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Point of view

Neural–endocrine–immune complex in the central modulation of tumorigenesis: Facts, assumptions, and hypotheses

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Abstract

For the precise coordination of systemic functions, the nervous system uses a variety of peripherally and centrally localized receptors, which transmit information from internal and external environments to the central nervous system. Tight interconnections between the immune, nervous, and endocrine systems provide a base for monitoring and consequent modulation of immune system functions by the brain and vice versa. The immune system plays an important role in tumorigenesis. On the basis of rich interconnections between the immune, nervous and endocrine systems, the possibility that the brain may be informed about tumorigenesis is discussed in this review article. Moreover, the eventual modulation of tumorigenesis by central nervous system is also considered. Prospective consequences of the interactions between tumor and brain for diagnosis and therapy of cancer are emphasized.

Keywords: Autonomic nervous system; Brain; Cytokines; Tumorigenesis; Vagus nerve

1. Introduction

The central nervous system (CNS) provides a precise coordination of all body functions utilizing the signals from internal environments (Ádám, 1998). To aid such coordination in organisms, highly differentiated systems of visceral receptors have been developed. Visceral receptors are able to monitor a wide range of biological parameters (e.g. concentration of chemical compounds in plasma, osmotic pressure, mechanical pressure, etc.). Therefore, visceral receptors are important components of internal conveying systems that participate in the maintenance of homeostasis (Berthoud, 2004).

A plethora of evidence, accumulated mainly during the first half of the 20th century, indicates that the endocrine and nervous systems integrate and regulate different body functions. In addition, many studies demonstrate that immune mechanisms may also be influenced by these systems (Besedovsky and del Rey, 1996). Lastly, rich interconnections take place between neural, endocrine, and immune systems (Andersson, 2005; Blalock, 2002; Downing and Miyan, 2000),which may constitute a neural–endocrine–immune functional complex (Kvetnoy, 2002). The hypothalamus with its paraventricular nucleus represents an important anatomical link in this complex, which integrates the activities of all three systems (Turnbull and Rivier, 1999).

The nervous and immune systems can bi-directionally communicate by using a common chemical language employing neurotransmitters, neurohormones, hormones, cytokines and the common respective receptors (Savino and

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Dardenne, 1995; Blalock, 2005). The immune system may work as a complex of sensors informing the nervous system about changes in the immune function of organism and about internal threats (Blalock, 1984). The genesis and progression of tumors are intimately interconnected with the immune system. The cells and molecules of the immune system are highly involved in tumorigenesis, on one hand playing an important role in eliminating and annihilating a wide scale of pathogens and transformed cells (Chaplin, 2003; Delves and Roitt, 2000a,b; Parkin and Cohen, 2001) and on the other hand in some cases facilitating tumorigenesis at various stages (Pikarsky et al., 2004; Balkwill and Mantovani, 2001). Tumorigenesis evokes both humoral and cellular responses of the immune system (Chiplunkar, 2001).

In this review, an attempt was done to extend and summarize the recent data supporting the hypothesis that the central nervous system can monitor and modulate tumorigenesis, beyond the role of the vagus nerve alone (Gidron et al., 2005). This assumption was based on a complex of anatomical and functional interrelationships between nervous, endocrine and immune systems, which in the future might open new avenues in cancer research with a possible impact on prevention, diagnosis and therapy of cancer.

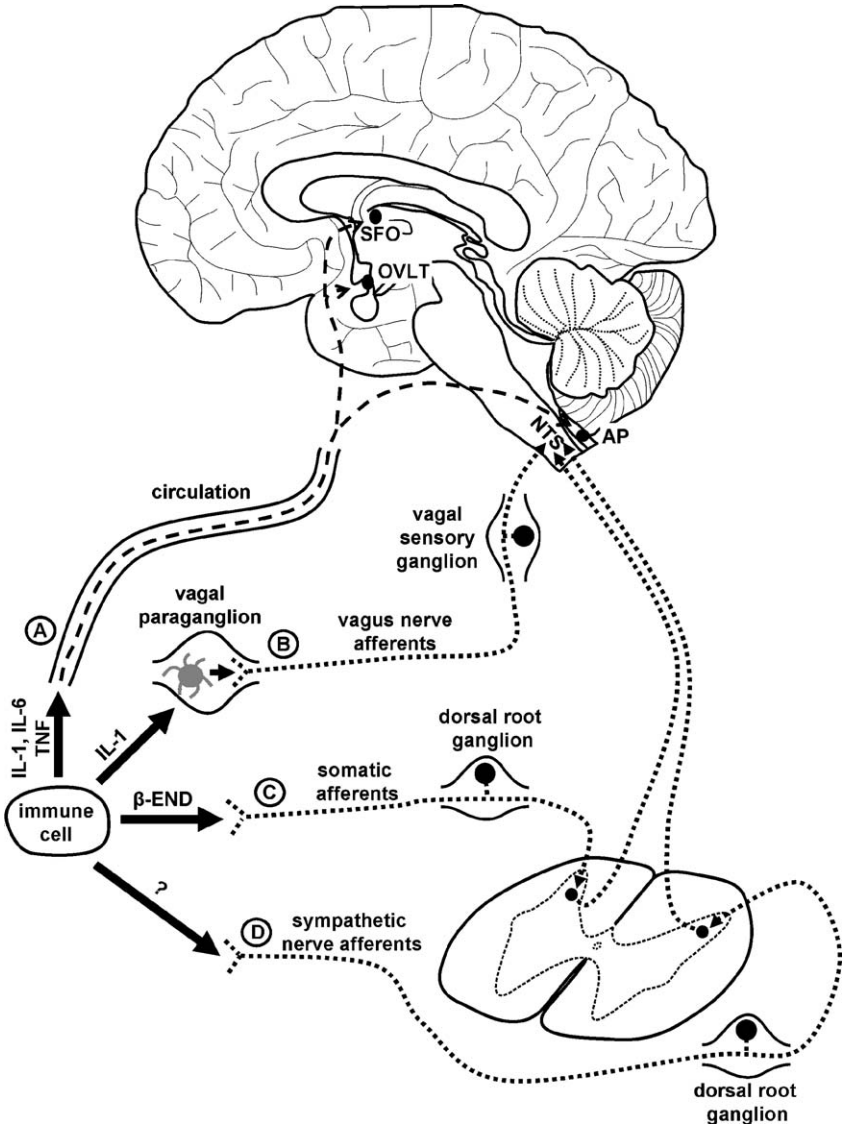

Fig. 1. Pathways, which transmit information from the immune system to the brain (A–D). (A) Cytokines (e.g. IL-1,a IL-6, TNF) circulating in blood stream influence brain activity via circumventricular organs (e.g. subfornical organ—SFO, organum vascullosum lamine terminalis—OVLT, area postrema—AP) or via interaction with brain endothelial cells. (B) Binding of cytokines (e.g. IL-1) to receptors on vagal paraganglion dendritic cells (grayish cell with protrusions) or directly to receptors of the vagus nerve activate vagus nerve afferents that transmit information to the NTS. (C) Endorphins (β-END) might bind to the endings of somatic afferents and produce an analgesic effect. (D) Whether sympathetic nerve afferents are influenced by some compound (?) released from immune cells remains to be investigated. Because the vagus nerve innervates only limited visceral areas, it is possible that information is carried via the sympathetic afferents.