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NON-THEMATIC REVIEW

Tumor dormancy and the neuroendocrine system: an undisclosed connection?

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Abstract Tumor dormancy is a poorly understood phenomenon conceptualized as a protracted quiescent state during which cancer cells are present but clinical disease is not apparent, a condition referred to as "cancer without disease" by Folkman. Examples include the incidental detection of occult *in situ* tumors in post-mortem organ analysis and cancer recurrence after long disease-free periods. Lack of angiogenic competency has been proposed as a major determinant of the fate of dormant tumors. Other proposed processes include establishment of homeostatic equilibrium between tumor cells and the host's immune system response and a non-permissive microenvironment for tumor growth. Recent cellular and molecular studies suggest that neuroendocrine mediators regulate the biology of tumor progression and act as endogenous modulators of angiogenesis, inflammation, and other molecular processes involved in tumor reactivation from dormancy. We review experimental and clinical evidence and propose that neuroendocrine dynamics of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis might contribute to the loss of tumor dormancy.

Keywords Tumor dormancy · Neuroendocrine system · Tumor microenvironment · Immunosurveillance · Cancer recurrence

1 Perspective

Recent research on cancer dormancy and recurrence has seen the convergence of two of Rudolf Virchow's most enduring scientific contributions: the link between inflammation and cancer and the role of socio-environmental factors in the alteration of disease risks. The molecular

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dynamics connecting psychosocial factors and neuroendocrine system with the dormancy status of a tumor begin to map the mechanisms of the relationship that Virchow pioneered more than 150 years ago.

2 The neuroendocrine/tumor dormancy hypothesis

Cancers have long been known to have the capacity to enter a state of dormancy in which they cease growth and disease progression but do not die or regress. Dormant tumors retain the capacity to reactivate (escape from dormancy) and resume active growth and progression and thus remain a significant health threat. However, the general physiologic factors that influence a tumor's entry into and exit from dormancy remain poorly understood. A growing body of research has begun to identify some of the specific molecular processes involved in the establishment and escape from tumor dormancy. Remarkably, a separate body of cancer research has begun to show that many of the same molecular dynamics involved in tumor dormancy are subject to regulation by the neural and endocrine systems. The goal of this review is to highlight that molecular intersection (Fig. 1a–c) and prompt new research to join these two literatures and test the hypothesis that neural and endocrine dynamics represent key general physiologic conditions that modulate tumor dormancy and thus direct the fate of clinically occult cancers.

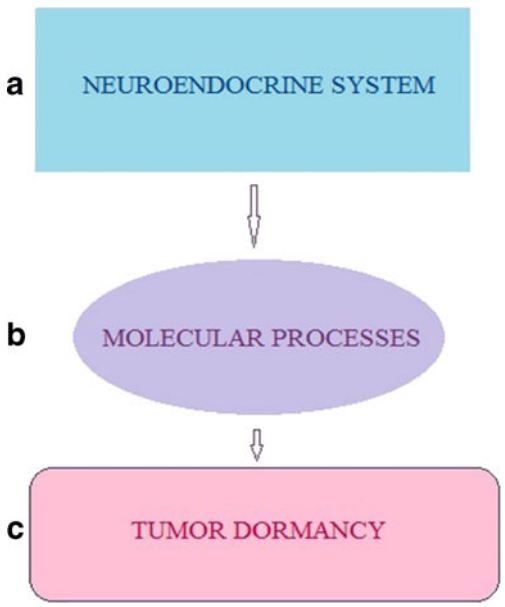

Fig. 1 *a–c* Conceptual model. Activation of the neuroendocrine system can affect molecular processes crucial for tumor development and progression; the same processes are involved in the modulation and control of tumor dormancy

3 Tumor dormancy: cancer without disease

Tumor dormancy reflects a period of arrested tumor growth that can be categorized based on the underlying cellular mechanisms. "Tumor mass dormancy" occurs in a population of cells undergoing indolent proliferation but not expanding in mass because the process is offset by a concomitant rate of cell death [1]. This dormant state has been hypothesized to stem from lack of adequate vascularization and immune system control activity, among other processes. "Tumor cell dormancy" refers to cancer cells in a state of cell growth arrest resulting from microenvironment signals unfavorable to tumor cell proliferation [1]. Both tumor mass dormancy and tumor cell dormancy may be reversed when microenvironmental conditions shift to support tumor expansion.

Experimental and clinical evidence suggest that adverse social and environmental factors can stimulate biological processes that support tumor progression, such as chronic inflammation and angiogenesis, and impair several aspects of the antitumor immune response. In particular, stress, depression, and other negative psychosocial and behavioral conditions may affect immunosurveillance [2, 3], alter the tumor stroma microenvironment [4–11], and cause inflammation [12, 13] through modulation of the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal gland (HPA) axis. These same biological processes have also been shown to influence dormancy dynamics. As outlined below, neural and endocrine modulation of cancer-related processes, such as p53 dysregulation, increased expression of vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines, such as IL-6 and IL-8, enhanced production of matrix metalloproteinases (MMPs), macrophage recruitment, and resistance to anoikis, may directly impact the dormancy status of *in situ* tumors and metastatic sites. Neuroendocrine promotion of an environment supportive of angiogenesis, inflammation, tissue invasion, and impaired antitumor immune responses causes modulation of the heterotypic interactions between malignant and non-mutated cells such as endothelial cells, fibroblasts, and leukocytes which promote tumor cells' escape from dormancy (Fig. 2). As a result, stress-induced neuroendocrine activation may hasten the progression of *in situ* primary lesions to clinically relevant cancers (Fig. 3). Similarly, neuroendocrine signaling pathways may affect the dormancy of disseminated tumor cells and of silent micrometastases, thus contributing to cancer recurrence (Fig. 4).

3.1 Primary *in situ* dormant tumor

Small *in situ* tumors are often identified in autopsies of individuals who die from non-cancer causes. For example, microscopic breast tumors were found in 39 % of women autopsied between the ages of 40 and 50 years old, although

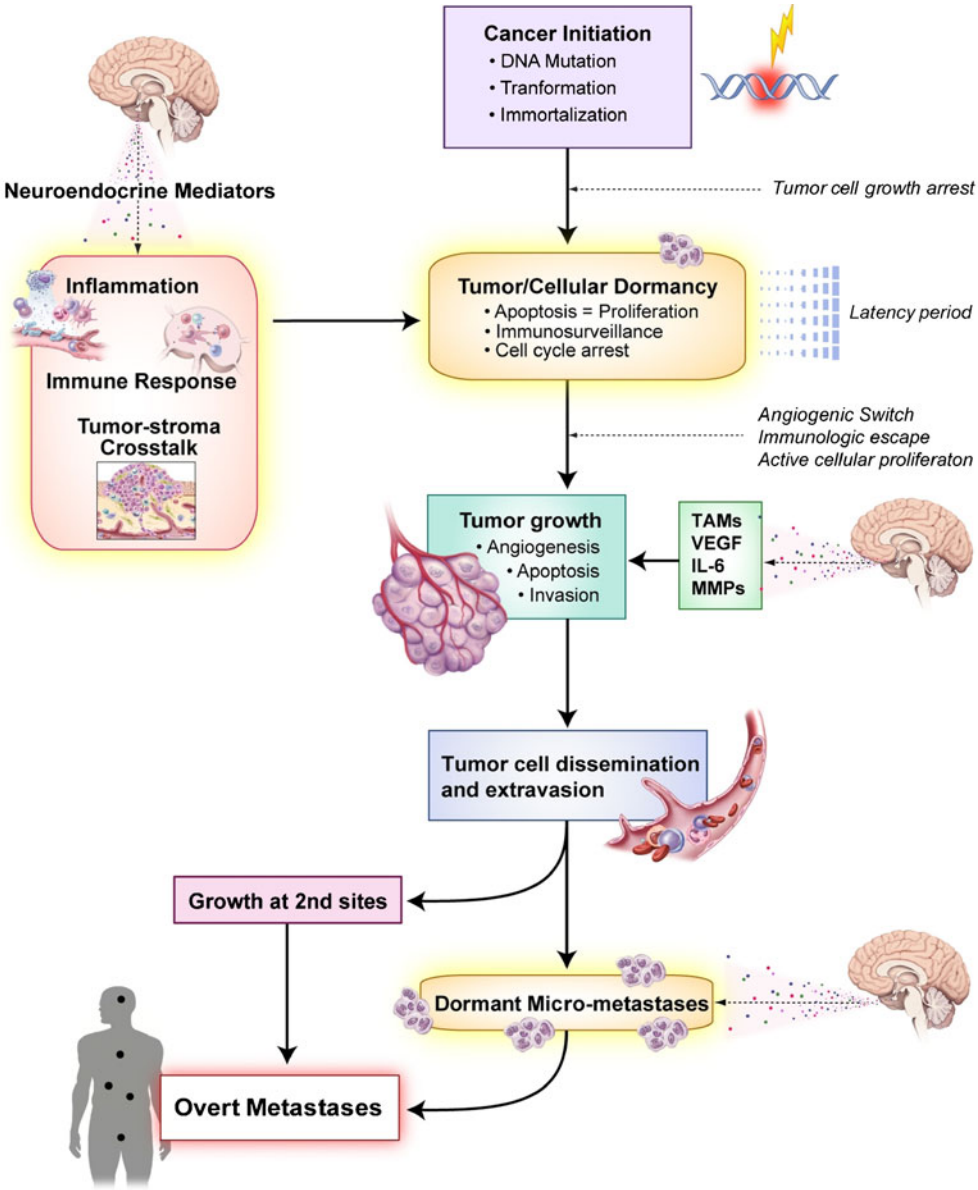

Fig. 2 Neuroendocrine influences on tumor dormancy. Psychosocial and/or environmental stressors may trigger activation of the neuroendocrine system initiating a cascade of neuroendocrine mediators that can affect the microenvironment of preexisting *in situ* dormant lesions, enhancing inflammatory states and interfering with the immune response. Ultimately, these processes may lead to angiogenic switch, tumor cells overcoming immune control, and escape from dormancy. Affective states may also result in the activation of crucial signaling pathways in tumor cells and the microenvironment of dormant metastases, altering their biology and leading to patient clinical relapse

the clinical incidence of breast cancer in women in the same age range is only 1 % [14, 15]. Similar data have been found for other types of cancer [16–18] indicating a higher frequency of silent tumors compared to the prevalence of the overt cancers. These small tumors can persist as microscopic lesions without detection or clinical manifestation, a condition referred to as "cancer without disease" by Folkman [19]. As physiologic conditions change, these tumors may move from a dormant state to become progressive invasive cancers (i.e., reactivation from dormancy).

3.2 Dormant metastasis

Cancer recurrence may occur years or decades after surgical excision and treatment of the primary tumor. Persistent minimal residual disease occurs for most types of cancer [1] and vital organ failure due to metastases represents the main cause of cancer death. This nonrandom and predictable tumor colonization of distant tissues and organs is mediated by disseminated tumor cells (DTCs). Bone marrow constitutes a common homing site and reservoir of DTCs originating from various epithelial tumors. Clinical detection and molecular characterization of DTCs or peripheral blood circulating tumor cells (CTCs) may constitute unique prognostic factors for follow-up risk assessment and therapy monitoring [20]. An extensive pooled analysis of 4,703 breast cancer patients from eight large studies found that the presence of DTCs in bone marrow at the time of cancer diagnosis was associated with poor prognosis and survival [21]. In addition, a European study showed that persistent bone marrow DTCs during postoperative clinical follow-up constituted an independent prognostic factor for breast

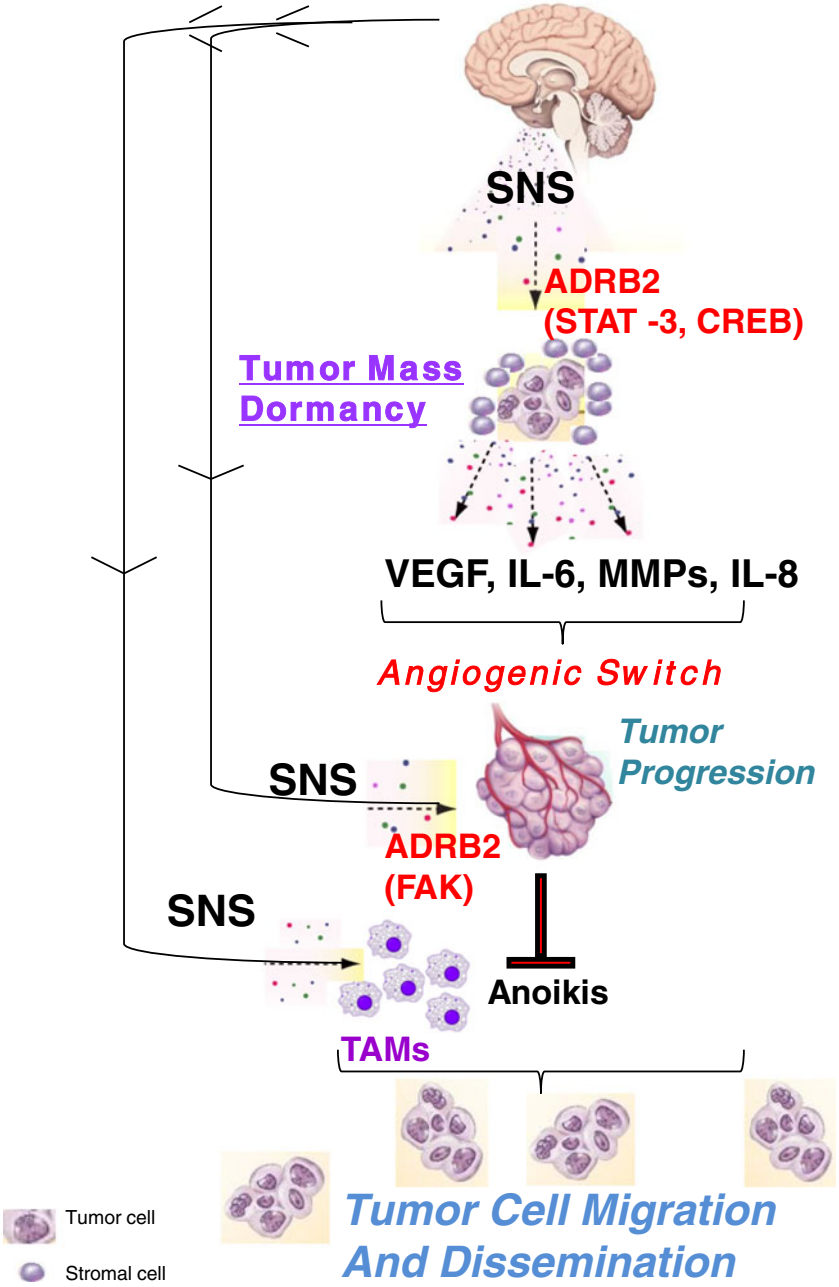

Fig. 3 Mechanistic model. *Neuroendocrine influences on tumor mass dormancy.* Social environmental influences can cause activation of the sympathetic nervous system which, in turn, can affect tumor mass dormancy and hasten the progression of *in situ* lesions to clinically relevant cancers. See text for detailed explanation. *ADRB2* β_2-adrenergic receptors; *STAT-3* signal transducer and activator of transcription-3; *CREB* cAMP response element-binding protein; *TAMs* tumor-associated macrophages

cancer recurrence and poor survival [22]. Results from meta-analyses of patients with colorectal or melanoma cancer revealed a clinically prognostic significance for CTCs [23, 24]. CTCs have been found in patients up to 22 years postsurgical removal of primary breast tumor [25]. This lag time does not reflect the primary growth kinetics of the tumor cell population, thus it is reasonable to hypothesize that sustained shedding of CTCs (which themselves survive for only hours in circulation [25]) reflects ongoing shedding from a clinically dormant population of DTCs. Accumulating molecular and clinical evidence supports a new conceptualization of the metastatic process in which metastases of early disseminated, primordial cancer cells are seeded in parallel with primary tumor progression [26]. Eyles [27] has proposed that this early tumor cell migration and dissemination is necessary to accommodate cell–cell competition for space and nutrients. In this context, dormancy of disseminated cancer cells might exemplify a potential therapeutic target to control disease course and the patient's subsequent fate (i.e., morbidity and survival).

3.3 Framing tumor dormancy in the context of the tumor microenvironment

The traditional view of carcinogenesis as a phenomenon that occurs at the subcellular level is evolving and cancer is now

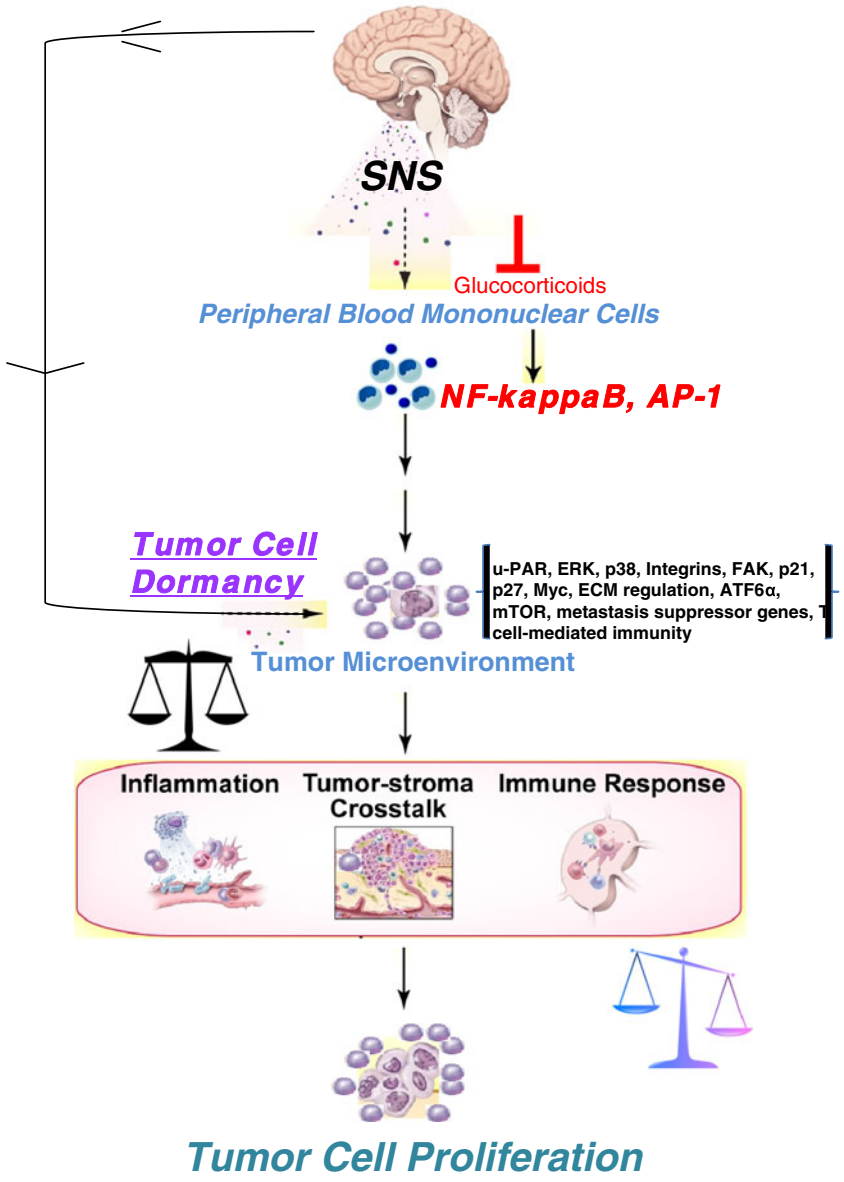

Fig. 4 Mechanistic model. *Neuroendocrine influences on tumor cell dormancy.* Stress-induced neuroendocrine signaling, through activation of the sympathetic nervous system, can affect the dormancy of disseminated tumor cells and of silent micrometastases, contributing to cancer recurrence. See text for detailed explanation. *AP-1* activator protein-1

recognized as the product of reciprocal interactions between tumor cells and the surrounding microenvironment, which includes fibroblasts, vascular endothelial, fat, immune and inflammatory and nerve cells. Tissue organization and tumor cell–microenvironment–host reciprocal interactions play fundamental roles in the process. Disruption of the microarchitecture that underlines a three-dimensional tissue structure and that defines the relationships among the tissue heterotypic cells constitutes a salient feature of carcinogenesis [28]. In close analogy with morphogen gradient sculpting and organizing activities of embryonic tissues, morphostatic fields regulate and control proliferation and apoptosis of tissues' target cells; physiological morphostatic signaling pathways may curb the expression of malignant phenotypes that would otherwise unfold in tumor-supportive microenvironments [28]. Conceivably, this crosstalk communication between cancer cells and their surrounding microenvironment may help restrain the malignant potential of disseminated tumor cells, keeping them in a dormant state.

Cells communicate with their microenvironment through interactions of signaling pathways with the extracellular matrix mediated by junctional and adhesion molecules. Acting as matrix receptors, integrins are signal transducer proteins that orchestrate multiple cellular processes (e.g., the coordinated organization of tissue structures) during morphogenesis and that are cardinal for cancer progression. In particular, β1-integrin exemplifies a key regulator function in the transition from cellular quiescence to active proliferation and this property may derive, at least in part, from integrin modulation of tissues' structural homeostasis. Bissell and colleagues, using a three-dimensional basement

membrane *in vitro* and an *in vivo* models, demonstrated that inhibition of β1-integrin function reverted the malignant behavior of mammary cancer cells and induced cellular quiescence [29]. Removal of the inhibition rescued the malignant phenotype pointing out the reversibility of the phenomenon and supporting the thesis that stabilizing (preserving) homeostatic and architectural structure of a tissue may cause a cellular phenotype to prevail over the malignant genotype [29] in contrast with the somatic mutation theory of cancer [30]. Several other studies [31–36] provided further evidence that β1-integrin and its signaling pathways encompassing Src and focal adhesion kinase (FAK), by regulating cells' proliferative behavior, can dictate tumor fate, and inhibition of the β1-integrin-FAK signaling axis may retain cancer cells in a dormant state. As outlined later, Src activation and FAK phosphorylation fall under the regulation of stress-mediated neuroendocrine activation of β_2-adrenoreceptors with increased neural activation augmenting FAK phosphorylation, emphasizing the striking network of mechanistic relationships existing between tumor dormancy and neuroendocrine regulation.

Additionally, the microenvironment may dictate the transition from dormancy to active proliferation through the miscellaneous actions of MMPs, a family of proteases with extracellular matrix (ECM) degrading properties that are mainly secreted by stromal cells such as vascular endothelial cells, pericytes, fibroblasts, macrophages, and other inflammatory cells [37]. In addition to their actions on the ECM, MMPs proteolytically cleave several non-matrix substrates including precursors of biologically active fragments [38]. For example MMP-9, by cleaving the heparin-binding domains of $VEGF_{165}$ and $VEGF_{121}$, enhances the bioavailability of these factors in the tumor microenvironment thus potentially intensifying the chances to activate the angiogenic switch necessary for the shift of dormant tumors to an active state [37]. MMPs may also cause the release from the ECM of angiostatic factors such as endostatin [39] and angiostatin [40] further adding to the complexity of the system. As noted earlier, MMPs are produced by several microenvironment components including tumor-associated macrophages (TAMs). Besides the production of MMPs, TAMs support tumorigenesis through plentiful actions directed to several cells that populate the tumor microenvironment resulting in the promotion of tumor angiogenesis, cancer cell survival, proliferation and invasion, and suppression of adaptive immune responses. A recent investigation [41] demonstrated that the extent of TAM infiltration and expression of pro-metastatic genes such as *Mmp9*, *Vegf*, *Cox2*, and *Tgfb* falls under the control of stress-associated SNS activation. In the same study, TAMs were shown to mediate tumor cell metastatic seeding and colonization [41].

3.4 Mechanisms of cancer dormancy

Folkman and colleagues [42–44] identified the switch from a phenotype unable to recruit new vasculature to an angiogenic phenotype as one of the principal molecular regulators of escape from tumor dormancy. Angiogenic proteins (e.g., VEGF, basic fibroblast growth factor), as well as angiogenesis-related proteins (e.g., ras, c-Myc, and p53), are involved in the process [45]. Additional "niche" mechanisms of dormancy may also exist. For example, an Italian study [46] posits that the microenvironment crosstalk between tumor and vascular endothelial cells, through Notch-Dll4 interactions and activation of the NF-κB pathway, deliver survival signals that trigger the escape of leukemia and colorectal cancer cells from dormancy. This investigation supports the existence of a vascular niche that embeds dormant cancer cells and elicits tumor-promoting activities [47]. Bidirectional signaling with the niches they inhabit may determine the fate of dormant cells, stressing the importance of microenvironmental control over the release of tumor cells from dormancy. Using an artificial liver metastasis model [48], Guba proposed that the presence of a primary tumor might halt the metastatic progression of solitary disseminated tumor cells by forcing them to enter into a state of dormancy at an early stage, before angiogenesis takes control and causes them to advance to macroscopic lesions.

Several studies highlighted a role for p53 in tumor dormancy through the modulation of angiogenesis. Holmgren et al. [49] showed that p53 gene therapy altered the angiogenic potential of a tumor and induced a state of dormancy in a mouse fibrosarcoma model, independent of p53's direct effects on cell cycle and apoptosis. The MAP kinase p38 is a stress-activated kinase involved in tumor cell dormancy; in a recent study [50], p53 transcriptional regulation was found to be important for p-38-induced cellular quiescence.

"Oncogene addiction" refers to the dependency of specific activated or overexpressed oncogenes for the maintenance of cancer cells' malignant phenotype [51]. Fluctuations in oncogene expression have been implicated in tumor dormancy. The ErbB2 (Her2) receptor is involved in the induction of several cancers and its upregulation correlates with poor prognosis in breast cancer patients [52]. Conditional activation of the ErbB2 rat homologue NEU in transgenic mice induces the development of invasive mammary adenocarcinoma while its downregulation causes the disappearance of all primary and secondary tumors [53], showing cancer cells' dependency on the continued expression of the oncogene. However, after regression of the tumors following abrogation of NEU expression, most of the animals harbored residual cancer cells that ultimately generated NEU-independent tumors [53]. Ursini-Siegel et al. argued that these recurrent tumors may derive from the reactivation of dormant tumor cells within the

primary tumor [52] that may have become sensitive to a different addictive pathway than NEU [54].

In a conditional transgenic mice model, the inactivation of the oncogene MYC caused liver tumor regression, tumor cell differentiation, and reversion to a dormant state [55]. Hepatocellular carcinoma cells were induced to differentiate into liver cells, causing tumor cell proliferation to arrest while retaining latent tumorigenic potential upon MYC reactivation. These findings support the existence of a link between tumor dormancy and epigenetic reprogramming associated with tumor cell differentiation and suggest that dormancy may involve differentiation of the transformed cells rather than only mere proliferation arrest. Shachaf and Felsher [56] proposed that MYC inactivation in hepatocellular carcinoma cells and their subsequent differentiation uncovers stem cell properties in liver tumor cells due to their ability to reemerge from dormancy and regain neoplastic proprieties upon MYC reactivation. Pontier and Muller postulated that single dormant cells may be derived from migrating cancer stem cells and that migration outside their niche requires integrin involvement, particularly $\alpha5\beta1$ integrin heterodimer formation [57]. The extracellular matrix may in fact dictate the fate of incipient dormant cancer cells by regulating the switch from quiescence to proliferation. Barkan et al. showed that the transition from dormancy to proliferation involved fibronectin-driven cytoskeletal architecture reorganization and actin stress fiber formation through the engagement of integrin $\beta1$ [33]. Furthermore, enrichment in type I collagen and the associated fibrosis induction may provide a fertile soil for the switch from dormancy to active proliferation [34]. The functional role of integrins and fibronectin in the regulation of tumor dormancy was previously highlighted through pioneering studies of Aguirre-Ghiso [58]. These investigations demonstrated that high levels of uPAR/$\alpha5\beta1$-integrin association, through fibronectin production, p38 activity suppression, and subsequent imbalance between ERK and p38, triggered head and neck carcinoma cells to escape from dormancy. Subsequent studies [59] identified a pivotal role for the transcription factor ATF6α as a survival element allowing dormant cancer cells to endure adverse microenvironmental conditions and nutritional or chemotherapy-induced stress, hence identifying the ATF6α–Rheb–mTOR axis as a determinant for the survival of dormant tumor cells [59].

The debate about the validity of the notion of host immunosurveillance has recently led to the concept of immunoediting, which recognizes that the immune system contributes to both impeding and aiding tumor progression through its immunogenic-sculpting actions [60]. The equilibrium phase of the cancer immunoediting process, during which host immunity is credited with restraining the outgrowth of occult cancer cells, corresponds to the tumor dormancy phase, while inhibition of T cell-mediated immunity may contribute to escape from dormancy. Koebel et al. showed that adaptive T cell immunity, through cytostatic and cytolytic actions, holds highly immunogenic tumor cells in a dormant phase of dynamic equilibrium in mouse models of sarcoma [61]. Targeted adaptive immunosuppression, however, can break down this equipoise state causing the edited, immunogenic-attenuated tumor cells to expand and grow [61]. In a transgenic melanoma mouse model, $CD8^+$ T cells were required for maintenance of the dormancy status of early disseminated tumor cells in visceral organs [27]. Furthermore, Zhang et al. demonstrated that adoptive $CD8^+$ T cell transfer is able to establish a stationary phase of equilibrium between host and cancer cells [62]. This induction of dormancy may be the result of effector T cell-mediated destruction of stromal myeloid-derived suppressor cells with subsequent reversion of the pro-angiogenic, inflammatory, and immunosuppressive phenotype. Kraman et al. found that deletion of a subpopulation of stromal cells expressing fibroblast activation protein-α caused immunogenic tumors to arrest growth and enter a dormant state by allowing host immunological control of tumor growth [63]. TNF-α and IFN-γ-induced hypoxic necrosis of both cancer and stromal cells was involved in the process.

4 Neuroendocrine regulation of molecular pathways involved in tumor dormancy

4.1 Neuroendocrine regulation of the adaptive stress response

Neuroendocrine and autonomic functional responses represent the essential components of the body's adaptive mechanisms to restore homeostasis after environmental and psychosocial challenges. As an integral component of the hormonal response to threatening stimuli, HPA axis activation is molecularly triggered by the release of corticotrophin-releasing hormone, along with arginin vasopressin; both of which, in turn, stimulate the release of adrenocorticotropin from the anterior pituitary gland. The final output of the system is mediated by the subsequent production of glucocorticoids [2, 3]. The sympathetic division of the autonomic nervous system (sympathetic nervous system), together with the adrenal medulla, elicits the production of epinephrine and norepinephrine, signaling physiological adaptive changes to a threatening situation [2, 3]. Both the HPA axis and the SNS have been shown to modulate tumor growth and dissemination [2, 64] and many of the specific molecular mechanisms involved in these dynamics are also hypothesized to modulate tumor dormancy.

4.2 Neuroendocrine regulation of crosstalk between the tumor cell and its microenvironment

Neuroendocrine dynamics can affect angiogenic, inflammatory, and invasion pathways crucial for tumor development

and progression. Norepinephrine and epinephrine can stimulate angiogenesis through the activation of STAT-3 [65] and by upregulating the expression of angiogenic factors such as VEGF, IL-6, and IL-8 [5–8]. Complementary findings have been documented in the clinical setting. In particular, increased amounts of norepinephrine were detected in the tumor microenvironment [65, 66] of ovarian cancer patients reporting higher levels of chronic stress and lower social support, while higher levels of VEGF were observed in plasma [67] and in tumor tissues [68]. Additionally, in an orthotopic mouse model of ovarian carcinoma [4], chronic stress upregulated tumor cell expression of VEGF, subsequently increasing vascularization and aggravating tumor burden. These effects were mediated through SNS activation and β_2 adrenergic receptor signaling. β-adrenergic receptor activation of the cyclic 3′,5′-adenosine monophosphate/protein kinase A (cAMP/PKA) may regulate gene expression via phosphorylation of multiple transcription factors and, under selected circumstances, PKA can cross-regulate the activity of the pro-inflammatory NF-κB [64, 66]. *Implications for dormancy:* Given the key role of angiogenesis in dormancy (reviewed above), SNS-mediated β-adrenergic signaling represents one major molecular pathway by which the nervous system could regulate tumor dormancy dynamics.

Neuroendocrine mediators also play a role in cellular DNA repair mechanisms by impairing the ability to correct genetic damage following stress or radiation [11, 69], altering the regulation of apoptosis mechanisms and even favoring mutagenesis through reactive oxygen species-derived damage [70]. A recent study [71] showed that catecholamine engagement of β_2-adrenoreceptors, via β-arrestin signaling, triggers DNA damage and promotes p53 degradation, leading to compromised genome maintenance and suggesting that stress pathways might potentially affect cancer initiation. Feng et al. showed that chronic stress, through glucocorticoid signaling, decreased p53 function and promoted the growth of xenograft tumors in a mouse model of colorectal cancer [72]. *Implications for dormancy:* Given the key role of p53 in the induction of tumor dormancy [49], HPA axis-induced p53 degradation constitutes another potential pathway by which endocrine dynamics might modulate tumor dormancy.

Growth factor signaling is also subject to regulation by the neural and endocrine systems. Shi et al. showed that the β_2-adrenergic receptor and ErbB2 are part of a positive feedback loop in human breast cancer cells [73]. Chronic catecholamine stimulation induces β_2-adrenoreceptor-mediated overexpression of ErbB2, triggering strong mitogenic effects; in turn, ErbB2 upregulation induces autocrine epinephrine release and upregulation of β_2-adrenergic receptor [73]. Furthermore, ErbB2 overexpression activated a transcriptional pro-inflammatory profile, involving IL-6 and STAT3, required for ErbB-mediated tumorigenesis *in vitro*, as well as in an *in vivo* mouse model of ErbB overexpression [74]. *Implications for dormancy:* Given the key role of ErbB2 in tumor dormancy [52], β-adrenergic regulation of this key growth control pathway represents yet another molecular mechanism by which the SNS might modulate tumor dormancy.

Anoikis represents a form of apoptosis induced by inappropriate cell–cell and/or cell–matrix interactions; its circumvention enhances the metastatic potential of malignant cells [75]. Sood and colleagues demonstrated that ovarian cancer cells *in vitro* and in an *in vivo* orthotopic mouse model are protected from anoikis following exposure to epinephrine or norepinephrine [76]. This effect is mediated by FAK through involvement of β_2-adrenoreceptors and subsequent Src activation and FAK phosphorylation. Importantly, these results mirrored clinical data from ovarian cancer patients showing positive associations between norepinephrine, increased FAK activation, and accelerated cancer mortality [76]. *Implications for dormancy:* Given the key role of FAK in tumor dormancy [32–34], β-adrenergic regulation of FAK and related cell survival processes represents an additional molecular mechanism by which the SNS might modulate tumor dormancy.

MMPs are modulators of the tumor microenvironment and represent key players in the molecular communication between tumor and stroma. Norepinephrine and epinephrine modulate cell migration and invasion by stimulating the production of MMPs-2 and -9 in ovarian [9] and nasopharyngeal carcinoma cancer cells [6] through involvement of β-adrenergic receptors. In ovarian cancer patients chronic stress, high levels of depression and low social support correlated with elevated MMP-9 expression in tumor-associated macrophages [68]. *Implications for dormancy:* Given the key role of MMP-2 and -9 in tumor dormancy [77, 78], β-adrenergic regulation of MMP expression represents yet another molecular mechanism by which the SNS might modulate tumor dormancy.

Tumor dormancy may result from T cell response to the tumor mass, and T cell inhibition may tip the balance towards tumor mass escape from dormancy [79]. Neuroendocrine stress responses may promote tumor growth by impairing immune cell function. Stress-signaling pathways mediate an increase in circulating IL-6 and VEGF [5–7] and both VEGF and IL-6 reduce T cell number and activity [80, 81]. Additionally, stress-mediated dynamics may directly inhibit cytotoxic T lymphocyte and natural killer cell responses [82, 83]. *Implications for dormancy:* To the extent that tumor dormancy depends on the ability of the immune system to control tumor cells [60, 61, 84], neural and endocrine regulation of antitumor cellular immune responses represents yet another molecular mechanism by which the neuroendocrine system might modulate tumor dormancy.

5 Future directions

Converging evidence from *in vitro*, *in vivo*, and clinical studies strongly point out a role for stress-mediated neuroendocrine regulation of several molecular pathways whose dysregulation is also cardinal for the fate of dormant tumors. At the moment, these observations exist in two separate bodies of literature within cancer research: one connecting neuroendocrine dynamics to cancer molecular mechanisms and a separate literature connecting those molecular mechanisms to tumor dormancy. These literatures could be integrated to include analyses of tumor dormancy dynamics in the context of experimental models of neural and endocrine regulation of tumor biology.

We suggest that the time is right to initiate a defined research agenda to explore both cellular and tumor mass dormancy dynamics and neuroendocrine influences on cancer progression in novel preclinical laboratory models, using new and improved *in vivo* paradigms. This research agenda may be initiated in the context of diseases, such as breast cancer, in which dormancy dynamics are relatively common and of substantial clinical significance in determining long-term health outcomes. Breast cancer might also be a particularly appealing model because previous research provides both observational clinical studies and preclinical experimental studies supporting a significant role of neuroendocrine dynamics modulating overall disease progression and dormancy-relevant molecular dynamics.

In a breast cancer mouse model, Sloan et al. [41] showed that stress-induced neuroendocrine activation of β-adrenergic signaling caused macrophage recruitment and a pro-metastatic gene expression signature indicative of M2 differentiation (associated with immunoregulatory, tissue remodeling, and tumor-promoting properties [85]). These results, in consort with other studies showing that stress-induced increase in tumor VEGF and angiogenesis was halted by the β-blocker propanolol [4–6], suggest that novel and promising experimental strategies to prevent cancer recurrence might leverage the use of β-blockers, inexpensive and well-understood drugs with minimal and easily managed side effects. Breast cancer would be particularly suitable to this purpose because of its late recurrence and the presence of noninvasive or low-grade cancers that may remain dormant for a long time. Two recent observational studies investigated the effects of β-blockers on breast cancer progression and mortality [86, 87]. Both reports concluded that β-blocker use was associated with reduction in metastasis development and tumor recurrence and improved survival. β-blocker treatment may inhibit signaling pathways important for tumor cell escape from dormancy, thus reducing cancer recurrence and mortality; hence, pharmacologic control of neuroendocrine activity may represent a useful adjuvant to traditional therapy.

A growing body of research is revealing the influences of stress-mediated neuroendocrine mediators on cancer progression and recurrence, while a similarly expanding body of literature investigating the molecular underpinnings of tumor dormancy is rapidly emerging. As we began to uncover the molecular mechanisms that cause tumor escape from dormancy, the general physiologic processes that promote the activation of those mechanisms remain unclear. We propose that stress and other psychological and social conditions represent contributing factors via their modulation of the neural and endocrine system. This framework challenges us with integrating the connections into a comprehensive cancer care setting that would allow manipulation and control of systemic neural and endocrine influences in order to maximally inhibit cancer progression and disease recurrence.

6 Concluding remarks

Due to his outspoken support in favor of social reforms and advancements in public health to improve economic and social conditions during the nineteenth century, Rudolf Virchow is considered the Father of Social Medicine. With his theory tracing social influences on the origin of diseases, and the identification of inflammation as a predisposing factor for tumorigenesis, Virchow pioneered a paradigm shift in mechanistic insights in the etiopathology of illnesses. By embracing his view of "disease" as "an expression of individual life under unfavorable circumstances," we begin to disentangle the dynamics connecting social conditions with the recurrence of cancer through the biological underpinning of tumor dormancy.

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

References

1. Aguirre-Ghiso, J. A. (2007). Models, mechanisms and clinical evidence for cancer dormancy. *Nature Reviews. Cancer, 7*(11), 834–846. doi:10.1038/nrc2256.
2. Antoni, M. H., Lutgendorf, S. K., Cole, S. W., Dhabhar, F. S., Sephton, S. E., McDonald, P. G., et al. (2006). The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nature Reviews. Cancer, 6*(3), 240–248. doi:10.1038/nrc1820.

3. Irwin, M. R., & Cole, S. W. (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology, 11*(9), 625–632. doi:10.1038/nri3042.
4. Thaker, P. H., Han, L. Y., Kamat, A. A., Arevalo, J. M., Takahashi, R., Lu, C., et al. (2006). Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Medicine, 12*(8), 939–944. doi:10.1038/nm1447.
5. Lutgendorf, S. K., Cole, S., Costanzo, E., Bradley, S., Coffin, J., Jabbari, S., et al. (2003). Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. *Clinical Cancer Research, 9*(12), 4514–4521.
6. Yang, E. V., Sood, A. K., Chen, M., Li, Y., Eubank, T. D., Marsh, C. B., et al. (2006). Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Research, 66*(21), 10357–10364. doi:10.1158/0008-5472.CAN-06-2496.
7. Nilsson, M. B., Armaiz-Pena, G., Takahashi, R., Lin, Y. G., Trevino, J., Li, Y., et al. (2007). Stress hormones regulate interleukin-6 expression by human ovarian carcinoma cells through a Src-dependent mechanism. *Journal of Biological Chemistry, 282*(41), 29919–29926. doi:10.1074/jbc.M611539200.
8. Shahzad, M. M., Arevalo, J. M., Armaiz-Pena, G. N., Lu, C., Stone, R. L., Moreno-Smith, M., et al. (2010). Stress effects on FosB- and interleukin-8 (IL8)-driven ovarian cancer growth and metastasis. *Journal of Biological Chemistry, 285*(46), 35462–35470. doi:10.1074/jbc.M110.109579.
9. Sood, A. K., Bhatty, R., Kamat, A. A., Landen, C. N., Han, L., Thaker, P. H., et al. (2006). Stress hormone-mediated invasion of ovarian cancer cells. *Clinical Cancer Research, 12*(2), 369–375. doi:10.1158/1078-0432.CCR-05-1698.
10. Fang, C. Y., Miller, S. M., Bovbjerg, D. H., Bergman, C., Edelson, M. I., Rosenblum, N. G., et al. (2008). Perceived stress is associated with impaired T-cell response to HPV16 in women with cervical dysplasia. *Annals of Behavioral Medicine, 35*(1), 87–96. doi:10.1007/s12160-007-9007-6.
11. Yang, E. V., & Glaser, R. (2003). Stress-induced immunomodulation: implications for tumorigenesis. *Brain, Behavior, and Immunity, 17* (Suppl 1), S37–S40.
12. Black, P. H. (2002). Stress and the inflammatory response: a review of neurogenic inflammation. *Brain, Behavior, and Immunity, 16*(6), 622–653.
13. Garcia-Bueno, B., Caso, J. R., & Leza, J. C. (2008). Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. *Neuroscience and Biobehavioral Reviews, 32*(6), 1136–1151. doi:10.1016/j.neubiorev.2008.04.001.
14. Black, W. C., & Welch, H. G. (1993). Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *The New England Journal of Medicine, 328*(17), 1237–1243. doi:10.1056/NEJM199304293281706.
15. Nielsen, M., Thomsen, J. L., Primdahl, S., Dyreborg, U., & Andersen, J. A. (1987). Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *British Journal of Cancer, 56*(6), 814–819.
16. Harach, H. R., Franssila, K. O., & Wasenius, V. M. (1985). Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer, 56*(3), 531–538.
17. Montie, J. E., Wood, D. P., Jr., Pontes, J. E., Boyett, J. M., & Levin, H. S. (1989). Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *Cancer, 63*(2), 381–385.
18. Kimura, W., Morikane, K., Esaki, Y., Chan, W. C., & Pour, P. M. (1998). Histologic and biologic patterns of microscopic pancreatic ductal adenocarcinomas detected incidentally at autopsy. *Cancer, 82*(10), 1839–1849. doi:10.1002/(SICI)1097-0142.
19. Folkman, J., & Kalluri, R. (2004). Cancer without disease. *Nature, 427*(6977), 787. doi:10.1038/427787a.
20. Pantel, K., Alix-Panabieres, C., & Riethdorf, S. (2009). Cancer micrometastases. *Nature Reviews. Clinical Oncology, 6*(6), 339–351. doi:10.1038/nrclinonc.2009.44.
21. Braun, S., Vogl, F. D., Naume, B., Janni, W., Osborne, M. P., Coombes, R. C., et al. (2005). A pooled analysis of bone marrow micrometastasis in breast cancer. *The New England Journal of Medicine, 353*(8), 793–802. doi:10.1056/NEJMoa050434.
22. Janni, W. J., Vogl, F. D., Wiedswang, G., Synnestvedt, M., Fehm, T. N., Jueckstock, J., et al. (2011). Persistence of disseminated tumor cells in the bone marrow of breast cancer patients predicts increased risk for relapse—a European pooled analysis. *Clinical Cancer Research*. doi:10.1158/1078-0432.CCR-10-2515.
23. Rahbari, N. N., Aigner, M., Thorlund, K., Mollberg, N., Motschall, E., Jensen, K., et al. (2010). Meta-analysis shows that detection of circulating tumor cells indicates poor prognosis in patients with colorectal cancer. *Gastroenterology, 138*(5), 1714–1726. doi:10.1053/j.gastro.2010.01.008.
24. Mocellin, S., Hoon, D., Ambrosi, A., Nitti, D., & Rossi, C. R. (2006). The prognostic value of circulating tumor cells in patients with melanoma: a systematic review and meta-analysis. *Clinical Cancer Research, 12*(15), 4605–4613. doi:10.1158/1078-0432.CCR-06-0823.
25. Meng, S., Tripathy, D., Frenkel, E. P., Shete, S., Naftalis, E. Z., Huth, J. F., et al. (2004). Circulating tumor cells in patients with breast cancer dormancy. *Clinical Cancer Research, 10*(24), 8152–8162. doi:10.1158/1078-0432.CCR-04-1110.
26. Klein, C. A. (2009). Parallel progression of primary tumours and metastases. *Nature Reviews. Cancer, 9*(4), 302–312. doi:10.1038/nrc2627.
27. Eyles, J., Puaux, A. L., Wang, X., Toh, B., Prakash, C., Hong, M., et al. (2010). Tumor cells disseminate early, but immunosurveillance limits metastatic outgrowth, in a mouse model of melanoma. *The Journal of Clinical Investigation, 120*(6), 2030–2039. doi:10.1172/JCI42002.
28. Potter, J. D. (2007). Morphogens, morphostats, microarchitecture and malignancy. *Nature Reviews. Cancer, 7*(6), 464–474. doi:10.1038/nrc2146.
29. Weaver, V. M., Petersen, O. W., Wang, F., Larabell, C. A., Briand, P., Damsky, C., et al. (1997). Reversion of the malignant phenotype of human breast cells in three-dimensional culture and *in vivo* by integrin blocking antibodies. *The Journal of Cell Biology, 137*(1), 231–245.
30. Soto, A. M., & Sonnenschein, C. (2004). The somatic mutation theory of cancer: growing problems with the paradigm? *Bioessays, 26*(10), 1097–1107. doi:10.1002/bies.20087.
31. Aguirre Ghiso, J. A., Kovalski, K., & Ossowski, L. (1999). Tumor dormancy induced by downregulation of urokinase receptor in human carcinoma involves integrin and MAPK signaling. *The Journal of Cell Biology, 147*(1), 89–104.
32. Aguirre Ghiso, J. A. (2002). Inhibition of FAK signaling activated by urokinase receptor induces dormancy in human carcinoma cells *in vivo*. *Oncogene, 21*(16), 2513–2524. doi:10.1038/sj.onc.1205342.
33. Barkan, D., Kleinman, H., Simmons, J. L., Asmussen, H., Kamaraju, A. K., Hoenorhoff, M. J., et al. (2008). Inhibition of metastatic outgrowth from single dormant tumor cells by targeting the cytoskeleton. *Cancer Research, 68*(15), 6241–6250. doi:10.1158/0008-5472.CAN-07-6849.
34. Barkan, D., El Touny, L. H., Michalowski, A. M., Smith, J. A., Chu, I., Davis, A. S., et al. (2010). Metastatic growth from dormant cells induced by a col-I-enriched fibrotic environment. *Cancer Research, 70*(14), 5706–5716. doi:10.1158/0008-5472.CAN-09-2356.
35. Shibue, T., & Weinberg, R. A. (2009). Integrin beta1-focal adhesion kinase signaling directs the proliferation of metastatic cancer cells disseminated in the lungs. *Proceedings of the National Academy of*

Sciences of the United States of America, 106(25), 10290–10295. doi:10.1073/pnas.0904227106.
36. White, D. E., Kurpios, N. A., Zuo, D., Hassell, J. A., Blaess, S., Mueller, U., et al. (2004). Targeted disruption of beta1-integrin in a transgenic mouse model of human breast cancer reveals an essential role in mammary tumor induction. *Cancer Cell, 6*(2), 159–170. doi:10.1016/j.ccr.2004.06.025.
37. Jodele, S., Blavier, L., Yoon, J. M., & DeClerck, Y. A. (2006). Modifying the soil to affect the seed: role of stromal-derived matrix metalloproteinases in cancer progression. *Cancer Metastasis Reviews, 25*(1), 35–43. doi:10.1007/s10555-006-7887-8.
38. McCawley, L. J., & Matrisian, L. M. (2001). Matrix metalloproteinases: they're not just for matrix anymore! *Current Opinion in Cell Biology, 13*(5), 534–540.
39. Heljasvaara, R., Nyberg, P., Luostarinen, J., Parikka, M., Heikkila, P., Rehn, M., et al. (2005). Generation of biologically active endostatin fragments from human collagen XVIII by distinct matrix metalloproteases. *Experimental Cell Research, 307*(2), 292–304. doi:10.1016/j.yexcr.2005.03.021.
40. Pozzi, A., Moberg, P. E., Miles, L. A., Wagner, S., Soloway, P., & Gardner, H. A. (2000). Elevated matrix metalloprotease and angiostatin levels in integrin alpha 1 knockout mice cause reduced tumor vascularization. *Proceedings of the National Academy of Sciences of the United States of America, 97*(5), 2202–2207. doi:10.1073/pnas.040378497.
41. Sloan, E. K., Priceman, S. J., Cox, B. F., Yu, S., Pimentel, M. A., Tangkanangnukul, V., et al. (2010). The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Research, 70*(18), 7042–7052. doi:10.1158/0008-5472.CAN-10-0522.
42. Udagawa, T., Fernandez, A., Achilles, E. G., Folkman, J., & D'Amato, R. J. (2002). Persistence of microscopic human cancers in mice: alterations in the angiogenic balance accompanies loss of tumor dormancy. *The FASEB Journal, 16*(11), 1361–1370. doi:10.1096/fj.01-0813com.
43. Naumov, G. N., Folkman, J., & Straume, O. (2009). Tumor dormancy due to failure of angiogenesis: role of the microenvironment. *Clinical & Experimental Metastasis, 26*(1), 51–60. doi:10.1007/s10585-008-9176-0.
44. Naumov, G. N., Akslen, L. A., & Folkman, J. (2006). Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. *Cell Cycle, 5*(16), 1779–1787.
45. Naumov, G. N., Folkman, J., Straume, O., & Akslen, L. A. (2008). Tumor-vascular interactions and tumor dormancy. *APMIS, 116*(7–8), 569–585. doi:10.1111/j.1600-0463.2008.01213.x.
46. Indraccolo, S., Minuzzo, S., Masiero, M., Pusceddu, I., Persano, L., Moserle, L., et al. (2009). Cross-talk between tumor and endothelial cells involving the Notch3-Dll4 interaction marks escape from tumor dormancy. *Cancer Research, 69*(4), 1314–1323. doi:10.1158/0008-5472.CAN-08-2791.
47. Favaro, E., Amadori, A., & Indraccolo, S. (2008). Cellular interactions in the vascular niche: implications in the regulation of tumor dormancy. *APMIS, 116*(7–8), 648–659. doi:10.1111/j.1600-0463.2008.01025.x.
48. Guba, M., Cernaianu, G., Koehl, G., Geissler, E. K., Jauch, K. W., Anthuber, M., et al. (2001). A primary tumor promotes dormancy of solitary tumor cells before inhibiting angiogenesis. *Cancer Research, 61*(14), 5575–5579.
49. Holmgren, L., Jackson, G., & Arbiser, J. (1998). p53 induces angiogenesis-restricted dormancy in a mouse fibrosarcoma. *Oncogene, 17*(7), 819–824. doi:10.1038/sj.onc.1201993.
50. Adam, A. P., George, A., Schewe, D., Bragado, P., Iglesias, B. V., Ranganathan, A. C., et al. (2009). Computational identification of a p38SAPK-regulated transcription factor network required for tumor cell quiescence. *Cancer Research, 69*(14), 5664–5672. doi:10.1158/0008-5472.can-08-3820.
51. Weinstein, I. B. (2002). Cancer. Addiction to oncogenes—the Achilles heal of cancer. *Science, 297*(5578), 63–64. doi:10.1126/science.1073096.
52. Ursini-Siegel, J., Schade, B., Cardiff, R. D., & Muller, W. J. (2007). Insights from transgenic mouse models of ERBB2-induced breast cancer. *Nature Reviews. Cancer, 7*(5), 389–397. doi:10.1038/nrc2127.
53. Moody, S. E., Sarkisian, C. J., Hahn, K. T., Gunther, E. J., Pickup, S., Dugan, K. D., et al. (2002). Conditional activation of Neu in the mammary epithelium of transgenic mice results in reversible pulmonary metastasis. *Cancer Cell, 2*(6), 451–461.
54. Campone, M., Juin, P., Andre, F., & Bachelot, T. (2011). Resistance to HER2 inhibitors: is addition better than substitution? rationale for the hypothetical concept of drug sedimentation. *Critical Reviews in Oncology/Hematology, 78*(3), 195–205. doi:10.1016/j.critrevonc.2010.04.012.
55. Shachaf, C. M., Kopelman, A. M., Arvanitis, C., Karlsson, A., Beer, S., Mandl, S., et al. (2004). MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature, 431*(7012), 1112–1117. doi:10.1038/nature03043.
56. Shachaf, C. M., & Felsher, D. W. (2005). Tumor dormancy and MYC inactivation: pushing cancer to the brink of normalcy. *Cancer Research, 65*(11), 4471–4474. doi:10.1158/0008-5472.CAN-05-1172.
57. Pontier, S. M., & Muller, W. J. (2008). Integrins in breast cancer dormancy. *APMIS, 116*(7–8), 677–684. doi:10.1111/j.1600-0463.2008.01026.x.
58. Aguirre-Ghiso, J. A., Liu, D., Mignatti, A., Kovalski, K., & Ossowski, L. (2001). Urokinase receptor and fibronectin regulate the ERK(MAPK) to p38(MAPK) activity ratios that determine carcinoma cell proliferation or dormancy *in vivo*. *Molecular Biology of the Cell, 12*(4), 863–879.
59. Schewe, D. M., & Aguirre-Ghiso, J. A. (2008). ATF6alpha-Rheb-mTOR signaling promotes survival of dormant tumor cells *in vivo*. *Proceedings of the National Academy of Sciences of the United States of America, 105*(30), 10519–10524. doi:10.1073/pnas.0800939105.
60. Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J., & Schreiber, R. D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nature Immunology, 3*(11), 991–998. doi:10.1038/ni1102-991.
61. Koebel, C. M., Vermi, W., Swann, J. B., Zerafa, N., Rodig, S. J., Old, L. J., et al. (2007). Adaptive immunity maintains occult cancer in an equilibrium state. *Nature, 450*(7171), 903–907. doi:10.1038/nature06309.
62. Zhang, B., Zhang, Y., Bowerman, N. A., Schietinger, A., Fu, Y. X., Kranz, D. M., et al. (2008). Equilibrium between host and cancer caused by effector T cells killing tumor stroma. *Cancer Research, 68*(5), 1563–1571. doi:10.1158/0008-5472.CAN-07-5324.
63. Kraman, M., Bambrough, P. J., Arnold, J. N., Roberts, E. W., Magiera, L., Jones, J. O., et al. (2010). Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. *Science, 330*(6005), 827–830. doi:10.1126/science.1195300.
64. Cole, S. W., & Sood, A. K. (2012). Molecular pathways: beta-adrenergic signaling in cancer. *Clinical Cancer Research, 18*(5), 1201–1206. doi:10.1158/1078-0432.ccr-11-0641.
65. Lutgendorf, S. K., DeGeest, K., Dahmoush, L., Farley, D., Penedo, F., Bender, D., et al. (2011). Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. *Brain, Behavior, and Immunity, 25*(2), 250–255. doi:10.1016/j.bbi.2010.10.012.
66. Lutgendorf, S. K., DeGeest, K., Sung, C. Y., Arevalo, J. M., Penedo, F., Lucci, J., 3rd, et al. (2009). Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. *Brain, Behavior, and Immunity, 23*(2), 176–183. doi:10.1016/j.bbi.2008.04.155.

67. Lutgendorf, S. K., Johnsen, E. L., Cooper, B., Anderson, B., Sorosky, J. I., Buller, R. E., et al. (2002). Vascular endothelial growth factor and social support in patients with ovarian carcinoma. *Cancer, 95*(4), 808–815. doi:10.1002/cncr.10739.
68. Lutgendorf, S. K., Lamkin, D. M., Jennings, N. B., Arevalo, J. M., Penedo, F., DeGeest, K., et al. (2008). Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. *Clinical Cancer Research, 14*(21), 6839–6846. doi:10.1158/1078-0432.ccr-08-0230.
69. Kiecolt-Glaser, J. K., Stephens, R. E., Lipetz, P. D., Speicher, C. E., & Glaser, R. (1985). Distress and DNA repair in human lymphocytes. *Journal of Behavioral Medicine, 8*(4), 311–320.
70. Flint, M. S., Baum, A., Chambers, W. H., & Jenkins, F. J. (2007). Induction of DNA damage, alteration of DNA repair and transcriptional activation by stress hormones. *Psychoneuroendocrinology, 32*(5), 470–479. doi:10.1016/j.psyneuen.2007.02.013.
71. Hara, M. R., Kovacs, J. J., Whalen, E. J., Rajagopal, S., Strachan, R. T., Grant, W., et al. (2011). A stress response pathway regulates DNA damage through beta2-adrenoreceptors and beta-arrestin-1. *Nature, 477*(7364), 349–353. doi:10.1038/nature10368.
72. Feng, Z., Liu, L., Zhang, C., Zheng, T., Wang, J., Lin, M., et al. (2012). Chronic restraint stress attenuates p53 function and promotes tumorigenesis. *Proceedings of the National Academy of Sciences of the United States of America, 109*(18), 7013–7018. doi:10.1073/pnas.1203930109.
73. Shi, M., Liu, D., Duan, H., Qian, L., Wang, L., Niu, L., et al. (2011). The beta2-adrenergic receptor and Her2 comprise a positive feedback loop in human breast cancer cells. *Breast Cancer Research and Treatment, 125*(2), 351–362. doi:10.1007/s10549-010-0822-2.
74. Hartman, Z. C., Yang, X. Y., Glass, O., Lei, G., Osada, T., Dave, S. S., et al. (2011). HER2 overexpression elicits a proinflammatory IL-6 autocrine signaling loop that is critical for tumorigenesis. *Cancer Research, 71*(13), 4380–4391. doi:10.1158/0008-5472.can-11-0308.
75. Simpson, C. D., Anyiwe, K., & Schimmer, A. D. (2008). Anoikis resistance and tumor metastasis. *Cancer Letters, 272*(2), 177–185. doi:10.1016/j.canlet.2008.05.029.
76. Sood, A. K., Armaiz-Pena, G. N., Halder, J., Nick, A. M., Stone, R. L., Hu, W., et al. (2010). Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. *The Journal of Clinical Investigation, 120*(5), 1515–1523. doi:10.1172/JCI40802.
77. Katori, H., Baba, Y., Imagawa, Y., Nishimura, G., Kagesato, Y., Takagi, E., et al. (2002). Reduction of *in vivo* tumor growth by MMI-166, a selective matrix metalloproteinase inhibitor, through inhibition of tumor angiogenesis in squamous cell carcinoma cell lines of head and neck. *Cancer Letters, 178*(2), 151–159.
78. Shintani, T., Komaki, R., Itasaka, S., Isobe, T., Shibuya, K., Wu, W., et al. (2004). Clinical tumor dormancy: biology and regulation of dormant lung metastases in a characterization of the dormant tumor; B16F10 murine melanoma model. *AACR Meeting Abstracts, 2004*(1), 1139-c-1140.
79. Farrar, J. D., Katz, K. H., Windsor, J., Thrush, G., Scheuermann, R. H., Uhr, J. W., et al. (1999). Cancer dormancy. VII. A regulatory role for CD8+ T cells and IFN-gamma in establishing and maintaining the tumor-dormant state. *Journal of Immunology, 162*(5), 2842–2849.
80. Ohm, J. E., Gabrilovich, D. I., Sempowski, G. D., Kisseleva, E., Parman, K. S., Nadaf, S., et al. (2003). VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. *Blood, 101*(12), 4878–4886. doi:10.1182/blood-2002-07-1956.
81. Trikha, M., Corringham, R., Klein, B., & Rossi, J. F. (2003). Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clinical Cancer Research, 9*(13), 4653–4665.
82. Zorrilla, E. P., Luborsky, L., McKay, J. R., Rosenthal, R., Houldin, A., Tax, A., et al. (2001). The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain, Behavior, and Immunity, 15*(3), 199–226. doi:10.1006/brbi.2000.0597.
83. Cohen, M., Klein, E., Kuten, A., Fried, G., Zinder, O., & Pollack, S. (2002). Increased emotional distress in daughters of breast cancer patients is associated with decreased natural cytotoxic activity, elevated levels of stress hormones and decreased secretion of Th1 cytokines. *International Journal of Cancer, 100*(3), 347–354. doi:10.1002/ijc.10488.
84. Teng, M. W., Swann, J. B., Koebel, C. M., Schreiber, R. D., & Smyth, M. J. (2008). Immune-mediated dormancy: an equilibrium with cancer. *Journal of Leukocyte Biology, 84*(4), 988–993. doi:10.1189/jlb.1107774.
85. Biswas, S. K., & Mantovani, A. (2010). Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nature Immunology, 11*(10), 889–896. doi:10.1038/ni.1937.
86. Barron, T. I., Connolly, R. M., Sharp, L., Bennett, K., & Visvanathan, K. (2011). Beta blockers and breast cancer mortality: a population-based study. *Journal of Clinical Oncology, 29*(19), 2635–2644. doi:10.1200/jco.2010.33.5422.
87. Powe, D. G., Voss, M. J., Zanker, K. S., Habashy, H. O., Green, A. R., Ellis, I. O., et al. (2010). Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. *Oncotarget, 1*(7), 628–638.