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Editorial Comment

The multifaceted value of antidepressants in cancer therapeutics

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Prostaglandins are ephemeral, infinitesimal lipid signalers self-regulating every cell in the body, including those subserving mood and immunity. At first, prostaglandins were perceived as master switches, but are now believed to regulate every component of cellular microanatomy and physiology,[1] including those of the organelles, cytoskeleton, proteins, enzymes and nucleic acids.[2] They signal cell-to-cell, tissue-to-tissue, organ-to-organ, brain-to-body, body-to-brain, and body as a whole and differentiate between function and dysfunction of every cell. Prostaglandins regulate the synthesis, inhibition and expression of genes,[3] and the growth, differentiation and replication of cells.[4,5]

Amongst the mechanisms of carcinogenesis are up-regulation of cyclooxygenase, oncogene synthesis and expression, viral activation, signal disruption, accelerated cell replication, failed apoptosis, tumour initiation and promotion, angiogenesis, metastasis, immunosuppression and autoimmunity. All fall within the orbit of prostaglandins and their forming and degrading enzymes.[6–10] Isolation of such isoforms of cyclooxygenase as COX-2, and the synthesis of selective COX-2 inhibitors has stimulated research into the expression of this isoform in cancer and its role in apoptosis. COX-2 is up regulated in many cancers.[11] In a population study, aspirin may have reduced the risk of colon cancer by 40%.[12]

When synthesised excessively, prostaglandin E2 depresses cellular and humoral immunity, allowing pathogens to replicate.[13–15] Prostaglandins regulate the physiology, immunity, replication and toxicity of microorganisms and the resistance of their hosts.[13–15] Lithium and antidepressants have potent anti-prostaglandin, immunostimulating[16,17] and antimicrobial properties. Evidence to date shows that lithium has antiviral and antibacterial properties, while antidepressants have antiviral, antibacterial, antiparasitic and fungicidal properties,[13–15] when it is estimated that pathogens cause 20% of cancers. As monoamine oxidase inhibitors, originally used in the treatment of tuberculosis, have potent antiviral and immunostimulating properties, it is not surprising that one of them, Matulane, (procarbazine), is effective in treating stage III and IV Hodgkin's disease.

Following Horton's 1966 report that prostaglandins have powerful actions on the brains of chicks and cats,[18] Horrobin showed that lithium carbonate inhibits prostaglandin E1[19] and Lee showed that by inhibiting the mobilisation of arachidonic acid, antidepressants inhibit prostaglandin E2, phenelzine (Nardil) exerting a more powerful effect in this regard than indomethacin.[20] Horrobin showed that such tricyclic antidepressants as imipramine and clomipramine are weak prostaglandin agonists and powerful antagonists,[21] Mtabaji showed that tricyclics antagonise thromboxanes,[22]and Yaron showed that fluoxetine inhibits prostaglandin E2.[23]

In 1998, B.W. J.H. Penninx and her co-workers reported that chronically depressed people over the age of seventy are 88%

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more likely to develop cancer than their sanguine peers.[24] This study raises the possibility of a potential role for antidepressants in preventing and treating cancer. Many *in vitro* studies show that antidepressants have potent anticancer properties with respect to various antidepressants, mechanisms of action, and cancer cell types.[25–27] Irrespective of their putative mechanism of action, the antidepressants destroyed the cells[25,26] arrested their proliferation,[27] and converted chemotherapy refractory cells to chemotherapy sensitive.[28]

Hydroxyprostaglandin dehydrogenase is the primary prostaglandin-degrading enzyme, highly expressed in normal colon mucosa but lost in human colon cancers. Lack of this enzyme promotes the earliest steps of growth of benign as well as malignant colon tumours. [29] When this enzyme was first characterised, every agent tested in the hope of stimulating it either had no effect or inhibited it. Eventually, Mak and Chen showed that amitriptyline and imipramine powerfully activated the enzyme in mice, especially the kidney enzyme, with more than a thousand fold activation by amitriptyline. Amitriptyline and imipramine had potent activating effects on this enzyme in the brain.[30]

Antidepressants have many uses in cancer care. They can reduce the severity and frequency of hot flashes in patients treated with chemotherapy, and venlafaxine (Effexor) can remit acute neurosensory symptoms secondary to oxaliplatin chemotherapy.[31] The monoamine oxidase inhibitors deprenyl and clorgyline protect non-malignant human cells from ionising radiation and chemotherapy toxicity,[32] and such antidepressants as nefadazone are capable of reversing chemotherapy-induced vomiting.[33] It remains to be determined whether antidepressants alone can reverse malignancies, and whether or when they need to be combined with chemotherapy or radiation.

While lithium has immunostimulating and antimicrobial properties, there is little evidence for its possible antineoplastic actions. Antidepressants have potent analgesic properties, alone or as potentiators of narcotics, and they enhance sleep, appetite and energy. In elevating mood, antidepressants stand to improve compliance with treatment, their immunostimulating and antimicrobial properties relevant to infection secondary to chemotherapy or radiation.

As the response to antidepressants is highly individualistic, many patients require multiple trials before responding, some refractory to all antidepressants, and some relapsing due to tachyphylaxis.[34] Prostaglandins are capable of paradoxically inducing pro- and anticancer actions. Wherever prostaglandin-synthesising enzymes convert arachidonic acid to prostaglandins are possible sites of action of antidepressants. By maintaining these enzymes within physiological limits, antidepressants may prevent cancer by preserving apoptosis and immune surveillance, inactivating viruses, activating suppressor genes, inhibiting oncogenes and normalising cell replication. Epidemiological studies have failed to confirm the suspicion that antidepressants may induce breast cancer. However, breast cancer has been reported in three men taking selective serotonin reuptake inhibitors.[35]

Of 20 antidepressants available in a particular location, some patients might respond to 10, others to only one. Successfully matching patients and antidepressants may require many therapeutic trials, when time is of the essence. Biological markers are clearly needed. As depressives have hypercoagulable blood, *in vitro* actions of antidepressants on platelet aggregation could be one such marker.[36] Alleviation of anxiety, fear of death, recrimination and remorse by antidepressants can benefit the individual patient, and the impact of antidepressants on the burden of illness of cancer may have a positive effect on health economics.

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