

Psychoneuroimmunology and Immunotoxicology: Implications for Carcinogenesis

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A number of researchers have documented an association between depression and immunological dysregulation (1, 2). Extending this line of work, Jung and Irwin (3) reported a provocative and potentially important finding: Major depression interacted with cigarette smoking to promote lower natural killer (NK) cell activity. Among 245 men, NK cell activity was similar in nondepressed smokers and nonsmokers; however, smokers who met diagnostic criteria for major depression had lower NK cell activity than depressed nonsmokers. Thus, immune changes could not be attributed to the simple effects of smoking.

These data are notable for several reasons. First and foremost, they address the question of depression as a risk factor for cancer, and suggest new avenues for exploration (3). However, they also have broader implications for the burgeoning field of immunotoxicology—they highlight the importance of assessing psychological variables such as depression or stress as cofactors in investigations of hazard identification and risk assessment (4). We consider each of these issues in turn.

DEPRESSION AND CARCINOGENESIS

Jung and Irwin (3) argue that their data provide one explanation for the inconsistent epidemiological evidence linking depressive symptoms and cancer risk. As they note, NK cells are thought to play a role in immune surveillance through their destruction of malignantly transformed cells; in addition, the sensitivity of NK cell lysis to depression or stress is well-documented (3, 5). Accordingly, depression-related deficits in immune surveillance in smokers could have an impact on tumor progression.

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However, depression also alters other processes relevant to the initiation of carcinogenesis. Most carcinogens seem to induce cancer by damaging DNA in cells, thereby producing abnormal cells; as a consequence, mechanisms for repair or destruction of damaged DNA are critical, inasmuch as faulty DNA repair is associated with an increased incidence of cancer (6).

Stress may alter these DNA repair mechanisms; for example, in one study, lymphocytes from psychiatric inpatients with higher levels of depressive symptoms demonstrated impairment in their ability to repair cellular DNA damaged by exposure to x-irradiation (7). In additional work, the levels of O⁶-methyltransferase, an important DNA repair enzyme induced in response to carcinogen damage, were significantly lower in splenic lymphocytes of rats subjected to rotational stress than controls (8). Stress was also associated with an increased frequency of sister chromatid exchange (SCE) in rat cells (9); SCE reflects cytogenetic damage and genomic instability that could be a preclinical marker for cancer (10). Consequently, there are several avenues through which depression and stress can promote carcinogenesis.

Stress also seems to modify another carcinogenesis-relevant pathway. Apoptosis is a process of genetically programmed alterations in cell structure that leads to failure of proliferation and differentiation, and eventual cell death (11). Induced by a variety of toxic insults, apoptosis is thought to function to protect against the appearance of heritable phenotypic changes in cells. Thus, apoptosis is another important defense against the development of malignant cells. Low concentrations of tumor-promoting phorbol esters specifically block apoptosis *in vitro* induced by either growth factor deprivation or ionizing radiation (12).

In an academic stress study, lymphocyte death was decreased during examinations relative to a lower-stress baseline after phorbol ester inhibition of radiation-induced apoptosis in peripheral blood leukocytes (PBLs) (11). Taken together, these data suggest that depression and stress might have direct effects on carcinogenesis through modifications in DNA repair and apoptosis (7, 8, 11), as well as indirect effects, through the poorer destruction or elimination of abnormal cells by reduced NK cell activity (3, 5).

IMMUNOTOXICOLOGY

Immunotoxicology is a relatively new field "... concerned with understanding the potential deleterious effects of chemical xenobiotics on the immune system"(Ref. 4, p. S131). Studies addressing relationships between exposure to potential toxicants and altered host resistance echo a theme that is quite familiar to psychoneuroimmunology (PNI) researchers: What are the clinical correlates of smaller immunological changes, and how should risk be measured? Although immunotoxicology researchers have not examined stress or depression as cofactors in risk assessments, the finding that smoking and depression were synergistic in their effects on NK cell activity (3) highlights the importance of incorporating psychological variables in hazard identification investigations.

Other data also have suggested that vulnerabilities are not merely additive. For instance, both stress and depression can augment the adverse effects of aging on immune function (2, 13). Indeed, individuals who demonstrate larger age-related immunological impairments may manifest the greatest clinical consequences related to stress; for example, antibody responses to an influenza virus vaccine were substantially poorer among chronically stressed spousal caregivers over the age of 70 than among those who were either younger and/or noncaregivers (13). The significantly increased mortality from influenza (as well as other infectious diseases) among older adults emphasizes the meaningfulness of these findings (13).

Immune dysregulation associated with exposure to an immunotoxicant may be exacerbated in a person who is depressed or stressed, thereby increasing the risk for adverse health outcomes. These effects may be measurable in an individual or on a population level, particularly in subpopulations that are more vulnerable, such as older adults. Age, genetic background, gender, and psychological stress may interact with environmental immunotoxicants and contribute to the increase risk for illness such as viral infections and cancer (14).

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