Chapter 11
Psychoneuroimmunology and Cancer

11.1 The Systems-Based PNI Frameworks

More and more evidences are showing that psychosocial factors may affect cancer development and progression. Systems-based psychoneuroimmunology (PNI) frameworks and the dynamical psychosocial models may help understand the changing demographics in cancer treatment and outcomes (Green McDonald et al. 2013; also see Chap. 1).

Although psychosocial care for cancer patients has been ignored historically, such quality clinical care has been recommended across various stages of treatment recently (Artherholt and Fann 2012). For instance, in a meta-analysis of 24 cancer-specific studies of psychosocial interventions that applied PNI-based outcome measures, cognitive-behavioral therapies were shown to have the most significant success using functional measures such as cytokines (Subnis et al. 2014).

Distress has been suggested as the sixth vital sign in the examination of cancer patients. Evidences from the studies in psycho-oncology have associated psychosocial factors with cancer, including distress, cognitive deficits, psychiatric morbidity, as well as coping methods applied by cancer survivors (Chaturvedi and Venkateswaran 2008). A recent study using rat models showed that isolation stress may have impacts on the development of tumors, even though stress itself is not a sufficient risk factor in cancer occurrence (De la Roca-Chiapas et al. 2016).

As an important psychological factor, stress is often experienced in cancer patients and harms the protective functions of the immune system. Various diverse interactions have been identified between malignant tissues and immunocytes. Animal studies have demonstrated that neuroendocrine and immunological mediators of stress have impacts on the sympathetic nervous system, NK cell activities, and cancer progression (Ben-Eliyahu et al. 2007).

As an example, breast cancer patients often blame "stress" as an important factor in the disease development. PNI studies have revealed the effects of stress on molecular and cellular pathways involved in carcinogenesis, especially the roles of immune cells in the development and progression of epithelial cancer (Pant and

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_11

Ramaswamy 2009). In addition, psychosocial factors including stress, pessimism, and sleep quality may be critical factors in the development of HPV-mediated cervical neoplasia among HIV-positive patients (Jensen et al. 2007).

In a recent study of 379 patients with breast cancer undergoing treatment, social support and positive worldviews were observed to have the most significant influences on survivorship experiences (Hulett et al. 2015). The study suggests that because breast cancer is an immune-associated disease, the care for long-term survivors needs to embrace psychosocial factors such as distress with influences on immune functions.

In the regulation of cancer progression, key roles have been identified for catecholamine hormones including norepinephrine and epinephrine, as well as their receptors including the β-adrenergic receptors (β-ARs) (Yang and Eubank 2013). These catecholamines may mediate the impacts of psychological stress on different stages of tumor progression such as proliferation, angiogenesis, and metastasis. Because of the important roles of β-ARs, the potential applications of β-blockers have been suggested for adjuvant cancer therapy (Yang and Eubank 2013). Such mechanisms emphasize the translational importance of biobehavioral impacts on tumor biology and cancer therapeutic outcomes.

Recent development in personalized medicine is improving the survival rate among breast cancer patients. However, many of the survivors still suffer from co-occurring psychoneurological symptoms with adverse influences on their quality of life. These co-occurring symptoms are also called "symptoms clusters" with the underlying epigenetic and genomic mechanisms associated with the interindividual variability during and after treatments (Starkweather et al. 2013).

Systems biology-based PNI studies including the elucidation of the stress response networks and inflammatory pathways may connect the genotypes with the phenotypic "symptoms clusters" to support the practice of personalized medicine. Because inflammation is a key factor in cancer development, the better understanding of the inflammatory networks is becoming more and more important. For more effective prevention and treatment, approaches including psychosocial instruments, systemic biomarkers, and PNI-based measures would be helpful toward the development of systems and dynamical medicine (Yan 2014; also see Chap. 1).

11.2 Inflammatory Pathways in Different Types of Cancer

11.2.1 Pancreatic Cancer and the NFATc2-STAT3-GSK-3β Pathway

Epidemiological evidences have demonstrated that chronic inflammation is one of the key risk factors for different types of cancer (Fan et al. 2013). Table 11.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

Table 11.1 Examples of stress- and inflammation-related pathways in cancers

Pathways and interactions	Associated pathogenesis/diseases	References
Inflammation-induced NFATc2 and STAT3 transcriptional networks, GSK-3β	Pancreatic cancer progression and growth	Baumgart et al. 2016
The β-Catenin signaling pathways	Inflammation, fibrosis, hepatocellular carcinoma (HCC)	Lee et al. 2014
The TGF-β signaling pathways	Inflammation, DNA damage in the forestomach, invasive squamous cell carcinoma (SCC)	Achyut et al. 2013
The PPARδ and PGE2 signaling pathways	Colorectal cancer (CRC)	Wang and DuBois 2014
The toll-like receptors (TLRs) signaling pathways	Colorectal inflammation and cancer	Fűri et al. 2013
The JNK1 stress signaling pathways	High breast density and the tumor stroma	Lisanti et al. 2014
The NF-kB signaling pathways	Chronic inflammation and cancer	Verstrepen and Beyaert 2014
The NF-kB signaling pathways (e.g., STAT3, p53, GSK3-β, p38, PI3K, TLRs)	Inflammation and cancer	Hoesel and Schmid 2013
The NF-kB and STAT3 signaling pathways	Tumor angiogenesis and invasiveness	Fan et al. 2013
The TNF signaling pathways, interactions with mutant p53, DAB2IP	Inflammation in cancer	Di Minin et al. 2014
The IL-1 associated signaling pathways (e.g., apoptosis, TLR, MAPK, NLR, and NF-kB)	Cancer, chronic inflammation	Acuner Ozbabacan et al. 2014
The IL-1 receptor-associated kinase signaling pathways	Tumor growth, metastasis, immune suppression, chemotherapy resistance	Jain et al. 2014
The IL-1β-mediated inflammatory pathways	Central nervous system (CNS) inflammation, cancer treatment-related symptoms (CTRSs)	Wood and Weymann 2013
The inflammatory signaling pathways (e.g., MMIF)	Microbial-triggered carcinogenesis	Kipanyula et al. 2013
The epithelial IL-6 signaling pathways (microbiota induced)	Inflammation-induced colorectal cancer (CRC) formation	Hu et al. 2013
The VEGF-associated pathways	Hematopoietic stem cell transplant (HSCT)	Knight et al. 2013
The HPA and SNS axes	HSCT	Costanzo et al. 2013
The HPA axis	Inflammation and cancer	Starkweather et al. 2013
The macrophage migration inhibitory factor-mediated signaling pathways	Prostate cancer cells proliferation and survival	Tawadros et al. 2013
The AMPK and autophagy signaling pathways	Prostate cancer (PCa) with neuroendocrine differentiation (NED)	Lin et al. 2016
The Erk/MAP kinase signaling pathway	NED of small-cell lung cancers (SCLC)	Chen et al. 2014

For instance, in pancreatic cancer, glycogen synthase kinase 3β (GSK-3β) is involved in the networks associated with proinflammatory oncogenic transcription factor nuclear factor of activated T cells (NFATc2) and STAT3 complexes (Baumgart et al. 2016; also see Table 11.1). Such interactions integrate the upstream signaling activities that control pancreatic cancer progression and growth. With the GSK-3β-associated phosphorylation of STAT3 and the formation of the NFATc2-STAT3 complex, the NFAT target promoters including cyclin-dependent kinase-6 may be stimulated to enhance tumor growth (Baumgart et al. 2016).

Experiments using mice models indicated that targeting the NFATc2-STAT3-GSK-3β module could suppress the proliferation and tumor growth, as well as block the inflammation-caused pancreatic cancer progression (Baumgart et al. 2016). The relevant networks have been suggested as the potential therapeutic targets for pancreatic cancer.

11.2.2 Hepatocellular Carcinoma (HCC) and the β-Catenin Signaling Pathway

The β-Catenin signaling pathway has been correlated with hepatocellular carcinoma (HCC) with a complex role in inflammation and fibrosis. A recent study using mice and human models addressed the importance of the abnormal intratumoral β-catenin stabilization (Lee et al. 2014; also see Table 11.1). Those who had predominant cytoplasmic with occasional nuclear (C/N) localization were associated with higher levels of intratumoral inflammation and proliferation.

11.2.3 Squamous Cell Carcinoma (SCC) and the Pathways of Tgfbr2, p21

Because stroma is pivotal in epithelial homoeostasis, the lack of tumor suppressor genes in stromal fibroblasts has been correlated with epithelial cancer development. In the neighboring epithelia of the forestomach, the lower levels of TGFβ receptor 2 (Tgfbr2) in the stromal fibroblasts (Tgfbr2(fspKO)) may cause inflammation and DNA damages (Achyut et al. 2013; also see Table 11.1). Such changes may lead to the lower levels of cyclin-dependent kinase inhibitors p15, p16, and p21, resulting in the development of invasive squamous cell carcinoma (SCC).

Because inflammation is essential in the epigenetic silencing of p21 in the tumor progression processes, anti-inflammation therapies have been found to restore p21 expression and block tumorigenesis (Achyut et al. 2013). These findings refer to the option of anti-inflammation for the therapy of human SCCs with the lower levels of TβRII in the stroma.

11.2.4 Colorectal Cancer and the Signaling Pathways of TLRs and PPARδ

The nuclear hormone receptor peroxisome proliferator-activated receptor δ (PPARδ) has been found essential for the chronic colonic inflammation and colitis-related carcinogenesis (Wang and DuBois 2014). It has also been correlated with fatty acid metabolism, obesity, and wound healing.

The COX-2-derived PGE_2 signaling pathway is a PPARδ downstream pathway that facilitates the communications between tumor epithelial cells and macrophages (Wang and DuBois 2014; also see Table 11.1). Such activities may enhance chronic inflammation and colitis-related tumor genesis. With its critical roles in inflammatory bowel disease (IBD) and colorectal cancer (CRC), the PPARδ-associated network may be the potential targets for the discovery of novel therapeutics of IBD and CRC.

In addition, the signaling pathway of toll-like receptors (TLRs) has been associated with the pathogenesis and treatment of inflammatory bowel diseases and colorectal cancer (Fűri et al. 2013; also see Table 11.1). TLR9 is one of the TLRs and its signaling is involved in colorectal carcinogenesis and colonic inflammation. It may facilitate cytokine productions in the colonic mucosa.

TLR9 can be stimulated by bacterial or viral DNA fragments, immunoglobulin–DNA complexes, or synthetic oligonucleotides (Fűri et al. 2013). These stimulants have unmethylated cytosine–guanine nucleotide sequences (CpGs). The stimulation of TLR9 through CpGs has been proposed as a possible therapeutic target for cancerous and inflammatory disorders.

11.2.5 Breast Cancer and Various Signaling Pathways

The gene set enrichment analysis (GSEA) of genome-wide transcriptional profiling data from low-density (LD) and high-density (HD) mammary fibroblasts has shown that HD fibroblasts have higher activities of the essential cellular processes (Lisanti et al. 2014). These processes include stress responses and inflammation. The transcriptional profiles of HD fibroblasts have indicated the functional similarities with those cancer-associated fibroblasts (CAFs) in the head and neck, liver, thyroid, lung, and breast cancers.

The GSEA also suggests that different signaling pathways can be relevant in the processes, such as those of the JNK1, iNOS, Rho GTPase(s), FGF-R, EGF-R, and PDGF-R-associated signal transductions (Lisanti et al. 2014; also see Table 11.1). These connections may generate a microenvironment that is proinflammatory, proproliferative, and cytokine rich. Other relevant gene profiles include those from smooth muscle cells under stress (JNK1) and activated/infected macrophages (iNOS). The JNK1 stress signaling has been related to tumor recurrence, the transition to malignancy, and the pathogenesis of breast cancer.

The shared features have been recognized among the genetic profiles of the HD fibroblast, wound healing, and the cancer-associated fibroblast phenotypes (Lisanti et al. 2014). Such mechanisms may indicate a framework of personalized medicine for different diseases sharing the common pathways such as those in the inflammatory microenvironment (also see Chap. 1).

11.3 The NF-kB- and p53-Associated Pathways

The family of the transcription factor NF-kB is essential in various cellular activities such as innate and adaptive immune signaling, inflammation, proliferation, and survival (see Chap. 4). The alterations in the NF-kB-associated pathways have been related to autoimmunity, chronic inflammation, and various stages of cancer initiation and progression (Verstrepen and Beyaert 2014; Hoesel and Schmid 2013).

The activation of NF-kB needs IkB kinase (IKK)α or β and can be affected by phosphorylation via certain IKK kinases and autophosphorylation. Various classes of molecules may be involved in the NF-kB-associated interactions, including reactive oxygen species (ROS) and miRNAs. Components associated with the canonical NF-kB signaling pathway also include lipopolysaccharides (LPS) and toll-like receptors (TLRs) (Hoesel and Schmid 2013).

Complex crosstalk has been identified between NF-kB and various transcription factors including the signal transducer and activator of transcription 3 (STAT3) and p53 or the ETS related gene (ERG) (Hoesel and Schmid 2013). The crosstalk may be mediated through different kinases including GSK3-β, p38, PI3K, c-Jun N-terminal kinases (JNKs), and can influence the upstream signaling pathways (see Table 11.1).

Recent studies have emphasized the interactions between NF-kB and STAT3 in colon, gastric, and liver cancers (Fan et al. 2013). STAT3 interacts with many genes in cellular responses, cell growth, and apoptosis. The STAT3 and NF-kB interaction is critical in the regulation of the communications between cancer cells and inflammatory cells, as well as tumor angiogenesis and invasiveness. The elucidation of NF-kB-associated signaling pathways such as the NF-kB and STAT3 cooperation may be helpful for finding novel chemopreventive and chemotherapeutic strategies (Fan et al. 2013; also see Table 11.1).

In addition, the tumor suppressor p53 is often mutated in cancer and the p53 missense mutants (mutp53) may have oncogenic features (Di Minin et al. 2014). The interactions between mutp53 and inflammatory cytokines may enhance the invasive activities of cancer cells. Specifically, mutp53 may stimulate NF-kB activation but inhibit the activation of ASK1/JNK by TNFα (Di Minin et al. 2014; also see Table 11.1). The mutant p53-associated networks may affect tumor evolution and the complex processes in inflammation.

Furthermore, the positive and negative feedback mechanisms may add another level of complexity to the NF-kB signaling pathways. For instance, the positive feedback molecules may include the X-linked inhibitor of apoptosis protein (XIAP), tumor necrosis factor α (TNFα), and interleukin-1 (IL-1) (Hoesel and Schmid 2013). The negative feedback circuits may include the NF-kB target genes such as

IkBα, Cylindromatosis (CYLD), and A20. The NF-kB-associated pathways have been proposed as the potential treatment targets for inflammatory disorders and cancer (Verstrepen and Beyaert 2014; also see Table 11.1).

11.4 The Interleukin-1 (IL-1) Cytokine Family and Associated Pathways

Interleukin-1 (IL-1) is a large cytokine family involved in innate immunity, chronic inflammation, oncogenic mutations, and cancer development. IL-1 proteins are critical in signaling pathways including those of apoptosis, TLR, MAPK, and NF-kB. In silico analysis and the comparison of the mutagenesis and binding energies have indicated that single nucleotide polymorphism (SNP) mutations may affect the complex interactions (Acuner Ozbabacan et al. 2014).

An important pathway that links chronic inflammation with the development of cancer is related to IL-1 receptor-associated kinases (IRAK). The IRAK family has four members including IRAK-1, IRAK-2, IRAK-3 (also named as IRAK-M), and IRAK-4. The IRAK-associated interactions are involved in the regulation of tumor growth, metastasis, immune inhibition, as well as chemotherapy resistance. The dysfunctions in the IRAK signaling pathway among cancer cells may enhance the inflammatory tumor microenvironment and result in cancer progression (Jain et al. 2014; also see Table 11.1).

In addition, the treatment using cytotoxic chemotherapeutic agents (CCAs) may induce a cluster of treatment-associated symptoms among cancer patients (Wood and Weymann 2013). Such cancer treatment-related symptoms (CTRSs) are often shown as fatigue, low appetite, sleep problems, depression, cognitive decline, and alterations in body composition. These symptoms may cause lower levels of quality of life, as well as physical and social difficulties.

Studies have revealed that CTRS may be strongly associated with CCA-caused interleukin-1β (IL-1β) signaling pathways (Wood and Weymann 2013; also see Table 11.1). CCAs may trigger the intracellular stress response networks with the higher levels of IL-1β, IL-6, IL-1 receptor antagonist, and soluble TNF receptor-I/II. Another important factor may be IL-1β-associated central nervous system (CNS) inflammation with the alterations in the hypothalamic and hippocampal functions. These mechanisms provide the implications for potential therapeutic strategies in relieving these symptoms among cancer patients.

11.5 Inflammatory Pathways in the Microbiota

Gut microbiota bacteria are mutualistic microorganisms in the gastrointestinal tract. They are essential in digestion, immunity, and cancer prevention. The alterations in the microbiota environment have been identified pivotal in the pathogenesis of inflammatory bowel disease (IBD)-related and inflammation-caused colorectal

cancer (CRC) (Hu et al. 2013; Kipanyula et al. 2013). Abnormal inflammatory conditions in microbiota have been correlated with CRC development.

In mice models, the deficiencies in the NOD-like receptor family pyrin domain containing 6 (NLRP6) and IL-18 were related to inflammation-caused CRC formation (Hu et al. 2013). Higher levels of tumorigenesis have been associated with inflammation that is microbiota caused and chemokine (C-C motif) ligand 5 (CCL5) driven. Such conditions may activate the IL-6 pathway and enhance epithelial cell proliferation, resulting in cancer formation (see Table 11.1). Moreover, in certain situations the components of microbiota may transmit the susceptibility of CRC between individuals.

These emerging evidences are supporting the correlations between inflammatory signaling pathways and microbial-stimulated carcinogenesis (Kipanyula et al. 2013; also see Table 11.1). Although microbial-stimulated inflammation may provide the protection against pathogens, persistent inflammatory responses may cause secondary damages to the host tissues and lead to tissue fibrosis and carcinogenesis.

For example, genotoxic and mutagenic pathogens such as *Escherichia coli* may lead to DNA damages in different cell types. Inflammatory responses caused by chronic infections from pathogens may also stimulate the carcinogenic activities. An altered microenvironment with increased levels of inflammatory signaling molecules may promote the carcinogenic conversion of host cells (Kipanyula et al. 2013).

The molecules generated during immune responses may result in further DNA damages and the oncogenic mutations. These molecules include the macrophage migration inhibitory factor (MMIF), the reactive oxygen, and nitrogen species' products superoxide and peroxynitrite (Kipanyula et al. 2013). Furthermore, proinflammatory cytokines, adhesion molecules, and growth factors may affect the microenvironment and enhance neoplastic cell survival and proliferation. These mechanisms suggest the importance of microbiota regulations in cancer prevention and treatment.

11.6 Biobehavioral Pathways in Hematopoietic Stem Cell Transplant Patients

As the psychosocial factors may affect cancer progression through biobehavioral pathways, such correlations may also be important among hematopoietic stem cell transplant (HSCT) patients (Knight et al. 2013). These pathways include the inflammatory signaling networks and the vascular endothelial growth factor (VEGF)-associated pathways.

Studies have demonstrated that psychosocial factors may influence the hormonal, messenger, and immune systems. Mediated by the biobehavioral pathways, such effects may have impacts on the overall success of HSCT including the mortality, relapse, progression, and survival (Knight et al. 2013; also see Table 11.1).

The correlations among psychosocial factors, immune functions, and clinical results are significant for the timely immune recovery, the immune control of infections, as well as the elimination of cancer cells (Costanzo et al. 2013). PNI research has indicated that the recovery stage after HSCT may be a "window of opportunity" because stress-associated behavioral factors may affect the survival and well-being of the HSCT recipients.

Specifically, these stress factors may influence the functions of the hypothalamic–pituitary–adrenocortical (HPA) and sympathetic nervous system (SNS) axes (Costanzo et al. 2013; also see Table 11.1). The molecules such as glucocorticoids and catecholamines associated with these networks may affect the bone marrow microenvironment and cell recovery processes. An inflammatory environment may be induced with possible results of severe graft versus host disease (GVHD). These mechanisms highlight the PNI factors in disease recurrence, survival, and quality of life.

11.7 The HPA Axis and the Roles of Melatonin

The individual variations and risk factors that may affect the psychoneurological symptoms in breast cancer patients include perceived stress, malfunctions in the HPA axis, and inflammation (Starkweather et al. 2013; also see Table 11.1). PNI studies of these factors and mechanisms may contribute to the understudied area of cancer research and improve the psychoneurological conditions among cancer patients and survivors.

Specifically, anticancer immunity is affected by psychoneuroendocrine functions including the pineal gland and brain opioid system. Immunosuppression therapies targeting cancer cells may rely on the neuroimmuno-modulation effects, which can be influenced by the blood levels of the pineal hormone melatonin (MLT) (Lissoni et al. 2008).

A study of 846 patients with metastatic solid tumors including non-small-cell lung cancer and gastrointestinal tract tumors showed that the administration of MLT alone could promote disease stabilization and survival time when compared with supportive care alone (Lissoni et al. 2008). The administration of both IL-2 and MLT provided a further improvement in tumor regressions and survival when compared with MLT alone.

11.8 Inflammatory Pathways Associated with Neuroendocrine (NE) Differentiation

In prostate cancer (PCa) cells, the neuroendocrine (NE) cells have been found to affect tumor growth and progression (Tawadros et al. 2013). The underlying mechanisms have been correlated with hormone refractory PCa (HRPC) and the repressor

element-1 silencing transcription factor (REST) (Lin et al. 2016). REST is a transcriptional inhibitor of neuronal genes associated with androgen deprivation and IL-6-caused NE differentiation (NED). It has a key role in hypoxia-caused NED of PCa cells.

Bioinformatics, gene ontology (GO), and gene set enrichment analysis (GSEA) of the transcriptome profiles have revealed the tight relationships among HRPC, REST reduction, and hypoxia-caused tumorigenesis (Lin et al. 2016). The activation of the AMPK signaling pathway and NE development is also essential (see Table 11.1). The elucidation of such mechanisms may contribute to potential therapeutic approaches for the treatment of HRPC, the aggressive type of cancer that is difficult to treat.

In addition, the proinflammatory cytokine macrophage migration inhibitory factor (MIF) has been closely associated with oncogenic activities and the aggressiveness of PCa (Tawadros et al. 2013). Higher levels of MIF during NED in PCa may mediate cancer progression or recurrence, especially in the condition of androgen deficiency. MIF may interact with the AKT and ERK1/2 signaling pathways and result in the cancer cell proliferation and resistance to paclitaxel and thapsigargin-caused apoptosis (see Table 11.1). The MIF-associated pathways have been suggested as the potential target for PCa treatment.

Furthermore, NED has been observed in almost all of the small-cell lung cancers (SCLC) and carcinoid tumors (Chen et al. 2014). In non-small-cell lung cancers (NSCLC), about 10–20 % have been related to NED. NED of NSCLC has been associated with various signaling pathways including the activation of Erk1/2-mitogen-activated protein kinases (MAPK) signal transductions (see Table 11.1). In addition, the suppression of the Akt signal transduction pathway may also be related. Further explorations of the complex Erk/MAPK signal transduction pathways may be helpful for identifying new targets for the therapy of NSCLC with NED.

References

Achyut, B. R., Bader, D. A., Robles, A. I., Wangsa, D., Harris, C. C., Ried, T., et al. (2013). Inflammation-mediated genetic and epigenetic alterations drive cancer development in the neighboring epithelium upon stromal abrogation of TGF-β signaling. *PLoS Genetics, 9*, e1003251.

Acuner Ozbabacan, S. E., Gursoy, A., Nussinov, R., & Keskin, O. (2014). The structural pathway of interleukin 1 (IL-1) initiated signaling reveals mechanisms of oncogenic mutations and SNPs in inflammation and cancer. *PLoS Computational Biology, 10*, e1003470.

Artherholt, S. B., & Fann, J. R. (2012). Psychosocial care in cancer. *Current Psychiatry Reports, 14*, 23–29.

Baumgart, S., Chen, N.-M., Zhang, J.-S., Billadeau, D. D., Gaisina, I. N., Kozikowski, A. P., et al. (2016). GSK-3β governs inflammation-induced NFATc2 signaling hubs to promote pancreatic cancer progression. *Molecular Cancer Therapeutics, 15*, 491–502.

Ben-Eliyahu, S., Page, G. G., & Schleifer, S. J. (2007). Stress, NK cells, and cancer: Still a promissory note. *Brain, Behavior, and Immunity, 21*, 881–887.

Chaturvedi, S. K., & Venkateswaran, C. (2008). New research in psychooncology. *Current Opinion in Psychiatry, 21*, 206–210.

Chen, Y., Nowak, I., Huang, J., Keng, P. C., Sun, H., Xu, H., et al. (2014). Erk/MAP kinase signaling pathway and neuroendocrine differentiation of non-small-cell lung cancer. *Journal of Thoracic Oncology, 9*, 50–58.

Costanzo, E. S., Juckett, M. B., & Coe, C. L. (2013). Biobehavioral influences on recovery following hematopoietic stem cell transplantation. *Brain, Behavior, and Immunity, 30*(Suppl), S68–S74.

De la Roca-Chiapas, J. M., Barbosa-Sabanero, G., Martínez-García, J. A., Martínez-Soto, J., Ramos-Frausto, V. M., González-Ramírez, L. P., et al. (2016). Impact of stress and levels of corticosterone on the development of breast cancer in rats. *Psychology Research and Behavior Management, 9*, 1–6.

Di Minin, G., Bellazzo, A., Dal Ferro, M., Chiaruttini, G., Nuzzo, S., Bicciato, S., et al. (2014). Mutant p53 reprograms TNF signaling in cancer cells through interaction with the tumor suppressor DAB2IP. *Molecular Cell, 56*, 617–629.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Fan, Y., Mao, R., & Yang, J. (2013). NF-kB and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein & Cell, 4*, 176–185.

Fűri, I., Sipos, F., Germann, T. M., Kalmár, A., Tulassay, Z., Molnár, B., et al. (2013). Epithelial toll-like receptor 9 signaling in colorectal inflammation and cancer: Clinico-pathogenic aspects. *World Journal of Gastroenterology, 19*, 4119–4126.

Green McDonald, P., O'Connell, M., & Lutgendorf, S. K. (2013). Psychoneuroimmunology and cancer: A decade of discovery, paradigm shifts, and methodological innovations. *Brain, Behavior, and Immunity, 30*(Suppl), S1–S9.

Hoesel, B., & Schmid, J. A. (2013). The complexity of NF-kB signaling in inflammation and cancer. *Molecular Cancer, 12*, 86.

Hu, B., Elinav, E., Huber, S., Strowig, T., Hao, L., Hafemann, A., et al. (2013). Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proceedings of the National academy of Sciences of the United States of America, 110*, 9862–9867.

Hulett, J. M., Armer, J. M., Stewart, B. R., & Wanchai, A. (2015). Perspectives of the breast cancer survivorship continuum: Diagnosis through 30 months post-treatment. *Journal of Personalized Medicine, 5*, 174–190.

Jain, A., Kaczanowska, S., & Davila, E. (2014). IL-1 receptor-associated kinase signaling and its role in inflammation, cancer progression, and therapy resistance. *Frontiers in Immunology, 5*, 553.

Jensen, S. E., Lehman, B., Antoni, M. H., & Pereira, D. B. (2007). Virally mediated cervical cancer in the iatrogenically immunocompromised: Applications for psychoneuroimmunology. *Brain, Behavior, and Immunity, 21*, 758–766.

Kipanyula, M. J., Seke Etet, P. F., Vecchio, L., Farahna, M., Nukenine, E. N., & Nwabo Kamdje, A. H. (2013). Signaling pathways bridging microbial-triggered inflammation and cancer. *Cellular Signalling, 25*, 403–416.

Knight, J. M., Lyness, J. M., Sahler, O. J. Z., Liesveld, J. L., & Moynihan, J. A. (2013). Psychosocial factors and hematopoietic stem cell transplantation: Potential biobehavioral pathways. *Psychoneuroendocrinology, 38*, 2383–2393.

Lee, J. M., Yang, J., Newell, P., Singh, S., Parwani, A., Friedman, S. L., et al. (2014). β-Catenin signaling in hepatocellular cancer: Implications in inflammation, fibrosis, and proliferation. *Cancer Letters, 343*, 90–97.

Lin, T.-P., Chang, Y.-T., Lee, S.-Y., Campbell, M., Wang, T.-C., Shen, S.-H., et al. (2016). REST reduction is essential for hypoxia-induced neuroendocrine differentiation of prostate cancer cells by activating autophagy signaling. *Oncotarget, 7*, 26137–26151.

Lisanti, M. P., Tsirigos, A., Pavlides, S., Reeves, K. J., Peiris-Pagès, M., Chadwick, A. L., et al. (2014). JNK1 stress signaling is hyper-activated in high breast density and the tumor stroma: Connecting fibrosis, inflammation, and stemness for cancer prevention. *Cell Cycle, 13*, 580–599.

Lissoni, P., Brivio, F., Fumagalli, L., Messina, G., Vigoré, L., Parolini, D., et al. (2008). Neuroimmunomodulation in medical oncology: Application of psychoneuroimmunology with subcutaneous low-dose IL-2 and the pineal hormone melatonin in patients with untreatable metastatic solid tumors. *Anticancer Research, 28*, 1377–1381.

Pant, S., & Ramaswamy, B. (2009). Association of major stressors with elevated risk of breast cancer incidence or relapse. *Drugs Today, 45*, 115–126.

Starkweather, A. R., Lyon, D. E., Elswick, R. K., Montpetit, A. J., Conley, Y., & McCain, N. L. (2013). A conceptual model of psychoneurological symptom cluster variation in women with breast cancer: Bringing nursing research to personalized medicine. *Current Pharmacogenomics and Personalized Medicine, 11*, 224–230.

Subnis, U. B., Starkweather, A. R., McCain, N. L., & Brown, R. F. (2014). Psychosocial therapies for patients with cancer: A current review of interventions using psychoneuroimmunology-based outcome measures. *Integrative Cancer Therapies, 13*, 85–104.

Tawadros, T., Alonso, F., Jichlinski, P., Clarke, N., Calandra, T., Haefliger, J.-A., et al. (2013). Release of macrophage migration inhibitory factor by neuroendocrine-differentiated LNCaP cells sustains the proliferation and survival of prostate cancer cells. *Endocrine-Related Cancer, 20*, 137–149.

Verstrepen, L., & Beyaert, R. (2014). Receptor proximal kinases in NF-kB signaling as potential therapeutic targets in cancer and inflammation. *Biochemical Pharmacology, 92*, 519–529.

Wang, D., & DuBois, R. N. (2014). PPARδ and PGE2 signaling pathways communicate and connect inflammation to colorectal cancer. *Inflammation and Cell Signaling, 1*.

Wood, L. J., & Weymann, K. (2013). Inflammation and neural signaling: Etiologic mechanisms of the cancer treatment-related symptom cluster. *Current Opinion in Supportive and Palliative Care, 7*, 54–59.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yang, E. V., & Eubank, T. D. (2013). The impact of adrenergic signaling in skin cancer progression: Possible repurposing of β-blockers for treatment of skin cancer. *Cancer Biomarkers, 13*, 155–160.