Colorectal cancer and enteric neurons: Should tumors be nervous?

Colorectal cancer (CRC) is one of the most frequent types of cancer in the world and is associated with a high mortality rate with over 700.000 deaths per year. Throughout the past decades, the development of CRC has been primarily associated with genetic mutations and epigenetic events. However, up to date it is recognized that cell types in the tumor microenvironment also play an essential role in cancer development and progression. Recently, the cells of the nervous system, in particular neurons and their nerve fibers, have become a major topic in cancer research. Multiple studies in different types of cancer (e.g. prostate, gastric, skin, pancreatic) have shown that a high nerve density increases the risk for cancer development and leads to cancer with a poorer outcome.

Interestingly, the role of the nervous system in CRC is still relatively unstudied, a remarkable observation considering that the gastrointestinal tract is predominantly innervated by its own autonomic nervous system: the enteric nervous system (ENS). The ENS, also referred to as ‘the brain of the gut’, plays a key role in regulating every intestinal function (e.g. motility, barrier function, secretion) via the release of neurotransmitters/peptides/hormones from its two cellular components: enteric neurons and enteric glial cells. The impact of the ENS on gastrointestinal function becomes apparent when the ENS becomes dysfunctional, leading to major health problems which can even be life-threatening. However, although knowledge has been gained regarding the ENS in the context of developmental, inflammatory and functional diseases, its role in CRC remains poorly understood.

So far, perineural invasion and neoneurogenesis are the only neuronal processes which have been defined in the context of CRC. The detection of perineural invasion is described as an independent prognostic factor for the 5-year disease-free, cancer-specific and overall survival and it is correlated with a more advanced and more aggressive disease. Similar conclusions have been drawn concerning neoneurogenesis in CRC.

Recently, several studies provided preliminary evidence for interactions between the ENS and CRC. The first line of evidence showed that none of the patients (n=802) with megacolon, a disease associated with decreased enteric neuronal innervation, developed colonic malignant neoplasms, while only three patients presented intestinal polyp formation. In addition to neuronal innervation promoting tumor development and progression, CRC-induced alterations within the ENS have also been described. Enteric neurons located near the tumor display different neurotransmitter expression profiles compared to unaffected regions. Moreover, a large variety of studies indicate that different neuromodulators can either promote or inhibit the growth of CRC, highlighting the importance of neurotransmitter release by the ENS in the pathogenesis of CRC. We recently showed that N-myc downstream regulated gene 4 *(NDRG4)*, an established biomarker for CRC, is specifically expressed in (enteric) neurons. Interestingly, a role for *NDRG4* in vesicle

transport in the peripheral nervous system has recently been described, suggesting that NDRG4 is able to modulate subcellular vesicle trafficking and exocytotic release of neurotransmitters.

Based on these observations, we believe that the ENS should be considered as an important player in colorectal carcinogenesis. However, more research is needed to understand the exact mechanisms of neuronal-epithelial communication. Consequently, targeting neuronal innervation represents an appealing new strategy for future anti-cancer therapy.

Glenn Rademakers[1], ***Nathalie Vaes***[1], ***Veerle Melotte***[1,2]
[1]Department of Pathology, GROW - School for Oncology & Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands
[2]Department of Clinical Genetics, University of Rotterdam, Rotterdam, The Netherlands

Publication

The role of enteric neurons in the development and progression of colorectal cancer.
Rademakers G, Vaes N, Schonkeren S, Koch A, Sharkey KA, Melotte V
Biochim Biophys Acta. 2017 Dec