Colorectal cancer and bone tissue

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Colorectal cancer (CRC) is the third most common cancer worldwide. There is a need for the early diagnosis of CRC for a better prognostic outcome. It is, therefore, crucial to understand the CRC pathogenesis in all its aspects. In many cases, one of the main causes of cancer-related deaths is the presence of metastases. In this context, an often overlooked aspect is the metastatic tropism, since CRC, like other cancers, is more prone to metastasize some organs rather than others. Beyond the liver and lung, and differently from other types of cancers, a not usual site of CRC metastases is the bone. However, it may assume a crucial role in the development and the outcome of the disease. Therefore, this review aims to discuss the complex relations between bone markers and CRC pathogenesis, suggesting the use of these molecules as potential targets for therapeutic purposes. Different osteogenic molecules, some of whom are growth factors and are implicated in the different osteogenic pathways, have been proved to also be involved in CRC progression. Some of them are oncogenes, while others oncosuppressors, and in a future perspective, some of them may represent new potential CRC biomarkers.

Keywords: Colorectal cancer ; bone tissue ; growth factors ; metastases ; bone metastases ; molecular relations

1. Introduction

Colorectal cancer (CRC) is widespread across the world; it represents one of the most common cancers, and is among the leading causes of tumor death. Although the etiology of CRC relies on genetic causes, other factors (e.g., family history, inflammatory bowel disease, sex, smoking, folate intake, high intake of fats, alcohol, red and processed meats, sugars) can often actively contribute to its onset [1][2]. Besides, in 70% of CRC cases, it develops from previous neoplasms, such as colorectal bowel adenomatous polyps [3]. The ability of healthy colon epithelial cells to transform into neoplastic cells through the adenoma–carcinoma sequence has been largely described [4]. This sequence is regulated by oncogenes and oncosuppressors, subject to mutations and dysregulations that favor tumor development. High-performance techniques allow for quickly associating phenomena of genomic instability correlated with those processes promoting the development of cancer. These advances point to the possibility of early diagnosis and related therapeutic intervention [5].

A large part of the mortality rate from cancer, as well as tumor recidivism, is due to the staging and the presence or absence of metastases, where it has metastasized and whether there are micro- or macro-metastases. The process of the formation of metastases is characterized by several steps, all fundamental and essential to each other. These steps are not yet fully understood, as well as the molecular pathways that may regulate their occurrence, which genes are expressed and which are not. It is necessary that epithelial cells, following genetic mutations, become the trigger of what then evolves into carcinoma in situ. Later, some cancer cells detach from the primary mass to spread and place themselves in a distant site in the body where they form a metastasis [6]. This process is possible due to the occurrence of a process known as the “epithelial–mesenchymal transition” (EMT).

In this sequence of events, epithelial cells lose their different types of cell–cell and cell–extracellular matrix (ECM) junctions, and the apical–basal polarity, while acquiring an invasive, migratory capacity and secreting multiple components of the ECM [7]. Consequently, these cells are termed circulating tumor cells (CTCs), which invade the ECM, and enter the vascular system. Thanks to the blood flow, CTCs can reach a more distant site, where inputs of the “mesenchymal–epithelial transition” (MET) allow them to acquire capacities to perform extravasation and spread in the parenchyma. Following the inversion of the EMT process, cancer cells acquire epithelial properties again and, first of all, the high proliferative rate to create metastases [8].

Each tumor has preferential sites in which it produces metastases, the so called metastatic tropism [9]. Cancer formation and progression cannot be detached from cancer stem cells (CSCs). CSCs are fundamental in different aspects of tumorigenesis, such as tumor transformation, progression, therapeutic resistance and in metastatic tropism and, consequently, in the formation of metastases [10][11]. Therefore, a greater understanding of these mechanisms is crucial.

The injection of allograft-derived pancreatic cancer tumor stem cells into wild type mice [9] demonstrated the production of metastases only in the liver or lung and liver, depending on whether the cell pool inoculation had been done by intrasplenic injection or in the caudal vein, respectively. It was also shown that the size of the metastatic masses is larger when they form in the liver than the lung. Overall, these findings support how metastatic tropism is affected by the presence of direct blood flow that, starting from the inoculation site, can reach distant organs. Following this event, the implantation of CSCs and the production of metastases is then influenced by the microenvironment of the host organ, which may be more or less suitable.

As for CRC, after total surgical removal of the primary tumor mass, recurrences in the form of metastases can occur preferentially in the liver, lungs, lymph nodes, peritoneum and bone [12] (Figure 1). In this context, the colon and bone tissue, apparently so distant, have something in common. A disease in one of these apparatuses may well affect the physiological state of the other. They are more related than one can imagine. This review aims to describe what is known in the literature, reporting the state of the art on this topic.

Figure 1. Colorectal cancer and its metastatic tropism. Primary tumor cells can be subjected to epithelial–mesenchymal transition (EMT), in order to generate mesenchymal cells with more motility and invasiveness. These mesenchymal cells enter the bloodstream, becoming circulating cancer cells (intravasation). Through the blood flow and under cellular signals, these cells reach distant sites where they metastasize. At this point, the circulating cancer cells come out from the blood stream (extravasation), undergo an inverse transformation, namely mesenchymal–epithelial transition (MET). Metastases are formed in preferential sites (metastatic tropism), such as liver, lung or bone.

2. CRC and Bone Metastases

Compared to liver and lung metastases, bone metastases in CRC occur only in 10–15% of cases [13]. In such patients, the five-year prognosis is less than 5% [14]. The diagnostic picture of these patients is very often characterized by skeletal-related events (SREs), which makes the clinical course of the disease worse. SREs can be constituted by the weakening of the bone structure, at both the trabecular and cortical level, and bone pain, as well as a higher probability of fractures. These pathological events worsen the patient's survival and their quality of life [15][16]. In addition, gender and age are among the factors related to poor survival, Babu et al. presented a clinical study in which CRC patients with bone metastases were male and young. However, whether sex affects the prognosis of these subjects needs to be deeply investigated [17].

Santini et al. [18] collected the clinical data of a cohort of Italian CRC patients with different skeletal problems and bone metastases. According to their findings, the most affected bones by CRC metastases were the spine (65% of cases), hip/pelvis (34% of cases), long bones (26% of cases) and other bone sites (17% of cases). These percentages highlight the need for the early diagnosis of bone problems related to CRC and, therefore, for an equally early intervention to improve and extend the patient's survival. To perform a timely early diagnosis of bone metastases, a scoring technique has been assessed using different clinical factors, such as tumor localization, lymph node metastases, and, finally, the presence of metachronous lung metastases as a third risk factor. This scoring technique can help clinicians immediately identify CRC patients most at risk for the development of bone metastases and make it possible to intervene directly with suitable therapies and relieve bone metastasis-related SREs [19][20].

Baek et al. [21] reported that only 1.1% of 5479 CRC patients showed CRC-related bone metastases. Most of these patients were at a late stage of cancer at the time of the CRC diagnosis. Bone metastases were already present at diagnosis in half of them, while the other half of the patients developed bone metastases during the course of the disease. As expected and independent from the presence of metastases in other organs, the presence of bone metastases is also associated with the presence of different SREs, and this situation led to painful patient survival.

In CRC, bone metastases usually develop later than those in other organs or tissue, such as liver and lung metastases, and there is a preferential link between bone and lung metastases. The prognosis is more severe in cases in which the metastasis of the tumor involves several sites simultaneously [22]. Bone metastases, perhaps more than others, are highly debilitating because of the various bone-related clinical pictures that they entail. Therefore, it would be helpful to be able to diagnose these metastases in a shorter time compared to their onset. Studies on this topic were performed by evaluating cases of rectal or colon cancer cases individually. Recently, Zhenghong et al. [22] have reported a higher percentage of bone metastases in rectal cancer patients than in CRC patients. Probably, this finding may depend on the broader vascularization in the rectum compared to the colon [23][24].

3. CRC and Bone Marrow

Several studies investigated the interactions between colorectal cancer and bone marrow (BM). Taketo et al. reported that the loss of the oncosuppressor SMAD4 is synonymous with CRC advancement. The authors noted, in both in vitro and in vivo experiments, that the loss of SMAD4 implies the lack of the block of expression of the gene C-C motif chemokine ligand 15 (CCL15) [25][26]. In this circumstance, CCL15 is expressed by cancer cells and induces the recruitment of CCR1+ myeloid cells from BM. The C-C chemokine receptor type 1 (CCR1)+ cells have the characteristic of expressing and secreting matrix metalloproteinase 9 (MMP9), which is involved in tumor invasiveness by promoting tumor–stromal interactions. The analysis of human liver metastases, related to CRC, have shown that CCL15 expression, linked to a higher content of CCR1+ cells, is associated with a lower patient survival with respect to CCL15-negative liver metastases [26][27]. SMAD4 and CCL15 are inversely correlated, since the action of SMAD4 induces a negative regulation of the promoter of CCL15, causing the inhibition of CCL15 gene expression. Moreover, inhibitors of the CCL15–CCR1 axis have been suggested as potential therapeutic agents [26].

The role of BM-derived CCR1+ myeloid cells in CRC pathogenesis was also investigated by others research groups. In this regard, Kiyasu et al. very recently reported that the depletion of CCR1 induced a reduction in CRC growth. In particular, after reconstituting sub-lethally irradiated wild-type mice with the BM of wild-type or $CCR1^{-/-}$ mice, they implanted colorectal cancer cells in these mouse models [28]. They noted that mice with CCR1 cell depletion showed a reduction in tumor growth and liver metastases, with respect to CRC mouse models with wild-type BM. The depletion of CCR1+ myeloid cells, genetically induced or by using an anti-CCR1 antibody, caused a suppression of CRC development, indicating CCR1 as a potential therapeutic target [28].

BM metastases, although rare, characterize CRC tumorigenesis due to their high vascularization. Furthermore, the formation of BM metastases is promoted by the slowness of the bone marrow bloodstream, which helps the deposition of the metastatic cells, and the presence of several growth factors, secreted following interactions between tumor cells and BM stroma [29]. The occurrence of these conditions creates the right conditions for tumor development. Metastases in BM often go unnoticed if they are mild, because they are not yet detectable with the most common imaging techniques, or they are detected late when they are well extended and cause severe pain or osteolytic fractures [29]. BM metastases are commonly observed in different solid tumors, such as breast, lung, prostate and, rarely, in CRC patients [30]. Chuwa et al. very recently described a case report of a CRC patient with BM metastases [31]. In particular, this patient presented disseminated carcinomatosis of bone marrow (DCBM). DCBM was diagnosticated by analysis of a BM biopsy, since the patient presented a persistent pancytopenia. BM biopsy analysis showed the infiltration of non-hematopoietic malignant cells and BM necrosis, pivotal features of DCBM [31]. The micro-metastasis of BM is related to poor prognosis [31][32].

An important role in CRC tumorigenesis is played by mesenchymal stem cells (MSCs). These cells, derived from BM, secrete growth factors, cytokines and chemokines into the stroma of developing tumors [33]. Nishikawa G. et al. reported that MSCs promote CRC progression through C-C chemokine receptor type 5 (CCR5) ligands, such as C-C motif chemokine ligand 3 (CCL3), CCL4 and CCL5. These ligands bind the receptor, CCR5, expressed by CRC cells [34]. The authors also observed that high serum levels of CCR5 ligands are related to a poor prognosis in CRC patients, therefore, CCR5 ligands could have value as predictive biomarkers. As previously reported by other groups, it was noted that an inhibition of CCR5, and consequently a reduction in the MSC–CRC cell interactions, corresponds to a reduction in tumor growth [34][35][36].

Although, to date, there are numerous studies indicating that CRC can present a bone-related symptomatology (i.e., osteolytic lesions, skeletal related events, etc.) due to bone metastases, it remains not fully clarified how CRC cells interact with bone cells. The result of this interaction is an imbalance between functional cells within the bone, i.e., osteoblasts and osteoclasts, usually in favor of the former, resulting in the formation of osteolytic metastases, due to a preeminent osteoclastogenesis [37]. In this process, chemokines play a relevant role, leading to the interaction between cancer and host cells. Different chemokines are implicated in the CRC cells' chemoattraction to bone tissue, promoting cancer cell metastasis. The metastatic tropism is due to the interactions between ligands present on cancer cells and their specific receptors present on the cells of certain organs, or vice versa. Gong ZC et al. [38] very recently showed the relevance of CCL3, expressed by BM-derived monocytes, in osteoclastogenesis in CRC bone metastases. The authors reported that CRC cell-derived Epidermal Growth Factor (EGF) activates BM-derived monocytes and stimulates their high CCL3 expression. CCL3 promotes osteoclast maturation and, consequently, osteoclastogenesis [38]. Another interaction implicated in cancer cell recruitment has been demonstrated between CXCR4, expressed in CRC cells, and CXCL12, located in BM-derived cells. Furthermore, Itatani Y. et al. [12] described in detail other interactions existing between CRC cells and other myeloid cells.

Several proteins are differently involved in the relations between bone tissue and CRC by promoting tumor cell invasion and increasing the activity of other molecules with possible interferences in osteoinductive processes. A series of molecules, which are involved in these processes to varying degrees, is addressed below (Table 1).

Table 1. Molecular factors and their mechanisms of action in bone tissue and in Colorectal Cancer (CRC).

Molecular Factor	Mechanism of Action in Bone Tissue	Mechanism of Action in CRC	References
BMP9	Stimulation of the production of bone tissue	Antitumoral, pro-apoptotic	[26][27][28][29][30][31][32][33][34][35][36]
BMP5	Stimulation of the production of bone tissue	Antitumoral, pro-apoptotic	[37][38][39][40]
OPG	Protection of bone tissue from the erosive action of osteoclasts	Oncogene/oncosuppressor	[41][42][43][44][45][46][47][48][49][50][51]
OPN	Involvement in bone remodeling/bone turnover	Promotion of tumorigenesis	[52][53][54][55][56][57][58][59][60][61][62][63]
BSP	Involvement in both bone formation and bone erosion	Protumoral biomarker	[64][65]
TRAP	Osteoclast maturation, bone erosion	Antitumoral biomarker	[66][67][68][69]
RUNX2	Involvement in osteoblastogenesis	Protumoral, anti-apoptotic	[70][71][72]
TGFβ1	Regulation of the proliferation and differentiation of osteoprogenitor cells	Antitumoral	[73][74]

4. Conclusions

Colorectal cancer metastasis is a complex process with many molecular components that act as oncogenes and oncosuppressors. Numerous clinic studies have clarified that bone biomarkers are important players in CRC, as some of them correlate with cancer development and prognosis.

After elucidating the molecular mechanisms that support the bone biomarkers' actions in CRC pathogenesis, new bone molecule-based therapies may be realized. Interestingly, the manipulation of endogenous bone biomarkers by administering siRNA inhibitors could be useful in modulating the expression of downstream pathways. To date, no therapies targeting these molecules have been developed to treat CRC in human clinical trials. Despite this, the use of these bone molecular factors as therapeutic targets is very promising since they are able to regulate the course of the neoplasm.

In conclusion, although the intestinal tract and bone tissue seem to be so far from each other in terms of anatomy, embryology and physiology, they are more related than one can imagine. Several relations have been demonstrated between these two organs, implicating different molecules. The study of their molecular relations opens new horizons for diagnosis and therapies for CRC patients.

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