Role of nervous system in cancer aetiopathogenesis

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There have been several reports on tumour tissue innervation, the effect of neurotransmitters on tumour growth, the development of metastases, and the effect of altered nervous-system activity on tumour cell proliferation. In this personal view, we summarise recent findings related to the interactions between the nervous system and tumour cells and suggest further research into the role of the nervous system in the aetiopathogenesis of cancer. Data showing the transmission of signals between the brain and tumour tissue create a complex view of the nervous system in the aetiopathogenesis of cancer. This neurobiological view of cancer aetiopathogenesis suggests that humoral and nervous pathways convey signals from tumour cells to the brain, and that the brain might consequently modulate the neuroendocrine-immune system to regulate tumour growth in peripheral tissues.

Introduction

Cancer research has largely focused on cellular control pathways (eg, mutation of proto-oncogenes and tumour suppressor genes) and the role of the immune system in the recognition and elimination of cancer cells.[1,2] However, as well as the immune system, other regulatory systems, particularly the nervous system, play a part in tumour progression and metastasis.[3] The idea linking the nervous system with the development and progression of cancer can be traced back to the second century AD, when the Greek physician Galen described that so called melancholic women developed breast cancer more commonly than did those of a more sanguine nature.[4] Psychoneuroimmunological studies have shown that psychological and behavioural factors influence the incidence and progression of cancer by changing cellular-immune responses.[5]

Psychoneuroimmunological research of cancer has focused mainly on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system.[6] However, in the past few decades data have shown that the nervous system might modulate tumour-cell proliferation and metastasis via several pathways, including both parasympathetic and sensory nerves. These findings suggest that both humoral and nervous pathways convey signals from tumour cells to the brain, and that the brain modulates tumour growth in the peripheral tissues.[7] This neurobiological hypothesis of cancer aetiopathogenesis is based on several observations, including the innervation of tumour tissues, the effects of neurotransmitters on tumorigenesis, the effects of stimulation or lesions of brain structures and peripheral nerves on tumour incidence and progression, the effects of stress on cancer development and progression, and changes in CNS activity in animals with tumours and patients with cancer.

Several studies have described the modulation of tumour progression by the nervous system and potential mechanisms that transmit signals from tumour cells to the CNS.[8,9] However, many findings remain questionable. In this personal view we summarise studies investigating the interactions between the nervous system and tumour cells, focusing on the interaction between the nervous system and tumours located in peripheral tissues, and we suggest further research in the neurobiology of cancer.

Innervation of tumour tissues

Tumours are not isolated structures within organisms, they interact with their environment by direct cell-to-cell contact and with signalling molecules. Many studies have shown how tumours stimulate the development of blood vessels (neoangiogenesis) to provide a supply of nutrients.[10] Moreover, growth of lymphatic vessels (lymphangiogenesis) and lymph-node metastases have been reported.[10] Evidence also suggests an important role of the nervous system in cancer progression and metastases. Lack of tumour innervation was generally accepted, but recent experimental data suggest that nerve cells can infiltrate and innervate tumours (neoneurogenesis).[11,12] This process is regulated by neurotrophic factors released by tumour cells that induce the adjacent nerve cells to project axons into the tumour. The nerve cells release neurotransmitters, to which tumour cells are responsive.[13] The innervation of tumours might provide support for the possibility of nerve-driven induction of tumour metastasis.[3,10,14]

The role of tissue and organ innervation is not limited to the transmission of signals between the nervous system and target tissues. Denervation and cross-reinnervation experiments have shown that neuronal signals might determine the phenotypic features of innervated striated muscle.[15,16] Therefore, the question as to whether nerves innervating tumours can exert a similar effect on tumour cells arises. If the phenotypic features of cancer cells can be modulated by the nervous system, then denervation of tumour cells, artificial stimulation of nerve fibres innervating tumours, or local application of certain neurotransmitters might offer new treatment approaches.

Effects of neurotransmitters on tumour cells

Close contact between nerve cells and tumour cells suggests the existence of a neuro-neoplastic synapse.[12,17] This contact would provide a basis for direct modulation of the activity of cancer cells by locally released neurotransmitters. This hypothesis is supported by evidence that tumour progression, metastasis, and therapy response of the most common cancers are strongly influenced by an imbalance of stimulatory and inhibitory neurotransmission.[18] Neurotransmitters released from autonomic nerves act as powerful regulators of many other cell and tissue functions (eg, release of