REVIEWS

Interrelations Between Psychological Stress and Cancer - Deciphering Molecular Signals in the Tumor Microenvironment

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Abstract: Current research has revealed some links between psychological stress and cellular mutation, neoplastic proliferation and metastasis in patients with cancer. In stressful situations, the stress-related neuroendocrine mediators (e.g., catecholamines, and glucocorticoids (GSs)) are being secreted, via stimulation of the sympathetic nervous system (SNS), and the hypothalamic-pituitary-adrenocortical (HPA) axis. Catecholamine may affect the malignant progression, since they can regulate various cellular signaling pathways, via adrenergic receptors (ARs) that are expressed by different types of neoplastic cells. The ARs increase the proliferation and invasive potential of such cells, and change their “behavior” in the tumor microenvironment. Similarly, cortisol and its glucocorticoid receptors (GRs) can promote stress-induced malignant growth and metastasis. Maladaptation to stressful situations, often relevant to the cancer diagnosis and treatment, may accelerate tumor growth and spread (e.g., via inflammation, angiogenesis, and migration). Studies have shown that psychological interventions can be helpful for adaptation to adverse circumstances during the therapeutic process in patients with cancer. This mini-review will address some interrelations between psychological stress and cancer. It will discuss how the receptor-mediated signaling pathways may lead to cancer initiation, propagation, and spread. In addition, it will describe a supportive role of the stress reduction strategies, for example, in patients with breast cancer (BC).

Keywords: Psychological stress; cancer; tumor microenvironment; cytokines; inflammation; immune system; cell signaling; stress reduction

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1. Introduction

Individuals, who are under stressful circumstances (e.g., related to real or imagined demands that exceed their resources) often experience psychological stress. Many recurrent or chronic stressors represent risk factors for various civilization diseases, such as cancer, cardiovascular disease (CVD), mental disorders, and immune system dysfunctions[1]. Chronic stress (e.g., physical, mental and emotional) may affect the incidence and progression of different cancers[2]. Supportive therapies, such as psychological, behavioral, and educational approaches can bring some beneficial effects to patients with malignancies[3]. Currently, some underlying mechanisms related to the impact of psychological stress on neoplastic cells have been explored. The recent evidence suggests that the effects of psychological stress on malignant cells are predominantly mediated through the main stress-related hormones and their receptors[4]. In particular, the in-coming stressors (e.g., stressful stimuli) initially activate the paraventricu-
lar nucleus (PVN) and the suprachiasmatic nuclei (SCN) in the central nervous system (CNS) (Table 1)\(^{[3,4]}\). It should be highlighted that the effects of psychological stress on neoplastic cells are transmitted by stress-related hormones and cytokines, and their respective receptors\(^{[4,5]}\). This molecular communication stimulates the proliferative and migratory signaling pathways within the normal cells, leading to neoplastic transitions\(^{[6,7]}\). In addition, such signals can reset the molecular clock within the malignant cells (Table 1)\(^{[8,9]}\).

As a consequence, chronic stress, often associated with depression can affect the HPA axis and the SNS, contributing to abnormal functioning of the immune system\(^{[10,11]}\). It should be noted that catecholamines can influence the neoplastic progression, since they regulate several cell signaling pathways, via adrenergic receptors (ARs) that are expressed by different types of cancer cells\(^{[4,11]}\). As a consequence, the ARs augment the proliferation and invasive potential of such cells\(^{[4,11]}\). Moreover, the ARs are able to change the “behavior” of cells in the tumor microenvironment, and govern the interactions between the cancer cells and their surroundings, leading to neoplastic progression\(^{[4,11]}\).

Likewise, some other stress-induced mediators (e.g., cortisol) and their glucocorticoid receptors (GRs) can also enhance stress-related malignant growth and spread\(^{[6,7,10,11]}\). Importantly, the patient’s poor adaptation to stressful situations, relevant to cancer diagnosis and treatment, may accelerate tumor growth and spread (e.g., via inflammation, angiogenesis, and migration)\(^{[13,14]}\). Also, concurrent impairment of the immune system functions, among many patients with cancer, who experience uncontrolled stress, leads to the deterioration of physiologic anti-cancer defenses\(^{[10,12]}\). Recent studies addressing these issues have shown that psychological interventions (e.g., cognitive, behavioral, social, and stress reduction therapies) can improve adaptation during the treatment process, in patients with cancer\(^{[12-13]}\). Moreover, such supportive interventions in patients with neoplastic diseases may enhance the results of the main anti-cancer therapies, and improve the patients quality of life and disease outcomes\(^{[13,13,14]}\).

This mini-review will present some interrelations between psychological stress and cancer, for example, in women with breast cancer (BC). It will briefly address how the receptor-mediated signaling pathways can lead to cancer initiation, invasion, and spread. It will describe the impact of the response to stress on cancer development and metastasis. Also, it will discuss the mechanisms of neuroendocrine system stimulation (e.g., by psychological stress and depression) among patients with BC. In addition, this mini-review will discuss the immunosuppressive role of stress-induced mediators in the tumor microenvironment.

### Table 1. Mechanisms involved in transition from psychological stress to the malignant cell transformation, growth and spread

<table>
<thead>
<tr>
<th>Description</th>
<th>Normal Cells</th>
<th>Cancer Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased GCs &amp; catecholamine-stimulated transcription of cytokine genes</td>
<td>Normal cell response</td>
<td>Cancer cell response</td>
</tr>
<tr>
<td>Elevated levels of GCs &amp; catecholamine mediate proliferation and spread of malignant cells</td>
<td>Normal cell response</td>
<td>Cancer cell response</td>
</tr>
<tr>
<td>GCs up-regulate several TFs and beta 2-ARs in tumor cells, cause growth/survival of neoplastic cells</td>
<td>Normal cell response</td>
<td>Cancer cell response</td>
</tr>
<tr>
<td>Chronic stressors interact with central circadian rhythms (in bidirectional manner)</td>
<td>Normal cell response</td>
<td>Cancer cell response</td>
</tr>
</tbody>
</table>

Abbreviations: ARs: beta-adrenergic receptors; & and: AC/cAMP/PKA; Adenylyl cyclase/cyclic adenosine monophosphate/dependent protein kinase A; GCs: glucocorticoids; IL: interleukin; IFN: interferon; PVN: the paraventricular nucleus; Rho: the Ras homologous protein; Rac: a subfamily of the Rho family of GTPases, small signaling G proteins; GT/Pase: guanosine triphosphate hydrodrolase; Ras/Raf/MEK/ERK: extracellular signal-regulated kinase signaling pathway; MEK: mitogen-activated protein kinase kinase; PI3K/akt: phosphatidylinositol-3-kinase; SGK: serum and glucocorticoid-induced protein kinase; SCN: suprachiasmatic nuclei; SNS: sympathetic nervous system; HPA: the hypothalamic-pituitary-adrenal axis; GFs: growth factors; c-Myc: proto-oncogene; Bcl-xL: anti-apoptotic protein; cIAP2: cytosolic caspase inhibitor; TFs: transcription factors
2. Can Chronic or Psychological Stress Cause or Exacerbate Cancer?

At present, there is no clear answer to this basic question, mostly due to the methodological heterogeneity of the relevant studies. It should be pointed out that certain external or internal events or circumstances can be stressful for some individuals, but neutral for the others. Furthermore, there are some biochemical changes, which occur during the physiologic stress response, that may accelerate tumor growth\[2,4,14\]. Recently, it has been reported that stress is related to increased levels of cellular and cytokine markers, indicating that stress is linked with immune and inflammatory processes, which may lead to malignant cells proliferation and survival\[15\]. Similarly, biochemical changes that often accompany stress, can also contribute to insulin resistance and inflammation, which in turn, may alter the tumor microenvironment, so that it is more conducive to malignancy\[16\]. In addition, chronically elevated concentrations of stress hormones (e.g., cortisol) may affect the patient’s mood and mental status, causing feelings of distress, anger, fear, anxiety, and depression\[10,14\]. These negative emotions may further elevate cortisol levels, perpetuate distress, deteriorate memory and other cognitive abilities, as well as impair judgment, problem-solving and decision making capabilities that can compromise the patient’s adherence to therapy, disease outcome, and quality of life\[10,17\]. Since an uncontrolled stress can increase the possibility of malignant progression and deterioration of the patient’s outcome, strategies to cope with stress should be of utmost importance, in the comprehensive anti-cancer therapy plan.

3. Potential Avenues from Stress to Cancer Development

Numerous carcinogens lead to the DNA damage and cell mutations, but due to the protective actions of the immune system, various enzymes are stimulated to detect and repair the damaged DNA, and then, to eliminate carcinogens and abnormal cells\[18,19\]. However, if these protective mechanisms do not work correctly, the mutated DNA can increase the cancer risk\[18,19\]. For instance, the uncontrolled stress may influence carcinogenesis via changes in DNA repair and sister chromatid exchange (SCE)\[20\]. It should be underscored that there is a connection between the personality type and cancer incidence\[21\]. However, in terms of methodology, it has been very difficult to determine possible associations between stress and the regulation of cell growth, the tumor microenvironment, and the malignant spread\[22\]. Since anxiety, depression, and psychological stress do not represent major risk factors or predictors of cancer, they have been considered only in combination with some other well-established risk factors (e.g., genetic predispositions, toxic substances, oncogenic viruses, and harmful behaviors, like tobacco smoking or alcohol abuse)\[23\]. It should be noted that the HPA axis has been found to promote tumor initiation and proliferation (e.g., via its influence on apoptosis of lymphocytes, genes that protect cancer cells from chemotherapy effects, oncogenic viruses, and immune responses to the tumor)\[24,25\]. Furthermore, with regard to the interactions between stress and immune functions (e.g., in the tumor microenvironment), among patients with cancer, it has been shown that the Tumor necrosis factor alpha (TNF-alpha) (which is related to cancer regression) was reduced in women with BC, who suffered from psychosocial distress\[25\]. In addition, traumatic life experiences, depression, and some other mental disorders have been found to interfere with central circadian rhythms. The stress-induced changes in the circadian rhythms of endocrine and immune systems have also contributed to the cancer progression\[26\]. For instance, abnormal circadian rhythms were observed in women with high risk for BC, and their HPA dysfunctions were related with inadequate sleep, marital problems, and mutations in circadian clock genes\[27\].

4. Labyrinth of Connections Between Psychological Stress, Inflammation, Central Nervous System and Cancer

In response to chronic psychological stressors, the serum cortisol levels remain high, without a physiologic circadian variation. If such a biological stress-induced response continues over a long period, the endocrine and metabolic imbalances occur. In addition, chronic inflammation is a common feature of many cancers. It is often manifested as a process that promotes immune suppression\[22\]. Moreover, inflammation is mediated via the microenvironmental cytokines and growth factors that in the context of cancer mediate the paracrine signaling between the tumor cells and noncancerous stroma\[28\].

When cytokine regulation in the tumor microenvironment is disrupted, the probability of tumor progression increases and the immune system functions are often suppressed (discussed in the tumor microenvironment section). In addition, the organism’s resources for repair
are often being exhausted, paving the way to pre-cancerous conditions to develop. Moreover, elevated levels of stress hormones can accelerate malignant tumor’s proliferation and metastases.

In addition, the stress physiology can be dysregulated by excessive use of alcohol, nicotine, caffeine, and consumption of high ratio of omega-6 to omega-3 fatty acids. Similarly, eating beyond physiologic needs (e.g., non-homeostatic eating), and consuming so-called “comfort foods” (e.g., highly-processed products, high-fat, high-protein, high-glycemic index carbohydrates, and sweetened beverages) in response to chronic stressors may further aggravate the situation. As a consequence, malfunction of the organism, under constant “bombarding” by abnormal stress hormone cascades compromises the immune system functions, elevating the risk for neoplastic development.

If the response to chronic stress remains uncontrolled (e.g., over a long-term), a phase of adrenal gland exhaustion (e.g., manifested by decreased serum cortisol levels) and a decline of the body’s immune system defense takes place. Since chronic stress can enhance malignant cells growth and spread, the strategies of coping with stress should represent a high priority in the comprehensive cancer management plan.

The impact of psychological stress on the human organism includes activation of the paraventricular nucleus (PVN) and the suprachiasmatic nuclei (SCN) in the central nervous system (CNS) by in-coming stressors (e.g., overwhelming work-load, time or financial pressures, family or personal problems, emotional trauma, social isolation, and various adversities related to chronic disease diagnosis and management). These signals are subsequently transmitted via the HPA axis and SNS. They can be further augmented through the uncontrolled production of the stress-related mediators, especially when the maladaptive behaviors, often associated with stressful situations, perpetuate this vicious cycle.

The chronic or psychological stress can affect neoplastic cells via the transmission of signals through receptors (e.g., AR and GRs), and subsequent stimulation of the downstream intracellular proliferative and migratory signaling patterns, which can lead to re-arrangements of the molecular biorhythms and metabolism in cancer cells. Furthermore, the stress-induced mediators often play the immunosuppressive and the mitogenic role in the tumor microenvironment.

5. Focus on Links Between Psychological Stress and Cancer

Interestingly, some studies conducted among medical students, during their examination session have revealed that even minor stressful events are related to a temporary deterioration of the immune system performance (e.g., in terms of reduction of the interferon (IFN) production and natural killer (NK) cell activity). Conversely, some behavioral interventions can improve the immune functions, as evidenced in elderly patients, who randomly underwent a relaxation training program, social activities, or no intervention. Similarly, some other studies have reported a connection between social relationships and NK cell cytotoxicity. On the other hand, the sad mood (e.g., relevant to bereavement), and hostility (e.g., in verbal communication) have a negative impact on the NK cell activity.

Overall, it was determined that stress can alter some important defense mechanism against cancer, in terms of changing behavior of different cell types of the immune system (e.g., inflammatory macrophages, NK cells, and cytotoxic T lymphocytes (CTL)), which are present in the primary tumors and their microenvironment. Both NK cells and CTL may be regulated by stress that can enhance malignant progression through associations with major histocompatibility complex (MHC) class I expression, IFN secretion, and apoptotic proteins perforins, gran-zymes A and B, and FasL. In addition, chronic inflammation has also been related to various types of cancer (e.g., BC), in terms of the increased levels of stress-mediated acute phase proteins associated with higher BC morbidity and mortality. Similarly, blood levels of interleukin-6 (IL-6) have been found to be possible predictors of survival in patients with metastatic BC.

It appears that the link between malignant progression and chronic inflammatory processes could possibly explain how some cancer-related genes (e.g., IL-6) may be involved in the effects of stress on cancer. IL-6 is secreted from stromal cells in the tumor microenvironment. In fact, stromal cells can “reprogram” the microenvironment in the direction of malignant progression. In addition, the expression of inflammatory cytokines or other pro-inflammatory factors (e.g., growth factors) can be upregulated by an uncontrolled response to stressors. Moreover, by communication with immune cells, the tumor can suppress the anti-cancer immune response and induce the immune cells to secretion of pro-inflammatory factors, which will further facilitate malignant invasion and spread.
On the one hand, it has been revealed that stress can modulate the inhibitory receptors, and mediate the influence of NK cells and CTL on malignant progression. On the other hand, stress can also contribute to some beneficial NK cells actions (e.g., via enhancing NK cells migration and activity), as well as increasing NK cells trafficking from the bone marrow, into the systemic blood circulation and body organs.

6. The Tumor Microenvironment – an Interplay within the “Triangle”: Cancer Cells, Tumor Stroma, and Immune System

The neoplastic tumor’s cells can “attract” some normal cells, which in turn, may acquire some abnormal features (e.g., the hallmarks of cancer) (Table 2). In consequence, both the tumor’s internal cells and the “tumor

<table>
<thead>
<tr>
<th>Hallmarks of cancer</th>
<th>Processes in tumor cells/ microenvironment (possibly exacerbated by stress)</th>
<th>Examples of current and emerging biomarkers of cell mutation, growth, neoplastic proliferation and spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome instability/ mutation</td>
<td>Cancer cells dominate in microenvironment</td>
<td>Endonuclease for DNA damage repair = ERCC1 – XPF; Nucleases involved in DNA repair = APEX1/APEX2</td>
</tr>
<tr>
<td>Sustaining proliferative signaling</td>
<td>Cancer cells become self-sufficient &amp; capable of growth out of control</td>
<td>Cell proliferation - as a prognostic &amp; diagnostic tool in cancers – biomarkers related to: DNA synthesis (e.g., BrDU, IdU, CleU, EdU), Cellular metabolism (e.g., MTT, XTT, WST-1), Proliferation proteins (e.g., PCNA, K67, MCM-2)</td>
</tr>
<tr>
<td>Evading growth suppressors</td>
<td>Malignant cells no longer respond to anti-growth signals</td>
<td>Rb1 = Retinoblastoma, regulates cell cycle &amp; differentiation; p53 = the “guardian of the genome”, regulates gene expression; APC = regulator of tumor growth, involved in cell adhesion/migration; BRCA1, BRCA2 = tumor suppressors regulating DNA repair/cell cycle; PTEN = a key regulator of cellular activities (e.g., PI3K-AKT-mTOR signaling via its lipid phosphatase activity)</td>
</tr>
<tr>
<td>Resisting apoptosis (programmed cell death)</td>
<td>Cancer cells can resist apoptosis &amp; may use autophagy to overcome nutrient limitations &amp; facilitate tumor growth (this can modulate tumor microenvironment by inflammatory responses &amp; angiogenesis)</td>
<td>Characteristics of apoptosis: cell shrinkage, membrane blebbing, chromosome condensation (pyknosis), nuclear fragmentation (karyoexesis), DNA laddering, and the engulfment of the cell by phagosomes; tumor-suppressor proteins that control the autophagy pathway: p53, Be2, and PTEN</td>
</tr>
<tr>
<td>Enabling replicative immortality</td>
<td>There are no limitations to the cancer cell’s reproduction (e.g., due to telomere/telomerase dysregulation, abnormal p53 signaling)</td>
<td>hTRET = the major component of telomerase activity; p53 = the main regulator of gene expression</td>
</tr>
<tr>
<td>Reprogramming energy metabolism</td>
<td>Cancer cells shift from energy production via mitochondria to less efficient glucose use</td>
<td>HIF/1α/HIF2α/HIF1β = heterodimeric DNA binding transcription factor regulating cellular systems to hypoxia; GAPDH &amp; Tom20 = glycolysis markers, upregulated in various cancers; COX IV = the inner; VDAC1/Porin = the outer mitochondrial marker</td>
</tr>
<tr>
<td>Tumor-promoting inflammation</td>
<td>Chronic inflammation in the tumor micro-environment is associated with cancer growth, transformation, evasion, invasion, angiogenesis and metastasis</td>
<td>NF-kappa B = a transcription factor regulating cytokines; IKK beta = a part of the IKK complex that negatively regulates transcription factor NF-κ kappa B; CD68 = a marker to recognize M1 and M2 macrophages in the tumor; CD163 = a scavenger receptor upregulated in macrophages in an anti-inflammatory environment; NOS3 = the main marker of M1 tumor associated macrophages</td>
</tr>
<tr>
<td>Avoiding immune destruction</td>
<td>Cancers can escape immune system attacks (e.g., by using immune checkpoints to evade detection/elimination by the immune system)</td>
<td>T cells = capable of selective recognizing &amp; killing pathogens or abnormal cells; coordinate immune responses (innate &amp; adaptive); PD-1, PD-L1 and CTLA-4 = biomarkers in immunotherapy</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>In process of angiogenesis, lymphangiogenesis, cancer uses normal cells to create a vascular network (for nutrients supply, waste removal)</td>
<td>The VEGF family = VEGF-A (the most potent inducer of angiogenesis), VEGF-B, VEGF-C, VEGF-D, VEGF-E, &amp; placental growth factor 1 and 2 (PIGF-1 &amp; PIGF-2). The binding of VEGF to VEGF-receptors activates signaling pathways: the Ras/MAPK (regulating cell proliferation &amp; gene expression), the FAK/paxillin (rearranging cytoskeleton), the PI3K/AKT (regulating cell survival), the RhoA/ROCK (forming new capillaries), the PLC gamma (controlling vascular permeability)</td>
</tr>
<tr>
<td>Activating of invasion and metastasis</td>
<td>Cancer spreads to other organs, using different molecules</td>
<td>Hyaluronan = glucoseaminoglycan in the extracellular matrix (ECM); Versican = expressed by cancer or stromal cells; invasion/metastasis; Collagen IV = compound for tumor angiogenesis; cell proliferation; CEACAM1 = down-regulated in many cancers; L-Form CEACAM1 has tumor suppressive function; its dysregulation is present in early carcinogenic stages; DCC = a transmembrane receptor for netrins; it promotes apoptosis in the absence of netrin ligands; E-Cadherin = a regulator of morphogenic process like cell-cell recognition, cytoskeleton regulation, and surface adhesion; Tenasin C = a compound interacting with ECM proteoglycans; interferes with tumor suppressor activity of fibronectin; Fibrinogen = fibrin deposits in stroma of many cancer types; affects the progression of tumors; Periostin = secreted adhesion-related protein expressed in the periostium and periodontal ligaments; plays a role in tumorigenesis.</td>
</tr>
</tbody>
</table>
“tumor microenvironment” play an essential role in the carcinogenesis and tumor progression (Table 2)\[18\]. In particular, the regulatory signaling is relevant to carcinomas, in which the neoplastic epithelial cells create the parenchyma, which is different from the surrounding mesenchymal cells forming the tumor-associated stroma (microenvironment)\[19\]. In this microenvironment, cancer cells interact with the stroma and the immune system.

Traditionally, the immune system has been considered to be a key component of the body’s protection against cancer progression. However, it can be inactivated or reprogrammed by malignant cells, so that it may even contribute to the tumor expansion (Table 2)\[12,18,30\]. Similarly, stromal cells and extracellular matrix (ECM) can also reveal pro- and anti-tumor properties\[44\]. In addition, an interconnected “triangle” of the cancer cells, immune system cells and tumor stroma, such as the “tumor microenvironment”, creates a “milieu”, in which chronic inflammatory processes facilitate malignant proliferation and metastasis. For instance, solid tumors are usually created from conglomerates of various cell types, which are capable of tumor proliferation and progression, and the pro-inflammatory cells of the immune system, (which are present in tumors) can exhibit both the tumor-promoting and the tumor-killing abilities (Table 2)\[18,30\]. Moreover, the different stromal cell types (in the “tumor microenvironment”) can change their properties, during the malignant invasion of healthy tissues, and in this way, cancer may spread to distant organs\[18\]. In addition, the premalignant steps of tumorigenesis are also associated with the microenvironment, when stress stimulates the production of many neuromediators and hormones, such as catecholamines, which may subsequently travel to the “tumor’s microenvironment” (e.g., via circulating blood or lymphatic vessels)\[12,18\]. In addition, activation of the adrenergic receptors (ARs) on immune cells can cause the secretion of immunosuppressive compounds (e.g., cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), arginase, and inducible nitric oxide synthase (iNOS))\[12,18\]. Concurrently, the catecholamines can block the activation of “beneficial” immune system cytokines, such as IFN, interleukin-2 (IL-2), and IL-12 (Table 2)\[18\]. Furthermore, elevated concentrations of catecholamines, in the tumor microenvironment may also augment the levels of indoleamine-2,3-oxygenase (IDO), programmed death-ligand 1 (PD-L1), and cyclooxygenase-2 (COX-2) from the stroma. This, in turn, can further aggravate immune derangements, and augment the malignant progression\[12,18,30\].

A neoplastic tumor represents a micro-ecosystem, which contains a conglomerate of cells, including cancer, stromal, and immune system cells, as well as the ECM\[18,44\]. Cancer cells interact with the ECM via different mechanical forces, enzymatic reactions, and molecular signaling. These interactions cause alterations in the inflammatory and oxidative processes in the tumor microenvironment, and in the intracellular signaling (Table 2)\[18,45\]. In addition, cancer cells interact with stromal cells (e.g., fibroblasts) through paracrine signaling, and via direct cell-cell contacts, in order to promote malignant progression\[18,46,45\]. Simultaneously, cancer cells interact with the immune system, evoking two types of behaviors: pro- and anti-tumor-directed\[16,18\]. It should be highlighted that the immune system participates in the maintenance of inflammatory state in the tumor microenvironment, that in turn, enhances angiogenesis in the tumor microenvironment, which enables neoplastic cell growth and spread (Table 2)\[16,18\]. Furthermore, cancer-associated fibroblasts (CAFs) may recruit immune system cells to the tumor, and direct their actions against malignant cells\[18,46\]. Also, CAFs participate in remodeling of the ECM, which may cause further neoplastic proliferation and spread\[46\]. The complex interplay between cancer cells, tumor stroma and immune system affects cancer proliferation, and spread, influencing the patient outcomes (Table 2)\[18\].

It should be highlighted that the cancer cells, via aberrant signaling and uncontrolled growth, produce a microenvironment that displays various behaviors of the immune system and stromal cells (e.g., stromal cells remodel the microenvironment, aiming at tumor progression and express different growth factors and pro-inflammatory cytokines)\[18,47\]. Moreover, cancer cells remodel the ECM (e.g., mechanically and enzymatically, via matrix metalloproteinases (MMPs) and similar enzymes). Using numerous signaling interactions with immune cells, the tumor can inhibit the anti-cancer immune response, as well as enhance the secretion of pro-inflammatory cytokines and growth signals to promote the malignant progression (Table 2)\[18,47\].

7. Cancer Cells Interactions with the Tumor Stroma and the Immune System

Cancer cells continuously interact with their microenvironment. For instance, the malignant cells modify their environment to form a more hospitable “terrain”, which is conducive to the neoplastic progression\[18,48\]. Within the tumor stroma, environmental conditions, mechanical forces and the ECM structure, stromal cells, and the activity of various extracellular signaling molecules and enzymes influence cancer cells activity, and vice-versa (cancer cells
have a multi-level impact on their microenvironment) (Table 2)\(^{[18,48]}\). The activity of signaling molecules (e.g., cytokines and growth factors) within the tumor microenvironment is crucial for cancer cell and immune cell behavior. Interactions between cancer cells and the immune system play a key role both in the cancer progression and anti-cancer response. These interactions can be categorized as follows: immunosurveillance, the anti-cancer immune response, immunosuppression, and cancer assistance (Table 2)\(^{[18,49]}\). The immunosurveillance means that the healthy immune system conducts on-going “examinations” of tissues, searching for signs of malignancy, the presence of tumor antigens (e.g., overexpressed proteins or oncoviruses). After detection of neoplastic cells, the anti-tumor immune response, mediated via helper and killer T cells destroys a majority of cancer cells. However, some malignant cells and cells that form the tumor microenvironment (e.g., CAFs) manage to escape or suppress the immune response (e.g., through blocking the proliferation of helper and killer T cells, or via enhancing the inflammation-mediated recruitment of the immunosuppressive regulatory T cells (T regs) and myeloid-derived suppressor cells (MDSCs) \(^{[16,49]}\). In addition, malignant cells can manipulate the immune system actions, to accelerate the tumor progression and spread \(^{[18,50]}\). For instance, some immune cells (e.g., macrophages, dendritic cells (DCs), lymphocytes, neutrophils, and NK cells) participate in the promotion or inhibition of the neoplastic spread (Table 2)\(^{[18,50]}\).

8. A Double-edged Sword – Immune Cells Playing the Role of Cancer Promoters or Suppressors

It should be highlighted that in the tumor microenvironment, immune cells can play two roles, either as tumor suppressors or promoters of tumor evasion\(^{[18,51]}\). For instance, macrophages can evolve to a pro-inflammatory (tumor-promoting) M1 state in the presence of macrophage colony stimulating factor, TNF or IFN-gamma\(^{[41]}\). In contrast, in response to IL-4, IL-10 or IL-13, the macrophages can polarize towards a M2, anti-inflammatory (anti-tumor) phenotype\(^{[18,52]}\). Also, while most T-cells produce IFN-gamma (that acts as an inhibitor for the cancer cells), some subsets of T-cells (e.g., T reg) express the surface marker CD25, or Th17 (producing IL-17), which can promote tumor growth by inhibiting the anti-cancer immune response\(^{[52]}\). With a deeper recognizing of various microenvironmental factors that affect tumor progression, some new anti-cancer therapies may emerge. In particular, paracrine signaling is essential to a cancer cells influence on the cancer-associated stromal cells and immune cells, recruited to the tumor microenvironment. Therefore, by changing signaling pathways, which favor immune cell polarizations, their pro-tumorigenic actions could be suppressed. Therefore, it is conceivable that therapies, which would address at the same time the key elements of cancer “triade” could more effectively destroy malignant cells or decrease the tumor progression and spread. Also, an interrupting of the microenvironment remodeling by cancer cells, may offer another anti-cancer therapeutic avenue, in the future.

9. Effects of Psychological Interventions on Stress-related Behavior and Health Outcomes in Women Undergoing Treatment for BC

BC represents a highly prevalent malignancy, and the convincing evidence exists that psychological interventions have an influence on clinical outcomes in patients with BC\(^{[53]}\).

The pioneering study, in women with BC, revealed that such interventions affect transcriptional changes\(^{[54]}\). Furthermore, the inflammation was recognized as one of the key factors that are responsible for the BC progression and reduced survival in BC patients\(^{[55,56]}\).

Studies have revealed that the various stress reduction interventions (SRIs) (e.g., cognitive-behavioral therapy (CBT) and meditation-based stress reduction (MBSR)) have a beneficial influence on psychological adaptation, and neuroendocrine or immune system functions, among patients with cancer\(^{[57]}\). For instance, SRI can be offered as a group based technique, including a combination of CBT with interpersonal skills training, delivered in form of educational and role-playing sessions, homework and practical exercises to cope with stress\(^{[57]}\). MBSR is a structured mindfulness meditation training that is delivered in a group session, (once a week, for at least two hours, during eight weeks course, combined with an individual daily practice for at least 30 minutes, and one-day retreat)\(^{[57]}\). Studies have shown that such SRIs have contributed to the reduction in serum cortisol levels (in the afternoon (PM)), the higher lymphocyte proliferative response, as well as the increased Th1 cytokine production and Th1/Th2 ratio\(^{[58]}\).

10. Stress Reduction Interventions (SRIs) and Their Impact on Endocrine and Immune System Functions in Patients with BC

A study, including patients with non-metastatic BC (who underwent surgery, and were subsequently scheduled for the adjuvant therapy) examined the influence of
the SRI on the neuroendocrine and immune system biomarkers [59]. In this study, women with BC were randomly assigned to the intervention group (that received the SRI for ten weeks) or the control group (that received the psychoeducation for one day). Women in the SRI group revealed improved mood and quality of life, which corresponded with the reduction in serum cortisol levels (in PM), and elevation in IL-2 and IFN-gamma production (from anti-CD3 stimulated peripheral blood mononuclear cells (PBMCs)) [59]. In addition, these data corresponded with faster recovery from the applied anti-cancer therapy [59]. Furthermore, the impact on Th1 cytokine production may support cellular immune actions that contribute to tumor eradication (e.g., CTCs and T regs) [60]. It should be highlighted that in similar studies, distress and cortisol level reductions were associated with more frequent and confident use of relaxation practices to control stress [5,61]. These results reflect on a “common denominator” of SRIs, such as anxiety or “internal tension” reduction, and the related neuroendocrine changes that are connected with the immune system activity. To further elucidate these issues, it would be necessary to conduct trials, in which the results of relaxation training could be separated from some other outcomes of multi-level SRIs (e.g., CBT or MBSR) [5,60,61]. It is still unknown whether or not women with BC, participating in trials using psychological interventions, which revealed neuroendocrine and immune effects of the stress management will experience less neoplastic recurrence [53,58]. Also, it is crucial to realize that the results of psychological interventions on cancer outcomes can be mediated by various stress-related mechanisms (e.g., some behavioral processes that are related with health-oriented behaviors, such as adequate nutrition, regular exercises, and adherence to anti-cancer treatment), as well as the effects of the oncology therapy [53]. Furthermore, inflammation and processes that participate in supporting tumor growth and spread (e.g., angiogenesis, tumor cell migration, tissue remodeling, anoixis, and resistance to apoptosis) should be further investigated to elucidate the influence of psychological interventions on clinical outcomes in cancer patients [14]. For instance, it was shown that the neuroendocrine hormones (e.g., glucocorticoids and catecholamine) may enhance signalization between tumor, endothelial, and stromal cells. This communication is crucial in modulating downstream signaling pathways, which are required for cancer progression [62]. With regard to cancer progression, an important principle for investigating the impact of psychological interventions on molecular signaling pathways is to assess whether or not these interventions are related to transcriptional changes in circulating WBC (e.g., leukocytes). For instance, considering that chronic stress and negative mood are associated with other physiological processes (e.g., inflammation, oxidation or glycation) which are related to malignant progression, it is crucial to investigate whether stress reduction strategies may influence inflammatory markers, and stress-induced neuroendocrine mechanisms (e.g., GRs sensitivity), which control inflammatory processes within circulating leukocytes [55]. It should be noted that the SRI downregulated the expression of specific genes, which contribute to the malignant progression and spread (e.g., MMP9). Moreover, women with BC, who underwent SRI, have revealed the concurrent increases in gene expression, which correlated with recovery of IFN-mediated cellular immunity. This phenomenon can be related to immune-surveillance of malignant micro-metastases or opportunistic infections during and after anti-cancer therapy [63]. These findings indicate that the advantages of SRI include not only psychological adaptation but also changes in the immune cell gene expression that may potentially influence BC outcomes in these patients [62,63].

11. Future Perspectives and Research Directions on the Stress and Cancer Intersection

A comprehensive understanding of the multi-level relationships between stress, carcinogenesis, and malignant progression is a crucial step for inventing some novel, helpful strategies to interrupt the maladaptive signaling pathways from stressors to neoplastic disease. In particular, psychological, educational, and behavioral interventions aimed at stress reduction (e.g., CBT and relaxation techniques) can improve the health outcomes, in many patients with cancer [64]. In addition, certain medications, including antidepressants and beta-blockers can be helpful for diminishing the impact of psychological stress on neoplastic cells, and thus, may be considered for individual patients (e.g., based on a specialist consultation, such as psychiatry, cardiology, internal medicine or psychology) [65,66]. However, many of the details related to the effects of psychological stress on malignant cells still remain unexplained [67]. Such explanations are essential for designing future, targeted interventions to protect patients with cancer from the detrimental consequences of uncontrolled psychological stress.

At present, the exact mechanisms connecting the biological changes stimulated by uncontrolled psychological stress and the molecular alterations in cells (e.g., related to DNA repair and apoptosis) and changes in the tumor
microenvironment are not clear yet\cite{18,67}. Nevertheless, the stimulation of the HPA axis and the SNS by stress-mediated hormones seems to represent potential innovative therapeutic targets\cite{12,67}. For instance, it is crucial to find out how exactly the chronic psychosocial stressors interact with the cerebral structures, such as PVN and SCN. Since there are numerous stress-related mediators “in charge of” the impact of psychological stress on neoeplastic cells, and they act on these cells “in concert” with others molecular signals, it is extremely difficult to design an effective therapeutic solution, which would be suitable for each patient. Furthermore, exploring how psychological stress influences the molecular rhythms of malignant cells is of utmost importance, considering that the circadian clock functions as a tumor suppressor, and thus, the psychological stress effects may possibly be reduced by the up-regulation of some circadian genes\cite{8,9,67}. Also, it has been indicated that psychosocial and behavioral factors may influence the incidence and progression of cancer via their impact on immune functions\cite{10,12,31}. For instance, this phenomenon has been illustrated in studies exploring the telomerase activity and telomere length in peripheral lymphocytes, with relation to psychological stress\cite{68}.

Moreover, cancer-specific stress is a valid individual variable, which may predict both psychological and medical disease outcomes. It has been suggested that the cancer-specific stress, during the therapy initiation could be a risk factor for worse psychological adaptation to the anti-cancer treatment process\cite{69}. Overall, the research evidence exists to support the psychotherapeutic, educational, and behavioral strategies, as safe and effective interventions that can improve functions of the immune system, quality of life, and disease outcomes, among patients with cancer, who often suffer from psychological stress and depression\cite{53,54,70}. This area certainly deserves further studies, especially in terms of early detecting patients, who are in particular need of stress reduction interventions (e.g., at the beginning of their long journey of burdensome anti-cancer therapies), in order to improve their management and outcomes.

12. Conclusion

Cancer can be viewed as a disease of serious miscommunication between cells and their ecosystem (the tumor microenvironment, containing cells of the immune system, and the tumor stroma, including stromal cells and ECM). A comprehensive model of malignancy, in the context of the multi-directional interplay of cancer cells, immune system, and the tumor stroma is essential for investigating safe and effective anti-cancer therapies that target the entire phenotype of this cancer-related “triangle”. It is important to note that the tumor cell behavior is influenced by mutual interactions between the malignant cells and the components of the tumor microenvironment. The aberrations in signaling pathways within the tumor and its ecosystem, as well as between cancer and its microenvironment play a prominent role in neoplastic proliferation and metastasis. Furthermore, some possible causal links exist between the relations of the individual with her/his environment or ecosystem and those of the tumor with its microenvironment. On the one hand, the favorable interactions of the person with her/his environment may evoke a beneficial interplay of the malignant cells with their microenvironment. On the other hand, however, the stress (e.g., chronic or psychological) and the maladaptive response to stressors may create a disequilibrium between the cancer cells and the microenvironment immune system. This, in turn, can cause mitotic “reawakening” of the dormant tumor cells. Chronic or psychological stress may affect the onset, progression, and outcome of various types of cancers. The effects of stress on malignant cells are mostly mediated via the stress-related hormones and their receptors. Such a molecular communication can stimulate the proliferative and migratory signaling pathways within the normal cells, causing their malignant transitions (Figure 1). In addition, there are complex relationships between psychological or behavioral factors and the various biological processes in cells, which can lead to cancer growth, progression, and dissemination (as outlined by the “hallmarks of cancer”).

Figure 1. The effects of uncontrolled, chronic psychological stress on central nervous system, tumor and tumor microenvironment [CNS: central nervous system; C: cortex; H: hypothalamus; P: pituitary gland; AG: adrenal glands; MN: medullary nucleus; inflamm.: inflammatory; meta: metastasis; SNS: sympathetic nervous system; tu: tumor].
Figure 2. A patient-centered, personalized approach, combining the psychological and behavioral interventions with the baseline oncology management.

At this point, identifying some “opportunity windows” within the anti-cancer treatment spectrum, when the psychological or behavioral interventions may bring the most desirable results for patients, should be explored in future trials. Furthermore, recognizing various kinds of psychological stressors, and “critical moments”, when the patients are most vulnerable to distress, anxiety or depression, during the cancer journey, would be helpful. Also, exploring the mechanisms of stress management interventions in oncology should focus on the patient’s personality, pre-morbid psychological characteristics, and clinically relevant biomarkers. In addition, it is crucial to determine the precise effects of the stress reduction interventions on clinical outcomes (e.g., disease recurrence and progression-free survival) in different cancer patient populations (e.g., women with BC).

Finally, it is conceivable that psychological interventions, addressing the cancer patient’s individual needs, goals, expectations, and fears (e.g., especially prior- and post-surgery for the primary tumor) can facilitate psycho-behavioral adaptation, and decrease exacerbations of stress-related processes, which in turn, may influence the cancer progression. In this light, some supportive approaches, such as psychological, behavioral, and educational therapies, aimed at stress reduction, can bring beneficial effects to patients with malignancies. Since anti-cancer treatments evolve towards a patient-centered, personalized approaches, consideration of the psychological and behavioral interventions may provide valuable and inexpensive options, which can be combined with the baseline oncology management (Figure 2).

References


