
Inflammation, Chronic Disease, and Cancer: Is Psychological Distress the Common Thread?

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Inflammation, the hallmark feature of immunological response to invading microbes, has been implicated in a growing list of major diseases, including rheumatoid arthritis and lupus, inflammatory bowel disease, pulmonary and cardiovascular diseases, obesity, and diabetes mellitus. The focus on chronic inflammation has intensified since it has been linked with specific types of cancer, particularly those associated with viral infection or an inflammatory response. Although some chronic diseases have long been acknowledged to increase risk of malignancies, it is only within the past decade that chronic inflammation has been hypothesized to be a key factor in the development of cancer. While there is as of yet little evidence to suggest that psychological distress, particularly chronic stress and depression, directly affects the pathogenesis of tumors, there is an increasing amount of scholarship indicating that psychosocial factors directly contribute to the development and maintenance of chronic inflammation. In fact, it is possible that while depression may contribute and increase the levels of circulating pro-inflammatory cytokines, inflammation may itself act on the brain to induce depressive symptomatology. This chapter focuses on the primary

disease categories in which inflammation is a known contributor and discusses the mechanisms by which the inflammatory process interacts with carcinogenesis as well as psychological aspects of chronic inflammation. Some clinical considerations are offered for interventions targeting the anxio-depressive symptoms associated with major illness that may also disrupt the chronic inflammatory cycle and its resultant disease process.

Inflammation and Cancer

In 1863, Rudolf Virchow hypothesized that cancerous tumors originated at sites of chronic inflammation within the human body [1]. Virchow identified the role of inflammation in carcinogenesis when he noticed the presence of leucocytes in neoplastic tissue and suggested that the “limphoreticular infiltrate” reflected the origin of malignancies where inflammatory processes occurred [1]. Virchow’s claim was not investigated for more than a century. Just recently, researchers have begun examining the hypothesized relationship and directing efforts to research the possible connection between chronic inflammation and cancer. Epidemiological studies have demonstrated that chronic inflammation predisposes individuals to a variety of cancers such as thyroid, bladder, cervical, prostate, esophageal, gastric, and colon [1, 2]. About 25% of all deaths from cancer worldwide are attributable to underlying infections and inflammatory

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responses [3]. Chronic infection and inflammatory responses are known to have associations with the development of certain cancers, such as the human papilloma virus (HPV) and its relationship to cervical cancer, or the infection of hepatitis B and C viruses leading to hepatocellular carcinoma (HCC) [4]. Increased risk of tumor growth is associated with chronic inflammation caused by microbial infections and autoimmune diseases (e.g., inflammatory bowel disease and the risk of colon and colorectal cancers), as well as inflammatory conditions resulting from uncertain origins such as prostatitis, which can lead to prostate cancer [5–7]. Chronic inflammation contributes to a tumor promoting environment through various avenues that may include cellular transformation, the proliferation and survival of malignant cells, development of angiogenesis and metastasis, reduction of adaptive immune responses, and tumor response to chemotherapeutic drugs and hormones [7]. The inflammatory response and resultant tumors may be conceptualized as wounds that do not heal [8].

The role of chronic inflammation in the development of cancerous tissue easily becomes convoluted with many aspects that must be considered such as the contributions of various inflammatory cells, mediators, and signaling pathways in cancer genesis [7]. The inflammatory process involves the presence of inflammatory cells and inflammatory mediators which include chemokines and cytokines in tumor tissues, tissue remodeling and angiogenesis [7]. The prime endogenous promoters include transcription factors such as nuclear factor-kappaB (NF- κ B) and signal transducer activator of transcription-3 (Stat3) as well as major inflammatory cytokines, such as Interleukin Beta (IL-1 β), Interleukin 6 (IL-6), Interleukin 23 (IL-23) and tumor necrosis factor alpha (TNF- α) [9–12]. TNF- α was the first factor isolated as an anticancer cytokine but at dysregulated levels within the immune system, its presence mediates a variety of diseases [13]. TNF- α has also been demonstrated to be a major predictor of inflammation [14]. Several pro-inflammatory cytokines have been related to tumor growth, indicating that inflammation is associated with carcinogenesis [1, 15]. These

include IL-1, IL-6, IL-8, and IL-18. Interleukins are involved in different steps of tumor initiation and growth. Specifically, Negaard et al. demonstrated that individuals with hematological malignancies have increased bone marrow micro-vessel density as well as elevated levels of IL-6 and IL-8, possibly contributing to the malignant phenotype [16].

Chemokines are a family of proteins that play several roles in cancer progression, including angiogenesis, inflammation, and cell recruitment and migration. Chemokines also play a central role in leucocyte recruitment to sites of inflammation [1]. Most tumors produce chemokines that are one of two major groups, Alpha and Beta chemokines [1]. Evidence from murine models and human tumors propose that Beta chemokines contribute vastly to macrophage and lymphocyte infiltration in melanoma, carcinoma of the ovary, breast, and cervix, as well as in sarcomas and gliomas [1, 17, 18]. A key molecular link between inflammation and tumor promotion and progression is transcription factor NF- κ B, which regulates TNF, interleukins, chemokines, and other molecular factors [9]. Although NF- κ B is inactive in most cells, there is an activation state that is induced by a wide variety of inflammatory stimuli and carcinogens that, in turn, mediate tumorigenesis [19].

Inter-relationship Between Depression and Inflammation

The relationship between the brain and the peripheral organs, often referred to as the “mind-body” connection, is based on alterations in the endocrine and immune systems that lead to the chemical changes that occur in clinical depression. Pro-inflammatory cytokines, particularly IL-6, have been found to occur in greater quantities in depressed patients [20]. It has also been shown that about 45% of patients being treated medically with pro-inflammatory cytokine interferon-alpha (IFN α) developed symptoms of depression that was reversed once the treatment ended [21]. Inflammation is not only a contributing factor in depression but also in many domains

of medical illness. Among patients diagnosed with major depression, there is evidence to suggest that relationships exist between severity and duration of depression and increased prevalence of other disease processes, such as cardiovascular disease, Type-2 diabetes, a variety of autoimmune diseases and cancer [22]. Major depressive disorders are also more prevalent in patients who suffer from illnesses that lead to chronic inflammation than healthy people [23]. While the presence of an inflammatory disease may initiate depressive symptoms in patients without preexisting psychological disorders, it is also the case that inflammation occurs in depressed patients who are not suffering from concurrent inflammatory disorders [24].

It is now known that the brain is not the “immune-privileged” organ that it was once presumed, as many thought it to be protected by the blood–brain barrier. Rather, the brain is very much influenced by the peripheral immune system where large molecules such as cytokines, chemokines and glucocorticoids originating in the peripheral organs can affect the neuronal pathways implicated in depression [20, 25]. Recently, it has been shown that symptoms of sickness (fatigue, decreased appetite, social withdrawal, disturbed sleep cycles, anhedonia and mild cognitive impairment), the normal bodily response to infection, are triggered by pro-inflammatory cytokines, including IL-1 α and β , TNF- α and IL-6 [20]. These cytokines are responsible for developing the body’s inflammatory (local and systemic) response to invading microbes. In doing so, they also impact neural circuitry within the brain, resulting in the behavioral symptoms of sickness. Such sickness behavior is remarkably similar to the symptoms of clinical depression. It is generally the role of anti-inflammatory cytokines to regulate the duration of these sickness symptoms, possibly by inhibiting pro-inflammatory cytokine production and interfering with pro-inflammatory cytokine signaling [26].

Despite the evidence to support the mechanism by which pro-inflammatory cytokines act on the brain, the directionality of the inflammation–depression relationship is as yet unclear.

As mentioned earlier, there is also research to suggest that depression may predispose people to developing illness. One study attempting to examine the directionality of the inflammation–depression relationship found that baseline depression scores of healthy (no medical illness) patients independently predicted change in IL-6. In contrast, IL-6 did not predict change in depression score [27]. The implication of those findings suggests that depression in previously healthy people may lead to inflammation and inflammation may be the mechanism through which depression potentiates chronic illness.

Rheumatic Disease

Rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are autoimmune conditions that often involve periods of painful swelling and inflammation in the joints and muscles. The inflammatory stages of RA involve the infiltration by inflammatory cells of the synovial sublining, activating the production of pro-inflammatory cytokines, chemokines, and growth factors that results in synovial lining hyperplasia [28]. This process results in the hyper-activation of macrophage and fibroblast-like synoviocytes, which releases additional cytokines, chemokines, and growth factors [28]. This process leads to systemic inflammation and the production of enzymes that destroy the organized extracellular matrix [29]. IL-6, a cytokine that regulates the immune and inflammatory response, is thought to play pathologic roles in RA [30]. Increased IL-6 levels have been found in both serum and synovial fluid in patients with RA, and are also known to correlate with increased disease activity [31, 32]. Baecklund et al. examined disease activity and various secondary symptoms of rheumatic disease, as well as drug treatment to evaluate risk factors for the development of lymphoma, a cancer associated with RA [33]. In a nested case–control study with 41 patients and 113 controls, no association was found between any specific immunosuppressive drug and increased risk of lymphoma. However, a strong association was seen between disease

activity and risk of developing lymphoma. In a similar study, Baecklund et al. investigated both RA patient cancer risk and the danger of anti-rheumatic treatment in lymphoma development [34]. After comparing 378 RA patients positive for malignant lymphoma history with 378 healthy controls, data revealed that individuals with severe disease activity were at increased risk of lymphoma. In addition, increased level of pro-inflammatory cytokines, not drug treatment, predicted lymphoma risk.

Although RA patients' increased risk for developing malignant lymphomas is not completely understood, there are several possible hypotheses that have emerged, including the role of immunosuppression, Epstein-Barr virus infection, and unregulated systemic inflammation [33–39]. In one systematic review and meta-analysis, Smitten et al. characterized the associated risk of four site-specific malignancies that included lymphoma, lung, colorectal, and breast cancer in patients with RA [40]. Results indicated that compared with the general population, RA patients have an approximately twofold increase in lymphoma risk and greater risk of Hodgkins than non-Hodgkins lymphoma. There was also data to suggest an increased risk of lung cancer but a decreased risk for colorectal and breast cancer.

The prevalence of psychological distress among patients with rheumatic diseases is a well known and highly documented phenomenon. Among patients with SLE, there is evidence to suggest a range of 16–65% of patients in active disease states who meet criteria for a psychological disorder [41, 42]. In particular, mood and anxiety disorders appear to be the most frequently occurring [41, 43]. One study showed that 69% of patients diagnosed with SLE were positive for a lifetime history of mood disorder and 52% for lifetime anxiety disorder [44]. Some research links psychological distress, particularly depression, with disease activity in SLE. Segui et al. evaluated patients for depression and anxiety during both active and inactive stages of their disease [42]. Forty percent of participants were diagnosed with a psychological disorder during

the acute phase, but only 10% met criteria a year later when the participants no longer displayed disease activity associated with SLE. However, it is often difficult to determine whether this phenomenon has biological influences or is a psychological adaptation to managing a chronic illness. In a study comparing depressive symptoms in patients with RA and patients diagnosed with osteoarthritis (a chronic non-inflammatory degenerative disease), those with the inflammatory disease were found to have significantly higher depressive symptoms [45]. The authors point out that while the two diseases are similar in terms of pain and functional impairments, the difference may be the neuroimmunobiological cytokine mechanism in inflammatory diseases, postulated to play a role in the development of depression. Psychological distress is associated with increased inflammation in both healthy individuals and RA patients [23, 46]. Depression could facilitate the development of inflammation by leading to poor health behaviors, hormonal dysregulation, and vulnerability to atherogenesis [47, 48]. Depression has also been specifically linked to increased levels of CRP and IL-6, as well as increased weight, which itself has been associated with the release of pro-inflammatory cytokines [49, 50].

While results suggest that some depressive symptoms are correlated with CRP and other biomarkers of inflammation, particularly among women with RA, the relationship may be at least partially explained by disease-related factors, such as increased pain among patients with higher levels of inflammation [51]. The proposition that inflammation leads to depression among RA patients may deserve closer evaluation in longitudinal studies. In addition to experiencing increased pain, patients with RA and SLE often have symptoms such as fatigue and sleep disturbance that may mimic or interact with depression. Results have indicated that depression is a stronger contributor to patient fatigue than self-reported disease activity [52]. Moreover, depression in patients with inflammatory disease predictor of mortality, affects quality of life, increases healthcare costs and contributes to disability [53].

Gastrointestinal Disease

Inflammatory bowel disease (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation and abnormal physiological immune response that flares and then remits throughout an individual's lifetime, often beginning in childhood. Current prevalence rates estimate that inflammatory bowel diseases affect 1.4 million people in the USA [54]. IBD is an example of a disease process where chronic inflammation is known to mediate the risk of cancer and involves both immune deregulation and autoimmunity. The precise mechanisms by which inflammation leads to tumor development are not yet clear; however, patients with IBD, both UC and CD, are at increased risk of developing colorectal cancer [55]. Ulcerative colitis is characterized by the inflammation of the mucosa of the colon and rectum. CD involves inflammation of the bowel wall and may include any part of the digestive tract from the mouth to the anus. Itskowitz and Yio highlight the various predisposing factors that contribute to the link between chronic inflammation and colorectal cancer (CRC) in IBD, explaining how risk of colorectal cancer in IBD increases with longer duration of colitis and with the extent of involvement of the large intestine [56]. There is also a positive association between the severity of colitis and the risk for colon cancer where the risk of colon cancer increases with the severity of disease. Rutter et al. examined risk factors for colorectal neoplasia in patients with UC using a case-control study. Sixty-eight participants were matched with two control patients from the same population on various factors [55]. Results revealed a highly significant correlation between colonoscopic and histological inflammation scores and the risk of colorectal neoplasia, demonstrating that the severity of colonic inflammation is an important determinant of colorectal neoplasia risk. Other studies have shown that IL-6 and STAT3 is activated in the intestinal mucosa in murine models of IBD and colitis-associated cancers [57, 58].

TNF- α concentration is also elevated in the serum and stool of IBD patients [59]. The increased level of TNF- α stimulates the production of other pro-inflammatory cytokines that further promotes the inflammatory process within the micro-environment [60]. Landi et al. examined the specific molecular elements that contribute to inflammatory responses in colorectal cancer and assessed the contributions of IL-6, IL-8, TNF- α , and peroxisome proliferator-activated receptor gamma (PPARG) genes toward the risk of colorectal cancer [61]. Results suggested that a polymorphism in the promoter of the IL-6 gene is associated with a significantly increased risk of colorectal cancer, whereas polymorphisms in the PPARG genes and IL-8 were related to significantly decreased risk. They concluded that IL-6 could be related to CRC through its role in affecting the low-grade inflammation status of the intestine.

The risk of colorectal cancer is much greater in a small subset of IBD patients who also have primary sclerosing cholangitis (PSC), a disorder characterized by inflammation, cholestasis, and fibrosis in the intra-hepatic and extra-hepatic biliary ducts [56, 62]. Shetty et al. compared patients with ulcerative colitis and co-occurring PSC with a random sample of UC controls without PSC and found that 25% of 132 UC patients with PSC developed colorectal cancer or dysplasia compared with 5.6% of 196 controls [63]. This study demonstrates that UC patients with PSC are at increased risk for developing colorectal cancer or dysplasia and therefore should be closely monitored by their physicians. Research also suggests that some anti-inflammatory medications can reduce the development of colorectal dysplasia and cancer [56, 64]. This last factor provides strong support for the relationship between chronic inflammation and resultant carcinoma and suggests that utilization of anti-inflammatory medications may reduce cancer risk.

Itskowitz and Yio suggest several possibilities that explain how inflammation may result in neoplastic transformation and progression in IBD [56]. One theory suggests that an increase in epithelial cell turnover occurs, perpetuating the

molecular and DNA damage caused by heightened levels of pro-inflammatory cytokines and potentially exacerbating the carcinogenic process [56]. Another theory is that the oxidative stress accompanying chronic inflammation among patients with IBD creates an environment that is malignancy prone [65]. While more research is needed to better understand the link, there is mounting evidence demonstrating that chronic inflammatory processes foster an environment where carcinoma is more likely to occur.

Major depression has been shown to occur in 31% of patients diagnosed with CD, and in 27% of patients with UC [66]. Compared with patients diagnosed with erosive esophagitis, those with Crohn's disease (and thus chronic inflammation) have been found to have significantly higher rates of depression (25.4% vs. 8.2%). Depression was also found to be highest among patients with active disease states. Patients with functional gastrointestinal disorders such as irritable bowel syndrome have been shown to have even higher depressive symptoms than patients with organic disorders, such as IBD, as well as more severe depressogenic dysfunctional attitudes [67]. While there is little evidence that psychological distress is related to the onset of IBD, there is more consistent evidence that psychological factors such as depression, anxiety and chronic life stress contribute to disease course. This may be particularly true of daily life stress and depression among patients with UC and CD [68]. One study evaluating more than 450 patients with CD discovered that the odds of a patient presenting with an exacerbation of their illness increased 1.85 times for 1 standard deviation of perceived stress. After statistically controlling for the mood and anxiety components, the association between perceived stress and exacerbation of illness no longer existed [69].

An interesting theory surrounding the recent increase in reported cases of IBD suggests that lack of exposure to certain micro-organisms in industrialized societies may play a role in sensitizing modern immune systems. The theory implicates the over-sanitation of these societies in the rise of major depressive disorder, which may arise from a lack of contact with sources of

anti-inflammatory, immunoregulatory signaling [70]. Due to a paucity of immune training, some predisposed individuals may be at greater risk of unnecessary inflammatory attacks on benign environmental and organic antigens. Increased levels of pro-inflammatory and depressogenic cytokines may lead to a higher prevalence of depressive disorders. This theory is often referred to as the "hygiene hypothesis" and though still in its infancy in terms of supporting evidence, the idea is rapidly gaining momentum. To this end, one randomized double-blind study was able to decrease anxiety in patients with chronic fatigue syndrome by introducing a probiotic [71]. Although these are certainly intriguing results, thus far there is little else in the clinical literature to suggest that intestinal microbiota may influence emotional state.

Patients with inflammatory bowel disease are viewed as a population at high risk for developing colorectal cancer, a leading cause of cancer-related mortality. One study evaluating the psychological implications of having such high-risk status found that among patients with IBD, those with higher perceived social support reported lower generalized distress [72]. Additionally, those with first degree relatives with both colorectal and non-colorectal cancers were found to have higher reported generalized distress. Although there is not yet much research connecting better psychological status with lower incidence of colorectal cancer, it is tempting to surmise whether psychological interventions could improve the course of irritable bowel disease and therefore decrease risk of related cancers.

Obesity and Type-2 Diabetes

The prevalence of obesity is increasing significantly in the USA and recent estimates demonstrate that nearly two-thirds of the population is currently either overweight or obese [73]. When abdominal obesity is accompanied by other metabolic risks such as insulin resistance, low HDL, and elevated triglycerides, individuals are at increased risk for developing Type-2 diabetes, hypertension, hyperlipidemia, and cardiovascular

disease [74, 75]. Type-2 diabetes, hypertension and cardiovascular disease are all complications of disease processes that also involve chronic inflammatory mechanisms. Obesity is associated with a chronic, low-grade inflammation and can itself be viewed as an inflammatory condition since weight gain activates inflammatory pathways [76]. Studies have demonstrated that numerous inflammatory markers are highly correlated with the degree of obesity and insulin resistance [77, 78]. Serum levels of pro-inflammatory cytokines, including IL-6, TNF- α , and CRP are generally all elevated in individuals with obesity and insulin resistance [79].

It is clear that the adipocyte is an active participant in the generation of the inflammatory state in obesity. Adipocytes secrete several pro-inflammatory cytokines that promote inflammation, including IL-6 and TNF- α [80, 81]. Among patients with Type-2 diabetes, these cytokines can enhance insulin resistance directly in adipocytes, muscle, and hepatic cells [82, 83]. Hotamisligil et al. examined the expression pattern of TNF- α in adipose tissue and found that TNF- α plays a role in the abnormal regulation of this cytokine in the pathogenesis of obesity-related insulin resistance [84]. The increased levels of cytokines lead to hepatic production and the secretion of CRP, plasminogen activator inhibitor-1 (PAI-1), amyloid-A, alpha1-acid glycoprotein, and haptoglobin, which are all inflammatory markers that appear in the early stages of Type-2 diabetes and increase as the disease progresses [85]. Panagiotakos et al. evaluated the association between various markers of chronic inflammation in a population-based sample of 3,042 adults and found that compared with participants with normal body fat distribution, individuals with central fat exhibited 53% higher CRP levels, 20% higher TNF- α levels, 26% higher amyloid-A levels, 17% higher white blood cell counts, and 42% higher IL-6 levels [86]. They also found that all inflammatory biomarkers were related to body-mass index (BMI), waist, and waist-to-hip ratios. This study demonstrates a relationship between central adiposity and inflammation that can be associated with increased coronary disease risk. Some research

suggests that obesity stimulates inflammation through oxidative stress, which can result either from high levels of free radical production, a decrease in endogenous antioxidant defenses, or both [87–89]. The oxidative stress that is created activates the pro-inflammatory transcription factor, NF- κ B, continuing to promote low-grade chronic inflammation [90, 91].

Several epidemiological studies have demonstrated that elevated weight and obesity, defined by a BMI higher than 25, results in significant increase for risk of cancer [92–94]. In a large population-based study, Calle et al. found that the relative risk of cancer-related deaths for men and women was 1.52 and 1.62, respectively [94]. The increase in risk was dependent on the type of cancer, with the largest observed risk being for HCC, the most common form of liver cancer. BMI, in both men and women, was also significantly associated with increased mortality due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney. Moreover, men with higher BMI were at increased risk of death from cancers of the stomach and prostate. Women showed increased risk for death from cancers of the breast, uterus, cervix, and ovary. Park et al. examined how obesity enhanced cancer risk and development by studying HCC in mice [95]. Results revealed that dietary and genetic obesity promoted the growth of tumors associated with the liver. There was a direct association between obesity-promoted HCC development and enhanced production of the tumor promoting cytokines IL-6 and TNF, both of which cause hepatic inflammation and activate the oncogenic transcription factor STAT3. Such data suggests that inflammatory mechanisms may mediate the association between obesity and cancer development.

The link between depression and obesity is a well-researched one with copious studies supporting it [96–98]. Both obesity and depression are public health problems with high prevalence rates and carry multiple health implications [99]. Evidence suggests that depressed individuals have about an 18% increased risk of becoming obese [96]. An examination of the association between obesity and depression revealed that large waist circumference and class III obesity

(BMI >40 kg/m²) were associated with higher prevalence of depression among female participants only [100]. In a systematic review and meta-analysis of longitudinal studies examining the relationship between depression, weight, and obesity, results suggested a reciprocal relationship between depression and obesity [101]. In a separate review, Taylor and MacQueen examined the role of adipokines (cytokines that are secreted by adipose tissue) in mediating the relationship between obesity and depression [102]. Data revealed that obesity was generally accompanied by the presence of pro-inflammatory cytokines as well as elevated levels of adipokines. Such inflammation increases the risk for individuals with obesity to develop functional bowel disorders such as irritable bowel syndrome, as well as colorectal cancer [103, 104]. Given that sweeping behavioral changes are often necessary to avoid the extensive tissue damage that may result in uncontrolled Type-2 diabetes, targeting possible depression in patients with obesity and/or diabetes appears to be an important area for clinical intervention. In fact, assessing overweight or pre-diabetic patients for depression may also be a crucial step in prevention of serious medical illness.

Pulmonary and Cardiovascular Disease

Pulmonary disease, in particular chronic obstructive pulmonary disease (COPD), deserves special mention due to the fact that it is a progressive illness initiated and exacerbated by inflammatory processes. The illness involves a significant and generally progressive limitation in airflow of the lungs after long term exposure to irritants and resultant inflammation [105]. COPD is a disease noted for its chronic inflammation in both stable phases and during periods where it becomes exacerbated. It is often associated with comorbidities including cardiovascular disease, diabetes, and hypertension, illnesses involving chronic inflammatory mechanisms. COPD is an important risk factor for atherosclerosis, the beginning stage of heart disease [106, 107]. Several studies have demonstrated that even minimal reductions

in expiratory flow volume elevate the risk of ischemic heart disease, stroke, and sudden cardiac death two- to threefold, independently of other risk factors [106–108]. Even though the mechanisms responsible for this link continue to be examined, persistent low-grade systemic inflammation is believed to play a significant role in the development of clot formation [109]. CRP specifically has been implicated in the pathogenesis of plaque formation [110–112]. Examined data from participants evaluated in the Third National Health and Nutritional Examination Survey to determine whether CRP and other systemic inflammatory markers are present in patients with chronic airflow obstruction and whether they may be associated with cardiac injury [113]. Results indicated that individuals with severe airflow obstruction had circulating leukocyte, platelet, and fibrinogen levels that were higher than in individuals without airflow obstruction. They also discovered that these individuals were more likely to have an elevated circulating CRP level. This data suggests that low-grade systemic inflammation was present in participants with moderate to severe obstruction and was associated with increased risk of cardiac injury.

One of the hallmarks of COPD is a chronic inflammation of the lower airway. COPD increases the risk of lung cancer up to 4.5-fold among long-term smokers [113–115]. Cigarette smokers develop some degree of lung inflammation but individuals with COPD develop a greater degree that progresses with advanced disease [116]. Cigarette smoke induces the release of several pro-inflammatory cytokines and growth factors including IL-1, IL-8, TGF-beta, and G-CSF through an oxidative pathway [117]. The activation of epithelial growth factor receptor (EGFR) is elevated in bronchial biopsies from smokers with or without COPD compared to nonsmokers [118, 119]. The increased activation of EGFR has been identified to be an early abnormality found in smokers at high risk for developing lung cancer [120]. Moreover, NF-kB is activated by inflammatory processes and by oxidative stress. Since NF-kB is highly activated in both COPD and lung cancer, it is possible that

it may provide the molecular association between inflammation and the pathogenesis of tumor in the lung [121].

Among patients with COPD, depression occurs with such a high prevalence that such psychological distress cannot be easily attributed to behavioral factors. In a recent study, prevalence of depression in a Japanese male sample of patients with COPD ranged from just under 30–40%, depending on the screening tool [122]. Severity of COPD also significantly predicted depressive symptoms in participants. In one study investigating whether depression was associated with systemic inflammation in COPD by using a range of biomarkers and several depression and fatigue scales, it was found that TNF- α was correlated with depression score. Patients with a higher TNF- α level had higher mean depression scores. A slightly weaker correlation occurred between TNF- α and fatigue [123]. As COPD results from inflammation and/or changes in immunological repair mechanisms, a “spill-over” of inflammatory mediators into circulation often results in greater systemic inflammation [124]. Systemic inflammation may aggravate any comorbid diseases, such as ischemic heart disease, lung cancer, diabetes and depression. Such co-occurring health problems may increase the severity of COPD, resulting in frequent hospitalizations, increased healthcare costs and disability. Psychological comorbidities, such as major depression and anxiety, affect the patient’s ability to adhere to their physicians’ recommendations and to cope personally with COPD.

Hypertension is a major risk factor for the development of cardiovascular disease, the prevalence of which is dramatically higher in women with a chronic inflammatory disease, such as SLE. In fact, some studies have shown that up to 74% of their patient samples have significant hypertension [125, 126]. It is likely that the pathogenesis of hypertension involves inflammatory mechanisms, including metabolic factors as well as pro-inflammatory cytokines. The inflammatory process involves adipose tissue, which produces cytokines (leptin and adiponectin) [127]. Blood pressure has been found to correlate with circulating inflammatory cytokines, such as IL-6, TNF- α ,

and CRP [128]. One study found that the concentration level of circulating IL-6 and adhesion molecules could be modified by decreasing blood pressure in hypertensive subjects. After successfully treating the high blood pressure of participants, the circulating IL-6 was found to be significantly lower [129]. Relationships between inflammation and autonomic function have also been observed: in a sample of cardiac patients, heart-rate variability (HRV) was demonstrated to be negatively correlated with inflammatory biomarkers, CRP and IL-6 [130].

Hypertension is a significant risk factor for the development of certain types of malignancies [131–133]. In a study of health records evaluating almost 364,000 men, data revealed a direct relationship between higher blood pressure and increased risk of renal-cell carcinoma [134]. Another association was found to occur between obesity and hypertension and higher risk of renal-cell carcinoma. Importantly, after the 6th-year follow-up, the cancer risk rose further with increasing blood pressure and decreased with lowered blood pressure. In a systematic review of articles published between January 1966 and January 2000 examining the relationship between hypertension and malignancy, Grossman et al. suggested that individuals with hypertension experienced an increased rate of global cancer mortality, particularly with regard to renal-cell carcinoma [135].

Evidence suggests that depression and anger suppression (as opposed to anger expression) are strong predictors of hypertension [136]. Other types of psychological distress that are known to relate to higher blood pressure and poorer cardiovascular outcomes include loss of social support, cultural alienation, and difficulty coping with stressful events [137]. In the USA, historically underserved populations are especially likely to have overlapping psychological distress and higher rates of hypertension, particularly among the urban American Indian and African American communities [138, 139]. Recent research demonstrates that this pattern is also true among newly urbanized peoples, such as urban black South African community. Among a sample of urban black South Africans with hypertension, psychological distress

was associated with higher blood pressure as well as left ventricular hypertrophy [140]. It is interesting to note that depression among historically neglected communities is linked not only to hypertension, but also to cardiovascular disease, obesity, and chronic inflammatory diseases.

Despite increased media attention focused on prevention of cardiovascular disease (CVD), it continues to be the leading cause of death in the USA and the second most common cause of death worldwide [141]. Researchers have recently begun to examine the role of inflammation in atherogenesis and thrombosis and found that inflammatory processes play a role in all stages of atherothrombosis, known to be the underlying cause of approximately 80% of all sudden cardiac deaths [142]. The molecular process involves a response to oxidized low-density lipoprotein cholesterol, injury, or infection whereby leukocytes bind monocytes to the site of a developing lesion. The monocytes become macrophages, forming foam cells and initiating fatty streaks [143]. The macrophages are the main atherosclerotic inflammatory cells that induce a micro-environment that facilitates inflammation. At this stage, activation of macrophages, T lymphocytes, and smooth muscle cells (SMCs) leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis [143, 144]. In a study of carotid artery intima-media thickness (IMT) in hypertensive older adults, researchers found that inflammation, as measured by CRP, was one of the few predictors of arterial IMT [145]. In fact, new therapies aimed at preventing and treating atherosclerosis have targeted cytokine-based inflammatory mechanisms precisely because of the role of chronic inflammation in the development of atherosclerotic plaques [146].

Several studies have shown that elevations in CRP predict future risk of coronary episodes [147, 148]. Specifically, Pasceri et al. examined the effects of CRP on the expression of adhesion molecules in both human umbilical vein and coronary artery endothelial cells and found that CRP induces adhesion molecule expression in human endothelial cells in the presence of serum [149].

These findings support the hypothesis that CRP may play a direct role in promoting the inflammatory component of atherosclerosis. Sakkinen et al. evaluated the relationship between CRP and the development of myocardial infarction (MI) over a 20-year period in men in the Honolulu Heart Program and found that the odds of MI increased not only in the first few years of follow-up, but also as far as 20 years into the follow-up period, indicating that inflammation continues to affect the atherosclerotic process throughout all stages [150]. IL-6 is understood to be the principle pro-coagulant cytokine and can increase plasma concentrations of fibrinogen, plasminogen activator inhibitor type 1 and CRP, thereby amplifying inflammatory and pro-coagulant responses [149, 151].

Recent attention has focused on the role of mood disturbance among cardiac patients recovering from acute MI as results have suggested that depression contributes to adverse outcomes following cardiac events [152, 153]. In addition to other complications of cardiovascular disease, depression is known to increase the risk of mortality among this population [154]. In fact, the rate of mortality among depressed patients with cardiovascular disease is twice that of their non-depressed peers. Depression has also been demonstrated to have a predictive role in the development of coronary heart disease (CHD) in healthy individuals [155]. The risk of developing CHD has been shown to be about 60% greater in depressed but otherwise healthy patients. Depression is associated with poor health behaviors, higher life stress, passive coping styles as well as behavioral risk factors such as smoking, high fat diets, sedentary lifestyle and lack of adherence to medical advice [154]. Depression also plays a role in the development of local and systemic inflammation, which is associated with CHD [156]. Following episodes of cardiac arrest and cardiopulmonary resuscitation (CPR), survivors often suffer global cerebral ischemia after periods of brain blood flow deprivation. The levels of pro-inflammatory cytokines have been shown to increase dramatically following cerebral ischemia and this often results in the transportation of circulating immune cells across the

blood–brain barrier [157]. Data indicate that the prevalence of depression rises considerably following the occurrence of cerebral ischemia, further exacerbating neuro-inflammation.

Treatment Considerations

Building on the past decade's examination of the psychological contributors to inflammation and consequent disease and cancer, an interesting question is whether psychological intervention may disrupt chronic inflammation and its resultant disease process. A few promising studies have attempted to shed light on the answer by targeting depressive symptoms in patients diagnosed with cancer. In one randomized clinical trial, newly diagnosed breast cancer patients with clinically significant symptoms of depression were assigned to one of two groups: one received the psychological intervention and the other only an assessment. Participants who received the psychological intervention demonstrated significantly reduced levels of depression, pain, fatigue, and pro-inflammatory biomarkers [158]. Interestingly, the effect of the intervention was mediated by its effect on depressive symptoms. In another randomized clinical trial, both depressed and nondepressed women post coronary artery bypass graft (CABG) surgery were assigned to either home-based cognitive behavioral therapy (CBT) or no intervention [159]. Depressed post-CABG women demonstrated decreased natural killer cell cytotoxicity (NKCC) as well as a higher frequency of infectious illness in the first 6 months after CABG. Depressed women who received the intervention demonstrated an increase in NKCC ($D=0.67$) and a decrease in IL-6 ($D=0.61$), CRP ($D=0.85$), and postoperative infectious illnesses ($D=0.93$). These results indicate that psychological status is related to impaired immunological functioning and increased rates of preventable illness.

Another angle examined in recent years has been the pharmacological treatment of depression, particularly with regard to selective serotonin-reuptake inhibitors (SSRIs) and tricyclics. Researchers have found that activation of the

serotonin 5-hydroxytryptamine (5-HT) 2A receptor, known for its role in brain neurotransmission, results in inhibition of TNF- α mediated inflammation [160]. One clinical trial that involved SSRI treatment of patients with major depression demonstrated a significant decrease in TNF- α and CRP [161]. The changes reflected similar decreases in self-reported depression symptoms. Similarly, other studies found that among patients with major depression treated with an SSRI, IL-6, IL-1 β and TNF- α levels were significantly lower post treatment [162, 163]. It has been demonstrated that the presence of serotonin is required for expression of the inflammatory markers IL-6 and TNF- α . However, it is interesting to note that lower serotonin levels increase, and higher levels decrease, the expression of pro-inflammatory cytokines [164]. The inverted U-shaped trend suggests that serotonin, and therefore mood state in general, is significant in influencing the inflammatory mechanism [160].

Conclusion and Future Directions

A current major debate among health care providers centers on the nature of the role of chronic inflammation in the pathogenesis of cancer. While it appears likely that the inflammatory mechanism is a major contributor toward a tumor-promoting environment that may also involve cellular transformation, the proliferation and survival of malignant cells, development of angiogenesis and metastasis, and reduction of adaptive immune response, direct causation between inflammation and tumor has not yet been established. Due to the rapid expansion of clinical and scientific literature on the topic, it is possible that more decisive evidence will be discovered within the next 5 years. Of perhaps equal interest (though perhaps to slightly different parties) is the interaction between psychological distress and chronic inflammation. While the directionality of this relationship remains unclear, and there is even evidence supporting bi-directionality, data suggests that psychological factors such as major depression, anxiety, chronic and daily life stress

and anger suppression may trigger an inflammatory response. Unregulated, and often aggravated by the contribution of behavioral factors (dietary obesity, smoking, sedentary lifestyle), such immunological response often develops into chronic disease, some of which have been discussed in this chapter. Although there is no evidence to support a direct effect of psychological distress on the development of malignancies, psychosocial factors should be a target of critical importance in clinical settings as they are often modifiable and such intervention may alter or even prevent the course of chronic diseases associated with cancer development. Much of the literature discussed in this chapter indicated that illnesses such as rheumatic disease, gastrointestinal disease, obesity and Type-2 diabetes, and pulmonary and cardiovascular disease all have increased risk cancer development associated with chronic inflammation. The obvious and necessary question that follows is whether, and to what extent, reduction of psychological distress could improve the course of certain inflammatory diseases (or diseases where inflammation is a major feature) and therefore decrease risk of cancer.

The interaction between psychological distress and chronic disease is most acute in the health disparities among historically underserved populations in the USA, particularly among some American Indian/Alaska Natives (AI/AN), African American and Hispanic communities. Various risk factors contribute to such health disparities including ethnicity, social economic status, age, gender, literacy, transportation, and availability of services [165]. Compared with non-Hispanic Whites, AI/AN, Hispanics, Asians, and Pacific Islanders have much higher rates of cancer [166]. National data revealed increased long-term rates of renal-cell, HCC, thyroid, melanoma, bladder and pancreatic carcinomas as well as increased mortality rates from melanoma, esophageal, pancreatic, and liver cancers [166]. Ethnic and racial minority groups in the USA, particularly non-Hispanic Blacks, have a higher prevalence of CVD risk factors. Racial discrimination contributes to disparities in health-related domains, as new studies have linked self-reported

experiences of discrimination to adverse cardiovascular health outcomes and hypertension and have been more pronounced for African Americans [167, 168]. In fact, among a sample of older African American adults, experiences of discrimination have been associated with increased levels of pro-inflammatory cytokines [169]. Understanding the role of psychosocial factors can provide important targets for clinical assessment, connection with resources and interventions. Clinical literature examining health disparities within the context of the interaction between psychological distress and chronic disease is a relatively new but rapidly expanding field and warrants more efforts in this promising direction.

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Psychological Aspects of Cancer

Carr, B.I.; Steel, J. (Eds.)

2013, XIV, 419 p., Hardcover

ISBN: 978-1-4614-4865-5