Neuroimmune mechanisms in cancer: implications for psychiatry

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Psychosomatic research has been long concerned with abnormal psychological mechanisms in cancer patients. This reflects the often huge emotional impact of the illness and persisting attitudes of fear and stigma that society attaches to it. At diagnosis, up to 30% of patients qualify for a formal psychiatric diagnosis, most commonly an adjustment disorder. As the illness progresses, incidence rises, roughly in parallel with increasing physical morbidity.[1]

The evidence that psychological processes can modulate tumour activity is now accumulating. Depressive spectrum disorders and certain abnormal coping styles as well as lack of social support, appear to reduce survival.[2] Several studies have shown enhanced survival in patients who have received psychological intervention.[3] The focus of much current work is concerned with the biological mechanisms by which this may occur. Psychoneuroimmunology (PNI) examines the sequelae of stress states on neuroendocrine and immunological systems and has, at this early stage of its development, produced some intriguing findings with relevance to oncology. What follows is a brief summary of the current neurophysiological status of PNI.

Immunity and health

The immune system is no longer seen as a functionally autonomous entity but one that is integrated with diverse body systems, in particular, endocrine, neural and psychic.[4] This is made possible by multiple reciprocal communications between these systems, where a response in one system has repercussions on the other. This allows for more rapid homeostatic adjustments to diverse stimuli (eg. infection, psychological stress) than would be otherwise possible. The integrative nature of the immune system provides the basis for behaviourally induced changes in immune function and vice versa.

The HPA axis and immunity

The hypothalamic-pituitary-adrenal (HPA) axis is thought to be activated by psychological stress through its afferent connections with the limbic system.[5] In response, corticotrophin releasing factor (CRF), released by the hypothalamus, releases adreno-corticotrophic hormone (ACTH) and related pro-opiomelanocortin – (POMC) peptides from the anterior pituitary into the systemic circulation. The adrenal gland produces glucocorticoids in response. The resultant hypercortisolaemia (well documented in stress states) has multiple inhibitory effects on immunological parameters including inducing lymphocyte apoptosis and inhibiting lymphokines (particularly interleukin-2 and interferon-γ) and cell surface molecules; these effects are probably mediated via cytoplasmic inhibition of nuclear factor kappa B (NF-κB) in lymphocytes.[6] The relevance of this to oncology has been demonstrated using stress paradigms in animals, which produce cortisol-dependant increases in tumour growth.[7] *In vivo* administration of glucocorticoids decreases the anti-tumour capacity of cytotoxic lymphocytes.[8]

Autonomic and opioid pathways

Other pathways of glucocorticoid-independent neuroimmunomodulation exist. Primary and secondary lymphoid organs receive extensive innervation from the sympathetic nervous system.[9] Lymphocytes themselves bear ß-adrenergic receptors and are inhibited *in vitro* and *in vivo* by ß-adrenergic agonists,[10] such as adrenaline. Sympathetic ablation in animals increases the severity of experimentally induced allergic encephalomyelitis and adjuvant-induced arthritis, although no data is available on the effects of same on tumour growth. Stress, depending on its duration, causes elevation of sympathetic tone in humans as reflected by increased serum concentrations of neuropeptide Y and urinary concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG).[11]

It has been known for some time that lymphocytes bear receptors for many of the pituitary-derived peptides, including opioids, ACTH, prolactin and growth hormone,[12] and can produce biologically active endorphins.[13] Stress paradigms leading to increased opioid secretion in animals generally has an inhibitory effect on immune parameters including natural killer activity (NKA) *(see below)*.[14] Adrenalectomy or adrenal-medullectomy attenuates opioid induced effects, as does naloxone.[15]

With regard to tumour studies, the findings are most intriguing. Animals subjected to stress paradigms that increase opioid secretion display increased experimental tumour growth whereas no increase is seen in stress paradigms that *don't* increase opioid release.[14] This suggests that there are non-glucocorticoid mechanisms involved in opioid-mediated tumour growth promotion.

Immune dysfunction in psychiatry and oncology

It is not therefore surprising to find that in states of distress (depression, bereavement, etc.) multiple abnormalities have been described in the immune system, enumerative and functional as well as more tangible indices of immune dysfunction, such as increased incidence of the common cold, slower wound healing and increased titres to herpes and Epstein-Barr viruses.[16,17]

A functional parameter, with particular relevance to

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oncology, is natural killer activity (NKA). NK cells, a subpopulation of circulating lymphoid cells, have spontaneous cytolytic activity against a variety of tumour cells and virally infected cells. There is increasing evidence that NK cells have the ability to mediate natural resistance against tumours *in vivo* (as well as certain viruses and other microbial diseases) and may play an important role in immune surveillance, particularly against metastasis formation, even in tumours not normally associated with a vigorous immune response, like breast or lung cancer.[18] Serum from patients with various metastatic solid tumours inhibits NKA and animals with low levels of NKA have been shown to develop an increased number of spontaneous and experimental tumour metastases.[19]

With regard to breast cancer, it has been suggested that the oestrogen receptor antagonist, tamoxifen, may exert its effects by augmenting NKA. ß-oestradiol has potent NK inhibiting properties and significant increase in NKA has been found after short-term tamoxifen treatment.[20] Importantly, decreases in NKA are seen in depressive illness, which recover on treatment of same.[21]

Psychological intervention in melanoma patients has been shown to improve survival *in parallel with* concomitant increases in NKA.[3] This apparent ability to manipulate immune parameters *in vivo* has apparently long been known in animal models. More recently Spector *et al*[22] demonstrated an up to 40-fold increase in NKA using classical conditioning models in rats.

So while a potential mechanism exists whereby psychological mechanisms may affect biological ones, it is also worth noting that the reverse may occur. Certain cancers (particularly pancreatic) may present with psychological symptoms. This may be due to the central effects of tumour-derived cytokines, such as interleukin-1 and tumour necrosis factor-α.[23] Saturable transport mechanisms exist for these and other cytokines and limbic cortical areas bear receptors for them.[24] Indeed, central (intracerebroventricular) or peripheral administration of pro-inflammatory cytokines promotes reliable increases in ACTH release.[12]

Clinical implications

The at times bewildering complexity of these and other neuro-immune interactions as well as their influence on psychological and endocrine systems, underpins the fact that we are now making serious inroads to one of the last unchartered territories of medical science: the mind-body interface. As psychiatry becomes assimilated into the general hospital setting it is only appropriate that the speciality actively integrates itself with research in this area.

On a more clinical note, it is important to emphasise that the primacy of the intrinsic biology of the neoplastic process is not being called into question by PNI research. While no data exist on the effects of appropriate psychopharmacological intervention on survival, a considerable literature exists to support improved survival, using psychotherapy models.

Spiegel[25] used weekly supportive group therapy and self-hypnosis for pain in 50 patients with metastatic breast cancer. Compared to untreated controls, patients lived significantly longer – 37 months vs. 19 months ($p < 0.0001$). Fawzy *et al*[3] reviewing educational, behavioural and individual and group psychotherapy interventions, in diverse groups of cancer patients, refer to five rigorous studies using one or more of the above models, that have shown improved survival in treatment groups. Moreover this latter trend paralleled improved psychological functioning. These results indicate that the administration of psychological care to cancer patients should no longer be seen as a fairly haphazard affair but as an important adjuvant to cancer treatment, with prognostic implications. This has been reflected by the establishment, and growth of, the sub-speciality of psycho-oncology within liaison psychiatry.

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