functions by mesenchymal cells could not only be a key process in embryonic development, but also be used by the postnatal organism when it suffers an injury and therefore needs to be repaired [5]. Thus, an acute or chronic injury could induce a mast cell-mediated dedifferentiation process with the expression of different and overlapping inflammatory phenotypes, i.e., hypoxic, immune and endocrine, that resemble the similar phenotypes expressed during embryo development. In particular, molecular and cellular amniotic and vitelline mechanisms involved in gastrulation would return [5].

Moreover, the relationship between inflammation and cancer could also be based on the mast cell orchestration of re-expressed extraembryonic functions. If so, cancer cells could successively induce mast cell expression of overlapping amniotic and vitelline-like phenotypes that promote the invasion, control and remodeling of the interstitium. The amniotic-like phenotype could offer cancer cells a hydrated interstitial axis, with cytokines and growth factors, favoring nutrition by diffusion, transport, excretion and bacteriostatic and anti-inflammatory protection [138]. In turn, the vitelline phenotype could favor the regulation of lipid metabolism genes [143], hematopoietic/bone marrow control [144, 145] and the induction of an "angiogenic switch [83, 118] to permit tumor tolerance, growth and metastasis [146]. The integration of both extraembryonic phenotypes by the cancer cell would support the functional and metabolic heterogeneity needed to modulate their microenvironment successively during their development in the host [147] (Fig. 4).

In particular, mast cells could influence tumoral development through increased angiogenesis by releasing many cytokines, chemokines and growth factors [148]. Among the angiogenic growth factors produced by mast cells stand out vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (FGF-2) [149]. In this way, tumoral angiogenesis induced by mast cell favors the development of a new tumoral metabolism that is associated with tumor growth and metastasis. This is the reason why new therapeutic strategies related with mast cell or their mediators have been proposed, including, mast cell stabilizerss as well as inhibitors of proteinase activated receptor (PAR), tyrosine kinase inhibitors and anti c-kit antibodies [149].

Recent studies have shown that it is possible to reprogram melanoma tumorigenic phenotypes by exposing melanoma cells to factors present in the embryonic microenvironment [150]. This suggests that melanoma cells may share some characteristics with stem cells that allow them to respond to cues from the embryonic microenvironment [151]. It became clear that neoplastic cells possess a more embryonic phenotype than their tissue of origin and that this involves the re-expression of embryonic genes [114, 152]. Both embryos and tumors display similar antigens, elaborate angiogenic growth factors and subvert apoptotic cell death. Furthermore, they may both escape immune destruction by similar

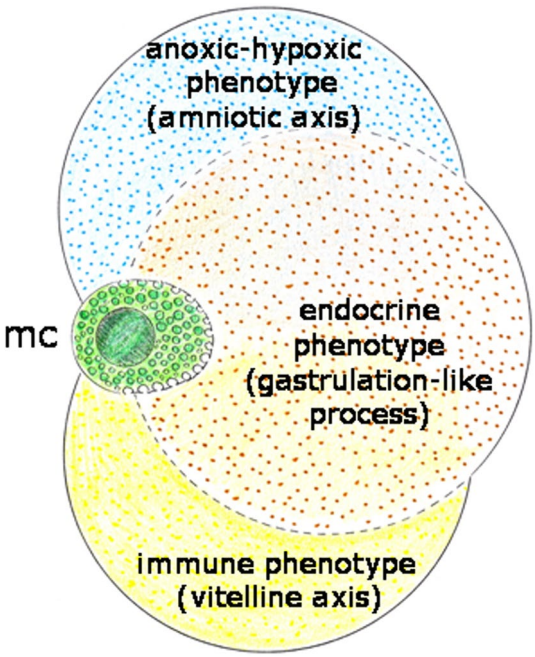

Fig. 4 The three inflammatory phenotypes, which are successively expressed by mast cell during cancer development, are maximally overlapped. The joint expression of these phenotypes in the tumoral tissue is favored by the chronicity of the inflammatory response, which characterizes carcinogenesis. mc: mast cell

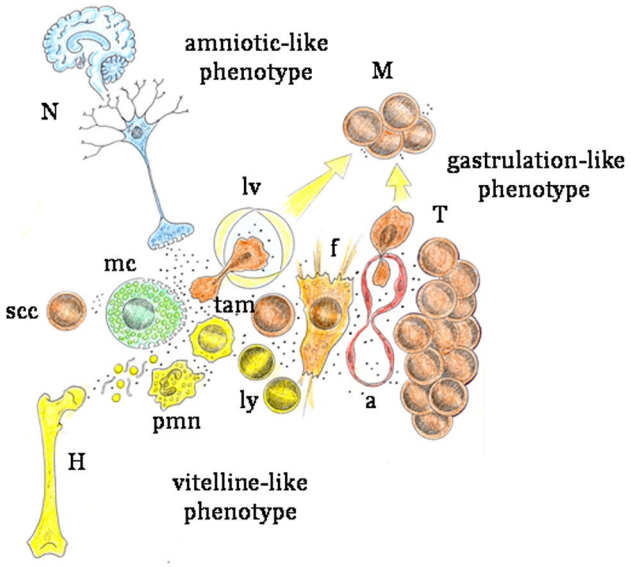

Fig. 5 Carcinogenesis would involve the re-expression of extraembryonic functions by the functional unit made up of the tumor cell and the mast cell. The interstitial overlapping of the extraembryonary functional axes, i.e., amniotic-like phenotype and vitelline-like phenotype, would allow the functional cancer-mast cell unit to induce the expression of a gastrulation-like phenotype with invasion of the tumoral interstitium by fibroblasts. After that, tumoral proliferation with metastasis would be produced by the mesenchymal-epithelial transition. *a* angiogenesis and distant metastasis, *csc* cancer stem cell, *f* cancer-associated fibroblast, *H* hematopoiesis, *lv* lymphangiogenesis and lymphatic metastasis, *ly* lymphocyte, *M* metastasis, *mc* mast cell, *N* neurogenic mediators, *pmn* polymorphonuclear neutrophil, *T* tumor, *tam* tumor-associated macrophage

mechanisms [67, 114]. The convergence of embryonic and tumorigenic mechanisms has indeed allowed the use of embryonic vaccines against cancer to be suggested in the past [114].

EMT are transdifferentiation programs that are also required for tissue morphogenesis during both embryonic and cancer development [1, 153, 154]. The conversion of epithelial cells to mesenchymal cells is fundamental to embryonic development and involves profound phenotypic changes, including the loss of cell–cell adhesion and the acquisition of migratory and invasive properties [153]. Recent evidence suggests that normal stem cells and cancer stem cells share a mesenchymal phenotype that enhances their ability to preserve stemness, to retain migratory properties and to respond to different stimuli during expansion and differentiation [153]. Thus, EMT induction in cancer cells results in the acquisition of invasive and metastatic properties [154]. Interestingly, these invasive cells with both a stem cell-like and a mesenchymal phenotype can generate an epithelial-like structure by mesenchymal to epithelial transition (MET), so they could be involved in the formation of macrometastasis [153] (Fig. 5).

An EMT process also occurs in mammalian embryos during gastrulation [127]. The nascent mesoderm generated during gastrulation could involve an internalization process of extraembryonic phenotypes [5]. In essence, gastrulation could be represented as the creation of an interstitial tissue thanks to the fundamental contribution made by the extraembryonary structures, i.e., amniotic and yolk sac. Moreover, cancer-associated fibroblasts need the extraembryonic-like functions developed by mast cells, which allows their presence to be tolerated by the host. Thus, mast cell functions could regulate cancer development and tissue repair in adult mammals, as organogenesis during embryonic development is regulated by extraembryonic functions. Moreover, similar mechanisms could regulate the interactions between fibroblasts and epithelial cells during organogenesis, cancer development and wound repair [154, 155]. It could be concluded from this reasoning that mast cells are needed to reproduce the extraembryonary functions in the entire process of new tissue formation, whether normal (embryo development, wound repair) or pathological (autoimmune disease, chronic inflammation, cancer development). Therefore, mast cells could represent the true reservoirs of inductive mediators of extraembryonic mechanisms for forming new tissues.

Mast cell mediators could induce the expression of amniotic-like interstitial functions. In particular, by creating a

hydrated interstitial axis with anti-inflammatory, bacteriostatic and trophic properties, the cancer stem cell would find a favorable survival medium. This hydrated interstitial medium would allow productive cross-talk to be established between mast cells and sensory nerves [36] with cancer cells, with the contribution of neurotransmitters, neuropeptides, cytokines and other mediators of the neuroendocrine response to stress [33]. In turn, the diffusion of these substances among the cancer cells would be ensured through low control concentration gradients in the interstitial–lymphatic axis (circulatory switch). In essence, they would create the morphogenetic basis that governs subsequent evolution of the tumoral interstitium (Fig. 5).

In this initial inflammatory interstitium, mast cells would produce mediators capable of inducing the expression of a vitellogenic phenotype. If so, the hematopoietic/bone marrow control of the host would begin with modulation of the innate and acquired immunity associated with an early angiogenic process (angiogenic switch) [89, 156]. Mast cells could elaborate numerous lipid mediators including prostanoids and leukotrienes. But they are also involved in insulin resistance and lipid metabolism, favoring accumulation of low-density lipoprotein-driven cholesterol [115]. In this way, the dysregulation of lipid metabolism could reduce mast cell survival [157].

Lastly, the interstitial overlap of the extraembryonic functional axes abovementioned, i.e., amniotic and vitelline, would enable mast cells to induce the expression of a gastrulation-like phenotype with invasion of the tumoral interstitium by fibroblasts [125] and development of a chaotic vasculature (granulation tissue). Tumor cells would obtain from the host the resources needed for their own growth and metastatic invasion through this tumoral stroma. In essence, thanks to this last interstitial remodeling, the tumor turns into an embryonic-like organism, which has multiple potential behaviors, including its great ability to develop at the expense of the host. However, the tumor never achieves by means of specialization the metabolic autonomy that would individualize it.

Conclusion

In summary, the etiopathogenesis of cancer could be favored by the association between cancer stem cells and mast cells. Both types of cells could develop complementary functions throughout tumoral evolution. Thus, in the early or first phase, mast cells would create a tissular interstitium with the appropriate conditions for cancer stem cell implantation and survival. In the second phase, mast cells would induce a privileged immunological environment with proliferation and the invasive ability of the cancer cells. Lastly, in a third phase, mast cells would favor the development of a tumoral tissue with its related vascular stroma. In essence, through angiogenesis and fibrogenesis induced by mast cells, the new tumoral tissue would have more metabolic support from the host blood. The metabolic involvement of these three phases would be successively more complex, while in the early phase the energetic requirements would be scarce compared to those obtained from anaerobic metabolism. On the contrary, in the following phases of the tumoral development, the increased metabolic requirements would be supported by an efficient use of the Krebs cycle. These evolutive characteristics of the malignant tumoral conditions resemble those found in embryonic development. In this way, the coupling between the amniotic and vitelline functions is the basis of the gastrulation process in embryonic development. This is the reason why we suggest that in the first inflammatory tumoral phase, amniotic-like functions would appear. In turn, in the second inflammatory tumoral phase, a nourishing vitelline-like phenotype would be expressed. Finally, during the third inflammatory tumoral phase, the association between the amniotic-like and the vitelline-like functions would induce a phenomenon similar to gastrulation with mesenchymal phenotype development. Therefore, it could be considered that mast cells are able to express extraembryonic functional phenotypes, enabling the body to recreate tissues, whether normal or pathological, by using the embryonic mechanisms described herein.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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