Are Mast Cells MASTers in Cancer?

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Prolonged low-grade inflammation or smoldering inflammation is a hallmark of cancer. Mast cells form a heterogeneous population of immune cells with differences in their ultra-structure, morphology, mediator content, and surface receptors. Mast cells are widely distributed throughout all tissues and are stromal components of the inflammatory microenvironment that modulates tumor initiation and development. Although canonically associated with allergic disorders, mast cells are a major source of pro-tumorigenic (e.g., angiogenic and lymphangiogenic factors) and antitumorigenic molecules (e.g., TNF-α and IL-9), depending on the milieu. In certain neoplasias (e.g., gastric, thyroid and Hodgkin’s lymphoma) mast cells play a pro-tumorigenic role, in others (e.g., breast cancer) a protective role, whereas in yet others they are apparently innocent bystanders. These seemingly conflicting results suggest that the role of mast cells and their mediators could be cancer specific. The microlocalization (e.g., peritumoral vs intratumoral) of mast cells is another important aspect in the initiation/progression of solid and hematologic tumors. Increasing evidence in certain experimental models indicates that targeting mast cells and/or their mediators represent a potential therapeutic target in cancer. Thus, mast cells deserve focused consideration also as therapeutic targets in different types of tumors. There are many unanswered questions that should be addressed before we understand whether mast cells are an ally, adversary, or innocent bystanders in human cancers.

Keywords: angiogenesis, cancer, inflammation, lymphangiogenesis, mast cells

INTRODUCTION

Mast cells were first identified in human tumors and named by Paul Ehrlich (1, 2). These cells are present in all classes of vertebrates, and it has been estimated that they have emerged >500 million years ago, long before the development of adaptive immunity (3). Mast cells are distributed throughout nearly all human tissues and often in close proximity to epithelia, fibroblasts, blood and lymphatic vessels, and nerves (4).

Human mast cells form a heterogeneous population of cells with differences in their ultrastructure, morphology, mediator content, and surface receptors (4, 5). Human mast cells derive from CD34+, CD117+ pluripotent hematopoietic stem cells, which arise in the bone marrow (6). Mast cell progenitors enter the circulation and subsequently complete their maturation in tissues. These cells store and release upon activation a wide spectrum of biologically active mediators that individually have been shown to have potential positive or negative effects on various target cells (7). Increasing evidence indicates that mast cells act as sentinels of the surrounding environment, with the
capacity to rapidly perceive tissue insults and initiate biochemical programs of inflammation or repair.

Mast cells are activated not only by IgE (8), specific antigens (5), and superallergens (9, 10), the main mechanisms which account for their function in allergic disorders, but also by a plethora of immunologic and non-immunologic stimuli (11–14). Figure 1 schematically illustrates the constellation of surface receptors expressed by human mast cells.

Mast cells and their mediators have been canonically associated with a detrimental role in allergic diseases (16, 17), viral (18) and microbial pathogens (19). Interestingly, epidemiological (20, 21) and experimental studies (22) indicate an inverse association between IgE-mediated allergies and cancer, implying tumor-protective effect of IgE.

The initiation and progression of cancer are multistep processes characterized by the accumulation of a variable number of genetic and epigenetic alterations (23). The immunosurveillance system recognizes and eliminates mutant cells constantly and superallergens (4–6), but these cells can induce a protective immune response of the host against noxious substances (11–14). The presence of mast cells in human tumors, initially reported by Ehrlich (1, 2), was extended by Eugen Westphal (31). Tumor-associated mast cells (TAMCs) are present in the microenvironment of experimental and human tumors (27, 28).

Normal microenvironment [immune cells, fibroblasts, blood and lymphatic vessels, and interstitial extracellular matrix (ECM)] plays a central role in maintaining tissue homeostasis and is a barrier to tumorigenesis (26). Incorrect signals (chemokines, cytokines, reactive oxygen species, lipid mediators, etc.) from an aberrant microenvironment alter tissue homeostasis and initiate/promote tumor growth. Thus, the multiple interactions between stromal and tumor cells are crucial for the initial phases of tumor development.

Prolonged low-grade inflammation or smoldering inflammation is a hallmark of cancer (27, 28). Several cells of the innate and adaptive immune system (macrophages, mast cells, lymphocytes, neutrophils, NK, and NK T cells) are stromal components of the inflammatory microenvironment that can promote the development of experimental and human tumors (29, 30).

**WHY ARE MAST CELLS INCREASING IN TUMORS?**

The presence of mast cells in human tumors, initially reported by Ehrlich (1, 2), was extended by Eugen Westphal (31). Tumor-associated mast cells (TAMCs) are present in the microenvironment of several human solid (32–46) and hematologic tumors (47–55).

Peritumoral and/or intratumoral mast cell density is increased in different types of human cancer (56). Tumor cells produce several chemotactic factors acting on receptors expressed by mast cells. Stem cell factor (SCF) (13, 57), also produced by...
mast cells (58), activates the mast cell Kit receptor (CD117), vascular endothelial growth factors (VEGFs) act on VEGFR-1 and VEGFR-2 (38, 59), angiopoietin 1 (AngI) acts on Tie2 receptor (60), and CXCL8/IL-8 acts on CXCR1 and CXCR2 (61). Mast cells express CCR2, CXCR2, and CXCR3, which can be important for TAMC localization because their respective ligands, CCL2, CXCL1, and CXCL10, are produced by human tumors (35, 38). PGE$_2$ and histamine are chemotactic for mature mast cells through the engagement of EP1 receptor (62, 63) and H1R, respectively (64). LTB$_4$ may be involved in recruitment of mast cell progenitors from the circulation via the activation of BLT1 and BLT2 (65). Finally osteopontin (OP), which is upregulated in human cancer (35), induces mast cell migration (66) and degranulation (35).

**THE CONTRIBUTION OF MAST CELLS TO CANCER IS TUMOR DEPENDENT**

The increasing heterogeneity of different subsets of immune cells (e.g., macrophages, T helper cells, mast cells, neutrophils, NK, NK T cells, etc.), their plasticity, and their reciprocal interactions have complicated the comprehension of the role of the inflammatory microenvironment in tumor initiation and development (29).

A large number of studies have tried to identify the contributory functions of TAMCs in tumor growth. In the majority of studies, TAMCs appear functional—either actively promoting or suppressing tumor development and growth—whereas in a few cases they may be simple inert bystanders. In several studies, mast cells appear to play a pro-tumorigenic role in human (Table 1) and experimental tumors (Table 2). Evidence for an antitumorigenic role for mast cells is provided in Table 3. Studies supporting a non-contributing role of mast cells in tumors are outlined in Table 4.

In several solid tumors, such as thyroid (38, 61), gastric (75–77, 122), pancreas (37, 84, 85, 94, 95, 123), bladder cancers (67), and Merkel cell carcinoma (33), mast cells always appear to be pro-tumorigenic. Similarly, in several hematologic tumors, such as different types of Hodgkin’s (53–55) and non-Hodgkin’s lymphoma (48, 50, 52), and plasmacytoma (47, 96), mast cells are associated with poor prognosis. There are certain tumors such as breast cancer (106, 107, 109) in which mast cells always appear to play an antitumorigenic role. The role of mast cells in the pathogenesis of human melanomas is still unclear and appears to depend on both the microlocalization of these cells (43) and the subtypes of tumor (83).

These apparently conflicting results are intriguing and suggest that the role of mast cells and their mediators in tumors could be cancer specific. Figure 2 schematically illustrates the role of mast cells in different human tumors.

**ROLE OF TAMCs IN TUMOR ANGIogenesis AND LYMPHANGIOGENESIS**

Angiogenesis, the formation of new blood vessels, is an essential process for supplying growing malignant tissues with essential nutrients and oxygen (124). Lymphangiogenesis, the formation of new lymphatic vessels, is important in the development of metastases (124). Judah Folkman, the father of angiogenesis, suggested that mast cells and macrophages could be attracted by chemotactic molecules produced by tumor cells and could be an important source of proangiogenic factors (125). Several groups have demonstrated that mast cells produce several proangiogenic (VEGF-A, VEGF-B, and FGF-2) (126–130) and lymphangiogenic factors (VEGF-C and -D) (38, 59, 131). In addition, we have found that VEGFs are chemotactic for mast cells (59), indicating that mast cells are a target, in addition to be a source, for VEGFs (132). Several studies have highlighted the association and/or the correlation in human tumors between increased mast cell density and angiogenesis by evaluating the expression of the proangiogenic isoform VEGF-A (42, 45, 70, 80, 96, 123).

The VEGF-A gene can be alternatively spliced to form the proangiogenic VEGF-A$_{165}$ and the antiangiogenic VEGF-A$_{165b}$ (133). The vast majority of the studies performed so far evaluated only the proangiogenic isoforms, whereas in certain tumors the antiangiogenic VEGF-A$_{165b}$ isoform is dominant (134). This finding suggests that the majority of results on VEGF-A plasma

| Type of cancer | Mast cell staining | Reference |
|----------------|--------------------|-----------|
| Angioimmunoblastic T-cell lymphoma | Tryptase | (60) |
| Bladder | Tryptase | (67) |
| Colorectal | Toluidine blue/tryptase | (68) |
| Cutaneous lymphoma | Tryptase | (48) |
| Esophageus | Toluidine blue | (74) |
| Follicular lymphoma | Tryptase | (61) |
| Gastric | Toluidine blue | (75) |
| Hepatocellular | Tryptase | (79) |
| Hodgkin’s lymphoma | Tryptase | (53–55) |
| Lung | Tryptase | (80, 81) |
| Malignant pleural effusion | May-Gruenwald–Giemsa toluidine blue | (35) |
| Melanoma | Gene expression/toluidine blue | (83) |
| Merkel cell carcinoma | Tryptase | (33) |
| Pancreas | Tryptase | (37, 84–86) |
| Plasmacytoma | Toluidine blue/tryptase | (47) |
| Prostate | Tryptase | (36, 40, 87, 89) |
| Splenic marginal zone lymphoma | Tryptase | (52) |
| Thyroid | Tryptase | (38, 61) |
levels in cancer need to be reinterpreted or require repeating with tools that can differentiate between the two isoforms of VEGF-A (135). For instance, we have recently demonstrated that human neutrophils, under certain circumstances, can produce both pro- and antiangiogenic isoforms of VEGF-A (136). The role of different pro- and antiangiogenic isoforms of VEGFs produced by TAMCs in primary cancers and in the formation of metastases needs further investigation.

Human mast cells produce different matrix metalloproteinases (e.g., MMP-9) (137) and proteases (tryptase and chymase), which regulate the digestion of ECM favoring the implantation of cancer cells in an aberrant microenvironment (13, 98).

Vascular endothelial growth factor-C, released by melanoma cells (138), TAMs (139), and TAMCs (59), likely represents a major lymphangiogenic factor in this tumor. Mast cells can be found in metastatic lymph nodes of cancer patients (140), and the role of lymphangiogenic factors in the formation of metastasis should be further addressed.

Epithelial-to-mesenchymal transition (EMT) is a mechanism by which tumor cells gain metastatic features and contribute to chemotherapy drug resistance (141, 142). In addition, in the context of tumors, EMT can generate cells with stem-like properties (e.g., stemness) (143). We have demonstrated that mast cells can induce EMT and stem cell features in human cancer through the production of CXCL8/IL-8 (61).

### THE ROLE OF MAST CELLS VARIES ACCORDING TO THE STAGE OF TUMORS

A recent study found that low mast cell count in perilesional stroma of deeply invasive melanomas predicted poor survival (43). By contrast, mast cell density was not correlated with prognosis in superficially invasive melanomas. The latter findings suggest that the role of mast cells in melanoma is dependent also on the stage of the tumor. The role(s) of these cells in human and experimental melanoma requires additional studies.
Pittoni et al. found that in prostate cancer mast cells exert different functions according to tumor stage. Mast cells were pro-tumorigenic in the initial stages of prostate cancer by supplying MMP-9 in the microenvironment, but became dispensable at later stages (40, 144).

In stage I non-small-cell lung cancer (NSCLC), but not in stage II, peritumoral but not intratumoral mast cell (tryptase+ chymase+) density was an independent favorable prognostic factor (111). Vascular endothelial growth factor-B, an angiogenic factor produced by human macrophages and mast cells (59, 139), could play a role in early colon cancer development at the stage of adenoma formation (145).

**THE ROLE OF MAST CELLS IN TUMORS VARIES ACCORDING TO THEIR MICROLOCALIZATION**

The vast majority of initial studies evaluating mast cell density in different cancers did not examine differences between the periphery and the center of tumors. There is increasing evidence that different stages of tumors can be associated with qualitative and quantitative changes in different types of immune cells in the periphery and center of tumors (146, 147). The pro- or antitumorigenic role of mast cells in different types of melanomas remains controversial (83, 148). Siiskonen and collaborators found that tryptase+ chymase+ mast cells in perilesional stroma of melanoma play a protective role (43). In NSCLC, mast cell infiltration of tumor islets confers a survival advantage independently of tumor stage (113, 114). In another study, it was found that only in stage I NSCLC increased peritumoral mast cells were associated with a better prognosis (111). In prostate cancer, high intratumoral mast cell density was initially associated with good prognosis (116). Subsequently, it was reported that intratumoral mast cells inhibited tumor growth, whereas peritumoral mast cells stimulated human prostate cancer (36).

Mast cells are increased in patients with both cutaneous T-cell lymphoma and cutaneous B-cell lymphoma compared with normal skin, particularly at the periphery of the tumors. Interestingly, the density of mast cells in the center of tumors was similar to normal skin. The density of peripheral mast cells correlated with disease progression (48).

Collectively, these findings suggest that the microlocalization of mast cells is an important aspect in the initiation and progression of several tumors.
Figure 3 schematically illustrates the mechanisms by which mast cells and some of their mediators may play a pro-tumorigenic or an antitumorigenic role.

**WHICH ARE THE ACTIVATORS OF TAMCs IN TUMOR MICROENVIRONMENTS?**

Peritumoral and intratumoral mast cells operate in an inflammatory microenvironment characterized by hypoxia, the accumulation of lactic acid, adenosine, PGE\(_2\), IFN-\(\gamma\), and by low pH (149–151). This milieu is likely to influence mast cell recruitment and activation. Mast cells can be recruited by SCF produced by several tumors and by mast cells themselves (13, 58). Mast cells can be recruited by VEGFs and Ang1 produced by tumor and immune cells through the engagement of VEGFR-1/VEGFR-2 and Tie2, respectively, expressed by human mast cells (38, 59, 60).

Hypoxia, a feature of tumor microenvironment (150), activates human mast cells to release IL-6 (152) and VEGF-A (153). Adenosine, produced by tumor cells and mast cells (154), is markedly increased (150) and is an immunosuppressive factor in tumor microenvironment (13). Adenosine potentiates histamine release (155) and the production of angiogenic factors from human mast cells and macrophages (61, 139, 156). Cyclooxygenase 2, overexpressed in tumors (150), generates PGE\(_2\) which induces angiogenic and lymphangiogenic factors from human mast cells (59). Several chemokines (CXCL1, CXCL10, and CXCL12) can activate mast cells and enhance mast cell secretion of CXCL8/IL-8 (38, 157). Thus, these chemokines can promote angiogenesis/lymphangiogenesis via the recruitment of mast cells to the edge of solid tumors.

The impact of IgE-mediated activation of mast cells on tumor development and progression has been investigated (158). Monomeric IgE, in the absence of antigen, induced VEGF-A production from mast cells and increased melanoma growth (8). Increased expression of immunoglobulin free light chains (FLC) was found within stroma of various human cancers. In a murine B16F10 melanoma model, inhibition of FLC-mediated mast cell activation reduced tumor growth (12). Alarmins are upregulated in cancers (159) and can activate mast cells (160). IL-33 is upregulated in squamous cell carcinoma (SCC) (161), and mast cell activation by IL-33 occurs in skin cancers (161). IL-33 induces the production of GM-CSF, CXCL8/IL-8, and VEGF-A from mast cells (128, 162, 163). In addition to the high-affinity receptor for IgE (Fc\(\varepsilon\)RI), human mast cells express the IgG receptors Fc\(\gamma\)RIIA and Fc\(\gamma\)RI (164, 165). Fc\(\gamma\)RI is upregulated by IFN-\(\gamma\) which is

![Figure 3](image-url)
highly expressed in tumors. In the tumor microenvironment, antitumor IgG immune complexes may activate mast cells (166). OP, upregulated in human cancer (167), is produced by mast cells (66) and induces their migration and degranulation (35, 66). Platelet-activating factor, produced by human mast cells (168), upregulates CXCR4 on mast cells and promotes their migration to lymph nodes (169, 170). In summary, a plethora of immunologic and non-immunologic factors present in tumor microenvironment can activate TAMCs.

**MAST CELLS AS A POTENTIAL THERAPEUTIC TARGET IN CANCER**

Several therapeutic strategies have been envisioned to limit tumor growth by targeting mast cells and their mediators. Mast cells play a pro-tumorigenic role in human bladder cancer through stimulating estrogen receptor β (ERβ) (67). In a murine model of bladder cancer, these authors showed that a selective ERβ antagonist inhibited mast cell-promoted tumor growth. It has been found that mast cells can promote the proliferation of colon cancer in vivo (71). Injection of Fcε-PE40 chimeric toxin, which induced mast cell apoptosis, inhibited colon tumor development in vivo.

Pharmacologic inhibition of mast cell degranulation by cromolyn inhibited Myc-induced pancreatic islet tumors (94), experimental pancreatic and thyroid cancer (37, 38, 95), and cholangiocarcinoma (46).

Pittoni and collaborators have demonstrated that pharmacologic inhibition by cromolyn and genetic ablation of mast cells inhibited prostate cancer in mice (40). However, mast cells protect from a malignant neuroendocrine tumor. It has been shown that mast cells can promote prostate cancer chemotherapy and radiotherapy resistance via modulation of p38/p53/p21. The authors suggested that targeting these signaling pathways may help to suppress chemo- and radiotherapy resistance in prostate cancer (97). In a mouse model, mast cells enhanced prostate cancer growth via modulation of androgen receptor and increasing MMP-9 expression (87). The authors suggested that targeting these mast cell-androgen receptor signals may inhibit tumor growth.

The UV wavelengths in sunlight are the prime etiological cause of skin cancers, including basal cell carcinoma and SCC. Exposure to UV affects skin mast cell migration by altering the CXCR4–CXCL12 axis (99). The pharmacological blockage of the CXCR4–CXCL12 pathway inhibited sunlight-induced skin cancer.

Collectively, these findings indicate that mast cells and their mediators deserve focused consideration as therapeutic targets in different types of cancer.

**OUTSTANDING QUESTIONS**

There is compelling evidence that human mast cells isolated from various anatomical sites respond to different stimuli and release distinct mediators (14, 59, 160, 166, 171). Peritumoral and intratumoral TAMCs are embedded by a wide spectrum of mediators and in close contact with several stromal cells. It will be important to identify the stimuli that can activate TAMCs in different tumor microenvironments. Similarly, it will be important to identify preformed and de novo synthesized mediators released in situ by TAMCs.

Studies on mast cell biology are routinely conducted at physiological pH and normoxia. By contrast, the metabolic phenotype of tumors is characterized by low pH and areas of either hypoxia or normoxia (150). Tumor-associated macrophages in normoxic tumor tissues express M1 markers, whereas those in hypoxic tumor tissues preferentially express M2 markers (172). These findings caution against the over interpretation of results from studies of whole TAMC populations. It will be of fundamental importance to investigate how hypoxic conditions and metabolism activate/modulate the production of pro-inflammatory and angiogenic/lymphangiogenic factors from TAMCs. Proteomic (173) and lipidomic analyses (174) of mast cells will help to characterize the proangiogenic and antitumorigenic profiles of TAMCs from different human tumors.

Analysis of mast cells in draining lymph nodes and in ectopic lymphoid structures of tumors has only recently begun (35, 43). The role of mast cells in draining lymph nodes, in tertiary lymphoid tissues, and at metastatic sites of different tumors remains to be explored.

IgE has been suggested to play a protective role in tumor growth (21, 158). Additional studies should investigate the role, if any, of IgE-mediated activation of mast cells in different human tumors.

The pro- or antitumorigenic role(s) of mast cells in different human tumors appears to be generally, but not always, cancer specific. We cannot exclude the possibility that subpopulation of TAMCs could play different, even opposite effects in various types/subtypes of tumors.

There is preliminary evidence that peritumoral mast cells (48) play different roles compared to intratumoral mast cells (36, 113, 114). Studies in other experimental and human tumors will clarify whether the microlocalization of mast cells can markedly influence their effects.

Within the last years, gene expression profiling has demonstrated that several individual human cancers (e.g., melanoma, gastric, lung, and breast cancers) are heterogeneous with a spectrum of molecular changes (83, 175–178). The complex heterogeneity (spatial, temporal, intratumor, intertumor) of the tumor microenvironment adds an additional layer of complexity (179, 180). An important task will be to correlate the role of TAMCs in different subtypes of human cancers as defined by genetic markers.

There is recent evidence in melanoma (43), in prostate (40), and in pancreatic cancer (37) that mast cells can play different roles in early and late phases of tumor initiation and growth. This fascinating hypothesis deserves to be further investigated in order to clarify the functional role of TAMCs in the progression of experimental and human cancers.

Two strains of mast cell-deficient mice with mutations affecting Kit, Kit<sup>W<sub>W</sub>-v</sup> (90, 91, 94, 98, 101, 104) and Kit<sup>W<sub>−/−</sub>W<sub>−/−</sub></sup> (14, 35, 40, 85, 89), have been extensively used to study the role of mast cells in tumor growth. These mice are profoundly deficient in mast cells and also exhibit several other abnormalities, such as basophil deficiency (181, 182). Recent evidence suggests that basophils can play a role in human pancreatic cancer (183). New
To increased levels of lactate, PGE₂, adenosine, IFN-γ, and a low pH (149, 150). This metabolic milieu can profoundly alter mast cell behavior. It has been shown that it is possible to reverse the immunosuppressive and pro-tumoral properties of tumor-associated macrophages (186, 187). A better knowledge of the pro-tumorigenic profile of TAMCs could help to “re-educate” these cells to play an antitumorigenic role.

Tumor cells evade host immune attack by expressing several checkpoint inhibitors, such as programmed cell death-1 (PD-1) ligands (PD-L1 and PD-L2) which inhibit PD-1+ lymphocytes in tumor microenvironment (188). Monoclonal antibodies targeting the PD-1/PD-L1 pathway unleash antitumor immunity and have revolutionized the management of a wide spectrum of malignancies (189). Certain cancer cells (e.g., melanoma) express also PD-1, in addition to PD-L1, providing an additional tumor intrinsic mechanism enhancing the pro-tumorigenic effect of PD-1/PD-L1 axis (190). Mouse mast cells highly express PD-L1 and, to a lesser extent, PD-L2 (191). An important task will be to investigate the role of PD-L1+ TAMC in tumor microenvironment.

All the above implies that elucidation of the roles of mast cells in different human tumors will demand studies of increasing complexity beyond those assessing merely mast cell density and microlocalization.

**CONCLUSION**

In several human and experimental tumors, mast cells and their mediators play a pro-tumorigenic role. However, in other tumors and even in the same tumor, mast cells seem to play a protective role. These apparently controversial results might reflect differences in stage, grade, and subtypes of tumors, different methods to identify mast cells (e.g., tryptase*, chymase*, toluidine blue, CD117*, Giemsa), or different microanatomical compartment (i.e., peritumoral vs intratumoral) analyzed in the various studies. Whatever the mechanisms, there are many unanswered questions that need to be addressed before we understand whether mast cells are an ally, adversary, or innocent bystander in human cancers.

**AUTHOR CONTRIBUTIONS**

GV, MG, and SL conceived and designed the review. All the authors contributed intellectually and to the writing of the submitted version of the manuscript.

**ACKNOWLEDGMENTS**

The authors apologize to the many authors who have contributed importantly to this field and whose work has not been cited due to space and citation restrictions. The authors thank Fabrizio Fioribianco for preparing the figures and Clarice Castaldo for excellent secretarial help. GM is the recipient of the 2016 Palasciano Award.

**FUNDING**

This work was supported in part by grants from Regione Campania CISI-Lab Project, CRÉMÉ Project, and TIMING Project.

**REFERENCES**

1. Ehrlich P. Beitrag zur Kenntniss der granulirten Bindegewebszellen und der eosinophilen Leukocythen. Arch Anat Physiol (Leipzig) (1879) 3:166–9.
2. Ehrlich P. Über die spezifischen Granulationen des Blutes. Arch Anat Physiol (Leipzig) (1879) 571–9.
3. Mulero I, Sepulcre MP, Meseguer J, Garcia-Ayala A, Mulero V. Histamine is stored in mast cells of most evolutionarily advanced fish and regulates the fish inflammatory response. Proc Natl Acad Sci U S A (2007) 104:19434–9. doi:10.1073/pnas.0704535104
4. Marone G, Galli SJ, Kitamura Y. Probing the roles of mast cells and basophils in natural and acquired immunity, physiology and disease. Trends Immunol (2002) 23:425–7. doi:10.1016/S1471-4906(02)02274-3
5. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nat Med (2012) 18:693–704. doi:10.1038/nm.2755
6. Kirshenbaum AS, Goff JP, Semere T, Foster B, Scott LM, Metcalfe DD. Demonstration that human mast cells arise from a progenitor cell population that is CD34(+), c-kit(+), and expresses aminopeptidase N (CD13). Blood (1999) 94:2333–42.
7. Krystel-Whitemore M, Dileepan KN, Wood JG. Mast cell: a multi-functional master cell. Front Immunol (2016) 6:620. doi:10.3389/fimmu.2015.00620
8. Jimenez-Andrade GV, Ibarra-Sanchez A, Gonzalez D, Lamas M, Gonzalez-Espinosa C. Immunoglobulin E induces VEGF production in mast cells and potentiates their pro-tumorigenic actions through a Fyn kinase-dependent mechanism. J Hematol Oncol (2013) 6:56. doi:10.1186/1756-8722-6-56
9. Genovese A, Borgia G, Bjorck I, Petraroli A, de Paulis A, Piazza M, et al. Immunoglobulin superantigen protein L induces IL-4 and IL-13 secretion from human Fc epsilon RI+ cells through interaction with the kappa light chains of IgE. J Immunol (2003) 170:1854–61. doi:10.4049/jimmunol.170.4.1854
10. Marone G, Rossi FW, Detoraki A, Granata F, Marone GC, Genovese A, et al. Role of superantigens in allergic disorders. In: Marone G, editor. Superantigens and Superallergens. Basel: Karger (2007). p. 195.
11. Andreu P, Johansson M, Affara NI, Pucci F, Tan T, Junankar S, et al. FcGamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell (2010) 17:121–34. doi:10.1016/j.ccr.2009.12.019
12. Groot Kormelink T, Powe DG, Kuipers SA, Abudukelimu A, Fens MH, Pieters EH, et al. Immunoglobulin free light chains are biomarkers of poor prognosis in basal-like breast cancer and are potential targets in tumor-associated inflammation. Oncotarget (2014) 5:3159–67. doi:10.18632/oncotarget.1868
13. Huang B, Lei Z, Zhang GM, Li D, Song C, Li B, et al. SCF-mediated mast cell infiltration and activation exacerbate the inflammation and immunosuppression in tumor microenvironment. Blood (2008) 112:1269–79. doi:10.1182/blood-2008-03-147033
14. Oldford SA, Haid ID, Howatt MA, Leiva CA, Johnston B, Marshall JS. A critical role for mast cells and mast cell-derived IL-6 in TLR2-mediated inhibition of tumor growth. J Immunol (2010) 185:7067–76. doi:10.4049/jimmunol.1001137
15. Borriolle F, Iannone R, Marone G. Histamine release from mast cells and basophils. Handb Exp Pharmacol (2017) 1–19. doi:10.1007/164_2017_18
16. Marchal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, et al. A beneficial role for immunoglobulin E in host defense against honeybee venom. Immunity (2013) 39:963–75. doi:10.1016/j.immuni.2013.10.005
Palm NW, Rosenstein KK, Yu S, Schenten DD, Florshiem E, Medzhitov R. Bee venom phospholipase A2 induces a primed phenotype that is dependent on the receptor ST2 and confers protective immunity. Immunity (2013) 39:976–85.

Wang Z, Lai Y, Bernard HJ, MacLeod DT, Cogen AL, Moss B, et al. Skin mast cells protect mice against vaccinia virus by triggering mast cell receptor STPR2 and releasing antimicrobial peptides. J Immunol (2012) 188:345–57. doi:10.4049/jimmunol.1101703

Chan CY, StJohn AL, Abraham SN. Plasticity in mast cell responses during bacterial infections. Curr Opin Microbiol (2012) 15:78–84. doi:10.1016/j.mib.2011.10.007

Jensen-Jarolim E, Bax HJ, Bianchini R, Capron M, Corrigan C, Castells M, et al. AllergyOncology – the impact of allergy in oncology: EAACI position paper. Allergy. (2016). doi:10.1111/1398-9995.13507

Platzer B, Epeke KG, Cremasco V, Baker K, Stout MM, Schulz C, et al. IgE/FcepsilonRI-mediated antigen cross-presentation by dendritic cells enhances anti-tumor immune responses. Cell Rep (2015) 10:1487–95. doi:10.1016/j.celrep.2015.02.015

Dawson MA, Kouzardides T, Huntly BJ. Targeting epigenetic readers in cancer. Nat Engl J Med (2012) 367:647–57. doi:10.1056/NEJMra1112635

Zitvogel L, Apetoh L, Ghiringhelli F, Andre F, Tesniere A, Kroemer G. The antitumor immune response: indispensable for therapeutic success? J Clin Invest (2008) 118:1991–2001. doi:10.1172/JCI31580

Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: re-instating immunosurveillance. Immunity (2013) 39:74–88. doi:10.1016/j.immuni.2013.06.014

Bissell MJ, Hines WC. Why don’t we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med (2011) 17:520–9. doi:10.1038/nm.2328

Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell (2012) 21:309–22. doi:10.1016/j.ccr.2012.02.022

Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Clin Cancer Res (2008) 14:4222–30. doi:10.1158/1078-0432.CCR-07-2608

Aoki M, Pawankar R, Niimi Y, Kawana S. Mast cells in basal cell carcinoma. Int Arch Allergy Immunol (2003) 130:233–41. doi:10.1159/000069515

Galdiero MR, Garfanda C, Jaillon S, Marone G, Mantovani A. Tumor-associated macrophages and neutrophils in tumor progression. J Cell Physiol (2013) 228:1404–12. doi:10.1002/jcp.24260

Galdiero MR, Marone G, Mantovani A. Cancer inflammation and cytokines. Perspect Biol (2017), (in press).

Westphal E. Über Mastzellen. In: Ehrlich P, editor. Klinik der Hautkrankheiten. Berlin: Hirschwald (1891). p. 17–41.

Aoki M, Pawankar R, Niimi Y. Mast cell involvement in chronic infections. AllergoJ (2007) 42:369–75. doi:10.1016/j.allergo.2007-11-125823

Ribatti D, Vacca A, Nico B, Quondamatteo F, Ria R, Minischielli M, et al. Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma. Br J Cancer (1999) 79:451–5. doi:10.1038/sj.bjc.660070

Rabenhorst A, Schlak M, Heukamp LC, Forster A, Theurich S, von Bergwelt-Baildon M, et al. Mast cells play a protumorigenic role in primary cutaneous lymphoma. Blood (2012) 120:2042–4. doi:10.1182/blood-2012-03-415638

Vezzoulaki R, Tsirakis G, Pappa CA, Devetagliou M, Tzardi M, Alexandrakis MG. The impact of mast cell density on the progression of bone disease in multiple myeloma patients. Int Arch Allergy Immunol (2015) 168:263–8. doi:10.1159/000443275

Tripodo C, Gri G, Piccaluga PP, Frossi B, Guarinotta C, Piconese S, et al. Mast cells and Th17 cells contribute to the lymphoma-associated pro-inflamatory microenvironment of angioimmunoblastic T-cell lymphoma. Am J Pathol (2010) 177:792–802. doi:10.1016/j.ajpath.2010.09.012

Taskinen M, Karjalainen-Lindsberg ML, Leppa S. Prognostic influence of tumor-infiltrating mast cells in patients with follicular lymphoma treated with rituximab and CHOP. Blood (2008) 111:6664–7. doi:10.1182/blood-2007-11-125823

Franco G, Guarinotta C, Frossi B, Piccaluga PP, Boveri E, Gulino A, et al. Bone marrow stroma CD40 expression correlates with inflammatory mast cell infiltration and disease progression in splenic marginal zone lymphoma. Blood (2014) 123:1836–49. doi:10.1182/blood-2013-04-497271

Molin D, Edstrom A, Glimeilus I, Glimeilus B, Nilsson G, Sundstrom C, et al. Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. Br J Haematol (2002) 119:122–4. doi:10.1046/j.1365-2141.2002.03576.x

Andersen MD, Kamper P, Nielsen PS, Bendix K, Riber-Hansen R, Steiniche T, et al. Tumour-associated mast cells in classical Hodgkin's lymphoma: correlation with histological subtype, other tumour-infiltrating inflammatory cell subsets and outcome. Eur J Haematol (2016) 96:252–9. doi:10.1111/ ejh.12583

Englund A, Molin D, Enblad A, Karlen J, Glimelius I, Ljungman G, et al. The role of tumour-infiltrating eosinophils, mast cells and macrophages in classical and nodular lymphocyte predominant Hodgkin lymphoma in children. Eur J Haematol (2016) 97:430–8. doi:10.1111/ejh.12747

Marone G, Varricchi G, Looffredo S, Granata F. Mast cells and basophils in inflammatory and tumor angiogenesis and lymphangiogenesis. Eur J Pharmacol (2016) 778:146–51. doi:10.1016/j.ejphar.2015.03.088

Yamamoto T, Katayama I, Nishioka K. Expression of stem cell factor in Vasa in breast cell carcinoma. Br J Dermatol (1997) 137:709–13. doi:10.1111/j.1365-2133.1997.19402055.x

de Paulis A, Minopoli G, Arbusenti D, de Crescenzo G, Dal Piaz F, Pucci P, et al. Stem cell factor is localized in, released from, and clefted by human mast cells. J Immunol (1999) 163:2799–808.
60. Prevete N, Staiano RI, Granata F, Detoraki A, Necchi V, Ricci V, et al. Expression and function of angiotriptins and their tie receptors in human basophils and mast cells. *J Biol Regul Homeost Agents* (2013) 27:87–39.

61. Visciano C, Liotti F, Prevete N, Cati G, Franco R, Collina F, et al. Mast cells induce epithelial-to-mesenchymal transition and stem cell features in human thyroid cancer cells through an IL-8-Akt-Slug pathway. *Oncogene* (2015) 34:5175–86. doi:10.1038/onc.2014.441

62. Ray LJ, Yeo WW, Peachell PT. Prostaglandin E2 activates EP2 receptors to inhibit human lung mast cell degranulation. Br J Pharmacol (2006) 147:707–13. doi:10.1038/bjpharm.0706664

63. Weller CL, Collington SJ, Hartnell A, Conroy DM, Kaise T, Barker JE, et al. Chemotactic action of prostaglandin E2 on mouse mast cells acting via the PGF2 receptor. *Proc Natl Acad Sci U S A* (2007) 104:11712–7. doi:10.1073/pnas.0701700104

64. Godot V, Arocot M, Garcia G, Capel F, Flyn C, Dy M, et al. H4 histamine receptor mediates optimal migration of mast cell precursors to CXCL12. *J Allergy Clin Immunol* (2007) 120:827–34. doi:10.1067/m.jaci.2007.05.046

65. Weller CL, Collington SJ, Brown JK, Miller HR, Al-Kashfi A, Clark P, et al. Leukotriene B4, an activation product of mast cells, is a chemotactic factor for lung mast cells. Exp Med (2005) 201:1961–71. doi:10.1084/jem.20042407

66. Nagasaka A, Matsue H, Matsuhashi A, Aoki R, Nakamura Y, Kambe N, et al. Osteopontin is produced by mast cells and affects IgE-mediated degranulation and migration of mast cells. *Eur J Immunol* (2008) 38:489–99. doi:10.1002/eji.200737057

67. Yao Q, Chen Y, Yeh CR, Ding J, Li L, Chang C, et al. Recruited mast cells in the tumor microenvironment enhance bladder cancer metastasis via modulation of ERbeta/CCL2/CCR2 EMT/MMP9 signals. *Oncotarget* (2016) 7:8742–55. doi:10.18632/oncotarget.8492

68. Aicalin MF, Onur U, Topcu I, Yasar B, Kiper H, Colak E. Tumour angiogenesis and poor prognostic factor related to protease-activated receptor 2 expression. *Acta Histochem* (2015) 15:840.

69. Akbari AF, Niroumand-Oscoei SM, Somi MH, Ghojazadeh M, Akbarzadeh M, Fakhrjou A, et al. High infiltration of mast cells positive to tryptase predicts worse outcome of interventional resection of colorectal liver metastases. *Surg Oncol* (2015) 24:115–24. doi:10.1016/j.suronc.2014.08.003

70. Takanami I, Takeuchi K, Naruke M. Mast cell density is associated with angiogenesis and poor prognosis in pulmonary adenocarcinoma. *Cancer* (2008) 108:2686–92. doi:10.1002/1097-0142(200806)88:12<2686::AID-CNCR6>3.0.CO;2-Y

71. Banat GA, Tretyn A, Pullamsetti SS, Wilhelm J, Weigert A, Olesch C, et al. Immune and inflammatory cell composition of human lung cancer stroma. *PloS One* (2015) 10:e0139073. doi:10.1371/journal.pone.0139073

72. Holzel M, Landsberg I, Glodde N, Bald T, Rogova M, Riesenb S, et al. A preclinical model of malignant peripheral nerve sheath tumor-like melanoma is characterized by infiltrating mast cells. *Cancer Res* (2016) 76:2561–3. doi:10.1158/0008-5472.CAN-15-1090

73. Strouch MJ, Cheon EC, Salabat MR, Krantz SB, Gounaris E, Melstrom LG, et al. Crosstalk between mast cells and pancreatic cancer cells contributes to pancreatic tumor progression. *Cancer Res* (2010) 70:2257–65. doi:10.1158/0008-5472.CAN-10-2900

74. Chang DZ, Ma Y, Li B, Wang H, Deng D, Liu Y, et al. Mast cells in tumor microenvironment promotes the in vivo growth of pancreatic ductal adenocarcinoma. *Clin Cancer Res* (2011) 17:7015–23. doi:10.1158/1078-0432.CCR-11-0607

75. Cai SW, Yang SZ, Gao J, Pan K, Chen JY, Wang YL, et al. Prognostic significance of mast cell count following curative resection for pancreatic ductal adenocarcinoma. *Surgery* (2011) 149:576–84. doi:10.1016/j.surg.2010.09.009

76. Li L, Dang Q, Xie H, Yang Z, He D, Liang L, et al. Infiltrating mast cells enhanced prostate cancer invasion via altering LncRNA-HOTAIR/PRE2- androgen receptor (AR)-MMP9 signals and increased stem/progenitor cell population. *Oncotarget* (2015) 6:14179–90. doi:10.18632/oncotarget.3651

77. Nonomura N, Takayama H, Nishimura K, Oka D, Nakai Y, Shiha M, et al. Decreased number of mast cells infiltrating into needle biopsy specimens leads to a better prognosis of prostate cancer. Br J Cancer (2007) 97:952–6. doi:10.1038/sj.bjc.6603962

78. Waisuk A, Dalton DK, Schpero WL, Stan RV, Conejo-Garcia JR, Noelke RJ. Mast cells impair the development of protective anti-tumor immunity. *Cancer Immunol Immunother* (2011) 60:2273–82. doi:10.1007/s00262-012-1276-7

79. Wiedenmeyer J, Galli SJ. Decreased susceptibility of mast cell-deficient Kit(W−/−) mice to the development of 1,2-dimethylhydrazine-induced intestinal tumors. *Lab Invest* (2005) 85:388–96. doi:10.1038/labinvest.3700232

80. Gounaris E, Erdman SE, Restaino C, Gurish MF, Friend DS, Gounari F, et al. Mast cells are an essential hematopoietic component for polyp development. *Proc Natl Acad Sci U S A* (2007) 104:19977–82. doi:10.1073/pnas.0704620104

81. Nordlund JJ, Askensk D. The effect of histamine, antihistamines, and a mast cell stabilizer on the growth of clonmaid melanoma cells in DBA/2 mice. *J Invest Dermatol* (1983) 81:28–31. doi:10.1111/1523-7747.ep12538356

82. Jeong HJ, Oh HA, Nam SY, Han NR, Kim YS, Kim JH, et al. The critical role of mast cell-derived hyposia-inducible factor-1 alpha in human and mice melanoma growth. *Int J Cancer* (2013) 132:492–501. doi:10.1002/ijc.27937

83. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. *Nat Med* (2007) 13:1211–8. doi:10.1038/nm1649

84. Soucek L, Buggy JJ, Kortlever R, Adimoolam S, Monclus HA, Allende MT, et al. Modeling pharmacological inhibition of mast cell degranulation as a therapy for insulinoma. *Neoplasia* (2011) 13:1093–100. doi:10.1593/neo.119980

85. Nakayama T, Yao L, Totsato G. Mast cell-derived angiopoietin-1 plays a critical role in the growth of plasma cell tumors. *J Clin Invest* (2004) 114:1317–25. doi:10.1172/JCI20809

86. Xie H, Li C, Dang Q, Chang LS, Li L. Infiltrating mast cells increase prostate cancer chemotherapy and radiotherapy resistances via modulation of p38/P53/p21 and ATM signals. *Oncotarget* (2016) 7:1341–53. doi:10.18632/oncotarget.6372
Varricchi et al.  

Mast Cells in Cancer

98. Coussens LM, Raymond WV, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, et al. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev (1999) 13:1382–97. doi:10.1101/ gad.13.11.1382
99. Sarchio SN, Scolyer RA, Beaugie C, McDonald D, Marsh-Wakefield F, Halliday GM, et al. Pharmacologically antagonizing the CXCR4-CXCL12 chemokine pathway with AMD3100 inhibits sunlight-induced skin cancer. J Invest Dermatol (2014) 134:1091–100. doi:10.1038/jid.2013.424
100. Tourinliac O, Santos DD, Xu L, Kutok J, Tai YT, Le Gouill S, et al. Mast cells in Waldenström’s macroglobulinemia support lymphoplasmacytic cell growth through CD154/CD40 signaling. Ann Oncol (2006) 17:1275–82. doi:10.1093/annonc/mdl109
101. Simonno MJ, Carter KJ, Sims LP, Lafleur B, Fingleton B, Matrisian LM. A protective role of mast cells in intestinal tumorigenesis. Carcinogenesis (2008) 29:880–6. doi:10.1093/carcin/bgn040
102. Yang XD, Ai W, Asfaha S, Bhagat G, Friedman RA, Jin G, et al. Histamine deficiency promotes inflammation-associated carcinogenesis through reduced myeloid maturation and accumulation of CD11b+Ly6G+ immature myeloid cells. Nat Med (2011) 17:87–95. doi:10.1038/nm.2278
103. Purwar R, Schlabach C, Xiao S, Kang HS, Elayyam W, Jiang X, et al. Robust tumor immunity to melanoma mediated by interleukin-9-producing T cells. Nat Med (2012) 18:1248–53. doi:10.1038/nm.2856
104. Siebenhaar F, Metz M, Maurer M. Mast cells protect from skin tumor development and limit tumor growth during spontaneous mouse model of novo carcinogenesis in a kit-dependent mouse model. Exp Dermatol (2014) 23:159–64. doi:10.1111/exd.12238
105. Hedstrom G, Berglund M, Molin D, Fischer M, Nilsson G, Thunberg U, et al. Mast cell infiltration is a favourable prognostic factor in diffuse large B-cell lymphoma. Br J Haematol (2007) 136:68–71. doi:10.1111/j.1365-2141.2007.06612.x
106. Dahiri S, Huntsman D, Makretsov N, Cheung M, Gilks B, Gadzik C, et al. The presence of stromal mast cells identifies a subset of invasive breast cancers with a favorable prognosis. Mod Pathol (2004) 17:690–5. doi:10.1038/modpathol.3800094
107. Amini RM, Aaltonen K, Nevanlinna H, Carvalho R, Salonen L, Heikilla P, et al. Mast cells and eosinophils in invasive breast carcinoma. BMC Cancer (2008) 8:277. doi:10.1186/1471-2407-8-277
108. della Rovere F, Granata A, Familiari D, D’Arrigo G, Mondello B, Basile G. Mast cells in invasive ductal breast cancer: different behavior in high and low hormone-receptive cancers. BMC Cancer (2008) 8:279. doi:10.1186/1471-2407-8-279
109. Hedstrom G, Berglund M, Molin D, Fischer M, Nilsson G, Thunberg U, et al. Mast cell infiltration is a favourable prognostic factor in diffuse large B-cell lymphoma. Br J Haematol (2007) 136:68–71. doi:10.1111/j.1365-2141.2007.06612.x
110. Amini RM, Aaltonen K, Nevanlinna H, Carvalho R, Salonen L, Heikilla P, et al. Mast cells and eosinophils in invasive breast carcinoma. BMC Cancer (2008) 8:277. doi:10.1186/1471-2407-8-277
111. Detoraki A, Granata F, Staibano S, Rossi FW, Ferrara AL, Galdiero MR, Gigantino V, et al. Immunological microenvironment in prostate cancer: relationship between mast cells and tumour angiogenesis in non-small cell lung carcinoma. J Med Virol (2013) 85:424–34. doi:10.1002/jmv.24076
112. Loffredo S, Borriello F, Iannone R, Ferrara AL, Galdiero MR, Gigantino V, et al. Group V secreted phospholipase A2 induces the release of anti-angiogenic factors by human neutrophils. Front Immunol (2017), (in press).
137. Baram D, Vaday GG, Salamoni P, Drucker I, Hershkoviz R, Mekori YA. Human mast cell release of metalloproteinase-9 on contact with activated T cells: juxtaaction regulation by TNF-alpha. J Immunol (2001) 167:4008–16. doi:10.4049/jimmunol.167.7.4008

138. Rinderknecht M, Detmar M. Tumor lymphangiogenesis and melanoma metastasis. J Cell Physiol (2008) 216:347–54. doi:10.1002/jcp.21494

139. Granata F, Frattini A, Loffredo S, Staiano RI, Petraroli A, Ribatti D, et al. Production of vascular endothelial growth factors from human lung macrophages induced by group IIA and group X secreted phospholipases A2. J Immunol (2010) 184:5232–41. doi:10.4049/jimmunol.0902501

140. Bowers HM Jr, Mahapatro RC, Kennedy JW. Numbers of mast cells in the axillary lymph nodes of breast cancer patients. Cancer (1979) 43:568–73. doi:10.1002/1097-0142(197902)43:2<568::AID-CNCR28238402253;2.0.CO;2-#

141. Zhang X, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature (2015) 527:525–30. doi:10.1038/nature16064

142. Fischer KR, Durrans A, Lee S, Sheng J, Li F, Wong ST, et al. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. Nature (2015) 527:472–6. doi:10.1038/nature15748

143. Scheel C, Weinberg RA. Cancer stem cells and epithelial-mesenchymal transition: concepts and molecular links. Semin Cancer Biol (2012) 22:396–403. doi:10.1016/j.semcancer.2012.04.001

144. Pittoni P, Colombo MP. The dark side of mast-cell-targeted therapy in prostate cancer. Cancer Res (2012) 72:8331–5. doi:10.1158/0008-5472.CAN-11-3130

145. Bry M, Kivela R, Leppanen VM, Alitalo K. Vascular endothelial growth factor-B in physiology and disease. Physiol Rev (2014) 94:779–94. doi:10.1152/physrev.00028.2013

146. Ersulanov EB, Bhognagarwa PS, Quatromoni JG, Stephens TF, Ranganathan A, Deshpande C, et al. Tumor-associated neutrophils stimulate T cell responses in early-stage human lung cancer. J Clin Invest (2014) 124:5466–80. doi:10.1172/JCI77053

147. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovian S, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med (2016) 375:819–29. doi:10.1056/NEJMoa1504958

148. Varricchi G, Galliandro MR, Marone G, Granata F, Borriello F, Marone G. Controversial role of mast cells in skin cancers. Exp Dermatol (2017) 26:11–7. doi:10.1111/exd.13107

149. Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. Cancer Res (2011) 71:6921–5. doi:10.1158/0008-5472.CAN-11-1457

150. Gottfried E, Kreutz M, Mackensen A. Tumor metabolism as modulator of immune response and tumor progression. J Immunol (2011) 187:4635–41. doi:10.4049/jimmunol.0902501

151. Motakis E, Guhl S, Ishizu Y, Itoh M, Kawaji H, de Hoon M, et al. Redefinition of Fc gamma RI or Fc epsilon RI. J Immunol (2011) 187:6904–11. doi:10.4049/jimmunol.1102450

152. Triggiani M, Hubbard WC, Chilton FH. Synthesis of 1-acetyl-2-acyl-sn-glycero-3-phosphocholine by an enriched preparation of human lung mast cell. J Immunol (1990) 144:4773–80.

153. Damiani E, Puebla-Osorio N, Gorbea E, Ullrich SE. Platelet-activating factor induces epigenetic modifications in human mast cells. J Invest Dermatol (2015) 135:3034–40. doi:10.1038/jid.2015.336

154. Chacon-Salinas R, Chen L, Chavez-Blanco AD, Limon-Flores AY, Ma Y, Ullrich SE. An essential role for platelet-activating factor in activating mast cell migration following ultraviolet irradiation. J Leukoc Biol (2014) 95:139–48. doi:10.1189/jlb.0814109

155. de Paulis A, Marino I, Ciccarelli A, de Crescenzo G, Concardi M, Verga L, et al. Human synovial mast cells. I. Ultrastructural in situ and in vitro immunologic characterization. Arthritis Rheum (1996) 39:1222–33. doi:10.1002/art.178090723

156. Motakis E, Loui D, Gysemans C, Baeten M, Stange V, Van den Bossche J, et al. Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6c(high) monocytes. Cancer Res (2010) 70:5728–39. doi:10.1158/0008-5472.CAN-09-4672

157. Motakis E, Guhl S, Ishizu Y, Itoh M, Kawai H, de Hoon M, et al. Redefinition of the human mast cell transcriptome by deep-CAGE sequencing. Blood (2014) 123:58–67. doi:10.1182/blood-2013-04-483792

158. Lundstrom SL, Saluja R, Adner M, Haeggstrom JZ, Nilsson G, Wheelock CE. Lipid mediator metabolic profiling demonstrates differences in eicosanoid production in two phenotypically distinct mast cell populations. J Lipid Res (2013) 54:1148–66. doi:10.1194/jlr.M030171

159. Sotiriou C, Puettai L. Gene-expression signatures in breast cancer. N Engl J Med (2009) 360:790–800. doi:10.1056/NEJMra0801289

160. Popper HH, Ryska A, Timar J, Olszewski W. Molecular testing in lung cancer in the era of precision medicine. Transl Lung Cancer Res (2014) 3:291–300. doi:10.3978/j.issn.2218-6751.2014.10.01

161. Kim SY, Kim SN, Hahn HJ, Lee YW, Choe YB, Ahn KJ. Metaanalysis of BRAF mutations and clinicopathologic characteristics in primary melanoma. J Am Acad Dermatol (2015) 72:1036–46.e1032. doi:10.1016/j.jaad.2015.02.1113

162. Riquelme I, Saavedra K, Esponina JA, Weber H, Garcia P, Nervi B, et al. Molecular classification of gastric cancer: towards a pathway-driven targeted therapy. Oncotarget (2015) 6:24750–79. doi:10.18632/oncotarget.4990

163. Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science (2013) 339:286–91. doi:10.1126/science.1232227
180. Bedard PL, Hansen AR, Ratain MJ, Siu LL. Tumour heterogeneity in the clinic. *Nature* (2013) 501:355–64. doi:10.1038/nature12627

181. Mancardi DA, Jonsson F, Iannascobili B, Khan H, Van Rooijen N, Huerre M, et al. Cutting edge: the murine high-affinity IgG receptor FcgammaRIV is sufficient for autoantibody-induced arthritis. *J Immunol* (2011) 186:1899–903. doi:10.4049/jimmunol.1003642

182. Feyerabend TB, Weiser A, Tietz A, Stassen M, Harris N, Kopf M, et al. Cre-mediated cell ablation contests mast cell contribution in models of antibody- and T cell-mediated autoimmunity. *Immunity* (2011) 35:832–44. doi:10.1016/j.immuni.2011.09.015

183. De Monte L, Wormann S, Brunetto E, Heltai S, Magliacane G, Reni M, et al. Basophil recruitment into tumor-draining lymph nodes correlates with Th2 inflammation and reduced survival in pancreatic cancer patients. *Cancer Res* (2016) 76:1792–803. doi:10.1158/0008-5472.CAN-15-1801-T

184. Rodewald HR, Feyerabend TB. Widespread immunological functions of mast cells: fact or fiction? *Immunity* (2012) 37:13–24. doi:10.1016/j.immuni.2012.07.007

185. Reber LL, Marichal T, Galli SJ. New models for analyzing mast cell functions in vivo. *Trends Immunol* (2012) 33:613–25. doi:10.1016/j.it.2012.09.008

186. Duluc D, Corvaisier M, Blanchard S, Catala L, Descamps P, Gamelin E, et al. Interferon-gamma reverses the immunosuppressive and protumoral properties and prevents the generation of human tumor-associated macrophages. *Int J Cancer* (2009) 125:367–73. doi:10.1002/ijc.24401

187. Hagemann T, Lawrence T, McNeish I, Charles KA, Kulbe H, Thompson RG, et al. “Re-educating” tumor-associated macrophages by targeting NF-kappaB. *J Exp Med* (2008) 205:1261–8. doi:10.1084/jem.20080108

188. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* (2015) 161:205–14. doi:10.1016/j.cell.2015.03.030

189. Tan S, Chen D, Liu K, He M, Song H, Shi Y, et al. Crystal clear: visualizing the intervention mechanism of the PD-1/PD-L1 interaction by two cancer therapeutic monoclonal antibodies. *Protein Cell* (2016) 7:866–77. doi:10.1007/s13238-016-0337-7

190. Kleeff S, Posch C, Barthel SR, Mueller H, Schlapbach C, Guenova E, et al. Melanoma cell-intrinsic PD-1 receptor functions promote tumor growth. *Cell* (2015) 162:1242–56. doi:10.1016/j.cell.2015.08.052

191. Nakae S, Suto H, Ikura M, Kakurai M, Sedgwick JD, Tsai M, et al. Mast cells enhance T cell activation: importance of mast cell costimulatory molecules and secreted TNF. *J Immunol* (2006) 176:2238–48. doi:10.4049/jimmunol.176.4.2238

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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