Large Intestine Innervation during CRC

Subjects: Oncology

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Colorectal cancer (CRC), classified as third most prevalent cancer worldwide, remains to be a clinical and research challenge. It is estimated that ~50% of CRC patients die from distant metastases. While, since the 1970s, the consensus is that tumors lack innervation, there are clear evidences of connections between the nervous system and cancer. CRC, as a tumor, possesses nerve fibres from peripheral nervous system (PNS), as part of its microenvironment, as well as axons from both branches of autonomic NS and primary sensory neurons. The structural-functional changes in enteric nervous system innervation of the tumor are important. A connection is suggested between nervous system dysfunctions and a range of neurotransmitters (Nts) (including neuropeptides, NPs), neurotrophins (Ntt) and their receptors in CRC liver metastasis (LM) development. More research is needed to understand the exact mechanisms of communication between the neurons and tumor cells.

Keywords: colorectal cancer, neuropeptides, innervation

1. Introduction

There is evidence of a direct link between the nervous system and cancer through synapses, non-synapse contacts, or humoral modulation, which contribute to two-way communication and influence cancer metastases. Similar to nerve structures, cancer cells produce Nts/NPs and their receptors [1][2]. In CRC patients, structural and functional changes of large intestine innervation can be observed. Interestingly, in the CRC LM, contrarily to the healthy liver, a lack of autonomic perivascular Protein Gene Product 9.5. (PGP9.5)- and Neuropeptide Y (NPY)-immunoreactive nerves can be observed [3].

2. Morphological Changes in Innervation and Neuropeptide Panel in CRC

Structural changes in CRC innervation mostly concern ENS, occurring most commonly in the form of gradual reduction, leading to the total destruction of the nerve structures [4][5][6]. Atrophy of submucosal and MPs within close proximity to the tumor occurs [6][7]. Among the NPs, a decrease in CGRP+ neurons and nerves was observed in both plexus types in the transitional zone between cancerous area and unchanged tissue. The decrease also concerned SP+ nerve fibers in all intramural plexuses [4] and NPY-ergic neurons, as well as the density of nerve fibers in both plexuses [5]. Interestingly, there were no significant quantitative differences in the numbers of SP+, SM+, Vasoactive Intestinal Polypeptide (VIP)-ergic and Pituitary Adenylate Cyclase-activating Peptide (PACAP)-ergic neurons, as well as SM+ nerve fibers in cancer, compared with healthy regions [4][5]. Lower numbers of VIP-ergic and PACAP-ergic nerve fibers were observed in submucosal and MPs than in control sections [5]. In turn, an unchanged density of galanin (Gal)-positive nerve fibers was observed, while the percentage of Gal+ neurons was higher in CRC (46%) than the healthy intestine (35%) [7]. A reduction in the size of Gal+ MPs in the vicinity of the tumor was also reported, as compared with unchanged tissue [6]. Mean Gal content in tumor was lower (9.38 ng/g) than in the morphologically unaltered intestine (12.27 ng/g) [7]. Ultrastructural changes in CRC patients include an increase in the mass of extracellular matrix (ECM), occurrence of myelin-like structures, numerous apoptotic cells, as well as the presence of mast and plasma cells in MPs in the tumor surrounding area [8].

3. The Perineural Invasion (PNI) in CRC

There are ongoing studies on the involvement of perineural invasion (PNI) of cancer cells in the modulation of tumorigenesis [1][2][9]. PNI might be an underestimated mode of metastasis spread, acting in combination with lymphatic and vascular invasion [9][10][11][12], as well as on its own [9]. In CRC, ~16–40% of the patients exhibited PNI characterized by neoplastic invasion of nerves, with altered molecular determinants of the process [9]. It is debated if nerve ablation can delay/inhibit the formation of tumors and/or reduce metastaticity [2].

The markers closely associated with PNI include Nts (e.g., ACh, NE and their receptors: AChR, NE-R), Ntt (NGF, Brain-Derived Neurotrophic Factor (BDNF), Glial Cell line-derived Neurotrophic Factor (GDNF) and their receptors: Neurotrophic Receptor Tropomyosin-related Kinase B (TrKB)), as well as typical NPs (e.g., SP, Gal, NPY/CGRP) [2][9]. PNI is a multistep process, during which a major role is played by the so-called perineural niche, together with numerous signaling molecules (including NPs/NP-Rs) [9]. There is a lack of detailed studies on the mechanisms of nerve–tumor interactions in PNI in CRC, as most of the research concerns different types of cancer (e.g., prostate and gastric cancers, pancreatic ductal adenocarcinoma) [2][9]. However, a prognostic role of PNI was proven in CRC. Defining PNI as a presence of cancer cells inside the nerve sheath, or at least 33% of the nerve periphery surrounded by cancer cells in CRC, shorter 5-year survival rates were observed compared with negative PNI. Additionally, positive correlations between PNI and lymph node metastases, tumor grade depth of invasion, clinical-stage, vessel invasion and tumor growth pattern were observed [13]. PNI was indicated as an independent bad prognostic factor in CRC [9][11][13], affecting both overall survival (OS) [13], cancer-specific survival (CSS) and disease-free survival (DFS) [12]. PNI is also an independent factor in CRC recurrence, points to a more malignant tumor phenotype and, as an important parameter, should be considered in pathological classification of CRC [9]. Recently, a large cohort study indicated that PNI is also more commonly observed in colitis-associated (90%) than in sporadic CRC [12].

4. Functional Innervation Disorders in CRC

Functional disorders in CRC and colitis concern mostly changes in interactions between large intestine innervation and the immune system [6]. Interestingly, such alterations occur on the level of NP-Rs, present on most of the immune cells. Anti-inflammatory roles of VIP and CGRP, as well as pro-inflammatory effects of serotonin and NPY, are also often underlined. In turn, SP has both anti- and pro-inflammatory effects. Apart from neurons, the production of Nts: ACh, choline acetyltransferase (ChAT), acetylcholinesterase, and both muscarinic/cholinergic and nicotinic ACh receptors, was also demonstrated on numerous immune cells (e.g., T and B cells, dendritic cells, macrophages), potentially extending the anti-inflammatory action of ACh in the large intestine [14].

Influence of some ANS Nts (e.g., NE, ACh) and their co-transmitters (e.g., NPY, adenosine triphosphate and/or VIP) on the proliferation of Intestinal Epithelial Stem Cells (IESCs) is also often underlined, despite little knowledge on the mechanisms of that process [15]. It seems that regulation of IESCs proliferation occurs with the participation of both branches of ANS, independently of ENS. Due to more numerous IESCs in the deeper regions of intestinal crypts, SNS and Nts can regulate the proliferation of these cells. ACh is also a PNS mediator, initiating a signaling cascade resulting in suppression of cyclin D1 and a downstream decrease in cell proliferation [15]. The role of ANS–IESC interactions is also considered in the context of differentiation of some kinds of colon cancers from somatic SCs, as well as maintenance of IESC-like properties under neoplastic conditions [15][16].

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