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Colorectal cancer associated with parathyroid hormone-related protein (review)

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ABSTRACT *Parathyroid hormone-related protein (PTHrP) is associated with various cancer types. This is the first review in the Russian, devoted to this topic, and it is aimed to contribute to the current knowledge about colorectal cancer, by means of summarizing all known information on the topic and identifying future directions for advanced research including on the role of parathyroid hormone-related protein in colorectal oncogenesis, signal channels that participate in mitogenic action of the protein on cancer cells, its effect on tumor angiogenesis. The review includes results of modern research involvement of PTHrP in the formation of chemoresistance of colorectal cancer cells, as well as its influence on the modulation of the epithelial-mesenchymal transition program and other events, associated with tumor invasion. The review presents information proving that PTHrP is related to colorectal cancer cells becoming of an aggressive phenotype; the work also describes molecular mechanisms involved in these processes. There is a growing interest to use this rather unique protein in therapies, which determines active development of pharmaceutical substances based on analogues of this protein. The final goal is to advance the development of effective therapeutic strategies, which could improve the treatment results of colorectal cancer in patients.*

KEYWORDS: *colorectal cancer, parathyroid hormone-related protein*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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INTRODUCTION

Colorectal cancer (CRC) remains the third most common type of cancer and second in mortality (9.4% of all cancer deaths) according to global cancer statistics [1]. The leading cause of patient death and relapse is the emergence of new subtypes of CRC and acquired resistance to currently used treatment methods [2]. In general, CRC is characterized by high heterogeneity due to the influence of various genetic and environmental factors [3]. Factors associated with colorectal tumorigenesis include damage to intestinal tissue, the presence of pathogens, and persistence of inflammatory reactions, which can lead to premalignant lesions that progress to neoplasm [4]. Importantly, neoplastic cells are strongly influenced by the extracellular matrix and surrounding cells, collectively known as the tumor microenvironment [5,6]. Bidirectional communication between the tumor and its microenvironment occurs through the release of autocrine and paracrine factors. As a consequence, numerous molecular mechanisms are activated in tumor cells that contribute to their aggressive abilities [7]. In this case, tumor cells show changes in their cell polarity and acquire a mesenchymal-like phenotype. This process, known as epithelial-mesenchymal transition (EMT), is associated with the acquisition of characteristics of cancer stem cells (CSCs) [8,9], which are a fraction of tumor cells with the ability to self-renew, differentiate, and drug

resistance [10]. The above events are associated with the development of a more aggressive phenotype of CRC cells.

Significant advances have been made in understanding the biology of CRC and the underlying mechanisms associated with the oncogenesis of this disease, in order to find new approaches to its diagnosis and therapy. Several mitogenic signaling pathways are known to play key roles in maintaining the growth and proliferation of CRC. Activation of ERK1/2 MAPK signaling is very common in CRC [11]. There is growing evidence that activation of the PI3K/Akt pathway is associated with CRC and can transform differentiated human colorectal mucosa into a less differentiated and more malignant phenotype. Akt is likely the main kinase that mediates the effects of PI3K on tumor growth and progression [12]. Akt is over expressed in colorectal cancer and correlates with cell proliferation and inhibition of apoptosis, as well as various clinicopathological parameters such as extent of invasion, vascular infiltration, lymph node metastasis, tumor stage and chemoresistance [13]. The regulator of both PI3K/Akt and MAPK signaling pathways is the non-receptor protein tyrosine kinase Src. Since 80% of CRC patients exhibit dysregulated Src expression, which is associated with metastasis and drug resistance, Src inhibition may be a promising approach for the treatment of CRC [14].

In this review, authors considered it appropriate to acquaint readers with information about the relationship between CRC and a unique multipotent biologically active factor — parathyroid hormone-related protein (PTHrP), which, according to world literature, is associated with the development of many types of cancer. It has been shown that PTHrP is expressed by such tumors of the digestive system as cancer of the pancreas [15], stomach [16], esophagus [17], large intestine [18], as well as a number of other systems and organs [19,20,21], and that tumor secretion of this protein is responsible for the formation and spread of tumors. This first Russian-language review on this topic aims to contribute to the current knowledge of PTHrP in CRC by summarizing existing information on this topic and identifying knowledge gaps and future research directions. The ultimate goal is to advance the development of effective therapeutic strategies that can improve cancer treatment outcomes for patients. Scientific achievements related to the study of PTHrP are becoming the subject of practical developments in the field of medicine. There is growing interest in harnessing the effects of this unique protein for therapeutic purposes. This determines the active development of pharmacological substances based on analogues of this protein, as well as its peptide domains, and the study of the possibility of their use as medicines. The effectiveness of blocking PTHrP has been shown in various types of cancer, suggesting its potential for therapeutic use. Despite these data, attempts to use PTHrP as a drug target have not yielded successful clinical results. In light of these conflicting data, we made a comprehensive review of studies of PTHrP in CRC, which allows us to evaluate the potential of targeting PTHrP in the treatment of this disease. Thus, the history of this multipotent protein is an example of translational research that was first initiated by the clinically significant problem of hypercalcemia occurred in cancer patients. The unsolved problem stimulated subsequent basic, biomedical, preclinical and clinical research, the results of which are now returning to the clinic in the form of medical technologies and pharmaceuticals.

Relationship between parathyroid hormone-related protein and colorectal tumorigenesis

The discovery of parathyroid hormone-related protein (PTHrP) was the result of many years of intensive work aimed at understanding the pathophysiology and identifying the cause of the humoral hypercalcemia syndrome in malignant neoplasms. In 1987, three independent groups of scientists [22,23,24] published the results of studies in which a previously unknown protein was discovered and isolated from the tissue of various malignant tumors, which had high N-terminal homology with parathyroid hormone and partially similar

biological properties to it activity. The similarity of this protein in structure and biological activity with parathyroid hormone determined its current name — parathyroid hormone-related protein.

Over the past years, many studies have established the wide distribution of this protein in various normal and oncologically transformed tissues, described numerous types of its biological activity, endocrine, paracrine, autocrine and intracrine mechanisms of action in physiological and pathological reactions, and proven its leading role in organogenesis [25–28]. Because PTHrP is widely distributed in normal tissues, its secretion by tumors likely represents eutopic overproduction rather than ectopic production of this protein. Evolutionary relatedness allows parathyroid hormone (PTH) and PTHrP to bind to one common receptor (PTH1R), the activation of which triggers the implementation of the pleiotropic functions of PTH and PTHrP [29]. PTHrP was subsequently found to be produced by tumor cells of many cancers, promoting tumor cell proliferation, survival, invasion, and mediating hypercalcemia. Excessive tumor production and release of PTHrP into the circulation stimulates bone resorption and renal calcium reabsorption, and thus the role of this protein in the development of malignant hypercalcemia has been elucidated.

The relationship between PTHrP and colorectal neoplasms has been studied for more than a quarter of a century. In early work, Malakouti S. et al. assessed PTHrP expression by immunohistochemical staining in tissue samples from normal colorectal mucosa, polyps, and colorectal carcinoma removed from the same patients [30]. In normal large intestine, 94.3% of tissue samples were negative for PTHrP immunoreactivity. In colorectal polyps, only 22.6% of cells showed positive immunostaining, whereas 91.5% of colorectal cancer samples were positive for PTHrP. In the case of polyps, the staining intensity was 1-3+; however, all adenocarcinoma samples stained at 4+ intensity. In positive samples, immunoreactivity was present throughout the cytoplasm of the glandular epithelium. These results indicate that PTHrP expression is increased in colorectal cancer tissue compared with normal colorectal mucosa and polyps. In addition, expression appears to be higher in polyps than in normal large intestine. The aim of the study by Nishihara M. et al. the connection between PTHrP and tumorigenesis and progression of colorectal adenocarcinoma was clarified [31]. Immunohistochemistry, hybridization, and reverse transcription polymerase chain reaction techniques were used to evaluate PTHrP expression in tumor-transformed colorectal tissue. None of the adenomas of the background non-neoplastic mucosal epithelium showed immunostaining for PTHrP. In contrast, PTHrP was expressed in 94.4% of colorectal adenocarcinomas. PTHrP immunoreactivity was higher in poorly differentiated adenocarcinomas than in well-differentiated ones. PTHrP expression was significantly correlated with differentiation, lymphatic invasion, lymph node metastasis, liver metastasis, and Dukes classification. PTHrP transcripts have also been detected in resected human colorectal adenocarcinomas by RT-PCR. These data suggest that PTHrP is associated with carcinogenesis, differentiation, progression, and prognosis of colorectal adenocarcinomas.

The role of PTHrP in cell cycle progression, proliferation and migration of colorectal cancer cells

The fact that PTHrP and its receptor PTHR1 were found in normal colorectal epithelium [32] clearly indicates that PTHrP is a factor that acts as a local regulator through a paracrine/autocrine pathway [33]. These studies, together with others conducted *in vitro* [34], provide information on how this protein acts through autocrine/intracrine mechanisms of action. Various cellular models play an important role in understanding the cellular events associated with the pathophysiological conditions in human CRC, as it is a heterogeneous disease with three distinct but partially overlapping molecular phenotypes reflecting different forms of DNA instability [35]. *In vitro* studies showed that proliferation and migration of

CRC-derived LoVo cells were increased when these cells over expressed PTHrP [36]. A positive correlation in human CRC cell line LoVo between the expression of PTHrP and the activity of the intracellular protein Rac1 from the GTPase super family, which plays critical roles in the regulation of various cellular processes, including act in cytoskeleton reorganization, cell cycle progression, cell migration and cell survival was reported by Mula R.V. et al. [37]. Knockdown of integrin $\alpha 6\beta 4$, which is activated by PTHrP, abolishes the PTHrP-mediated increase in Rac1 activation. Integrin $\alpha 6\beta 4$ provides a synergistic signal with growth factor receptors to activate the phosphatidylinositol 3-kinase (PI3-K) pathway. Taken together, these observations suggest a link between PTHrP and Rac1 activity through $\alpha 6\beta 4$ integrin, resulting in increased cell migration and invasion.

The study of the relationship between PTHrP and CRC was continued *in vitro* using other cell lines: Caco-2 and HCT116. Caco-2 cells are derived from human colorectal adenocarcinoma and differentiate spontaneously *in vitro* under standard culture conditions, thus exhibiting enterocyte-like structural and functional characteristics. The human colorectal carcinoma cell line HCT116 exhibits a more aggressive phenotype due to hyperactivating mutations in the *KRAS* and PIK3CA genes [35,38]. It has previously been shown that both Caco-2 and HCT116 cells express PTH1R and that exogenous PTHrP modulates cell cycle progression and exerts proliferative and protective effects through the MAPK and PI3-kinase/Akt signaling pathways [39,40]. Administration of PTHrP was found to increase the number of alive Caco-2 cells. PTHrP induces phosphorylation and nuclear translocation of ERK 1/2, α p38 MAPK and Akt without affecting JNK phosphorylation. In addition, PTHrP-dependent ERK phosphorylation is restored when PI3K activity is inhibited. Following MAPK nuclear translocation, the transcription factors ATF-1 and CREB were activated in a biphasic manner. In addition, PTHrP induces the nuclear translocation of β-catenin, a protein that plays a key role in maintaining the growth and proliferation of colorectal cancer, and increases the abundance of both the positive cell cycle regulators c-Myc and cyclin D. Studies with ERK1/2, α p38 MAPK and PI3K showed that PTHrP regulates Caco-2 cell proliferation through these signaling pathways.

Taken together, these results indicated that in CRC cells, PTHrP modulates cell cycle progression and proliferation through modulation of several mitogenic pathways, such as PI3K, Akt, ERK1/2 MAPK, p38 MAPK, and RSK. To confirm that the results obtained were solely mediated by PTHrP (1-34) and involved only PTHR1 activation, Novoa Díaz M.B. et al. [44] used an anti-PTHR1 antibody to block the PTHrP/PTHR1 interaction and then assessed the state of active ERK1/2 under these conditions, since this is a kinase that is involved in most of the processes induced by PTHrP. It was found that anti-PTHR1 antibody completely suppressed the response of both Caco-2 and HCT116 cells to PTHrP, indicating that ERK activation in CRC-derived cells is a result of PTHrP/PTHR1 interaction.

Effect of PTHrP on angiogenesis of colorectal cancer

Tumor angiogenesis is known to be one of the main mechanisms by which tumors can generate blood vessels and is an important process for cancer growth and metastasis, which may influence therapeutic efficacy. It is strictly regulated by a delicate balance between proangiogenic and antiangiogenic factors and is modulated by various signaling pathways. In cancer, this balance is disrupted due to the increased release of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), which are produced by tumor cells and the tumor microenvironment, stimulating endothelial cells and promoting tumor angiogenesis [45]. Disruption of this balance affects the progression of CRC [46]. Because of this imbalance, tumor vessels are incompletely formed, abnormal, tortuous, irregular, dilated and leaky, have poor adhesions, few pericytes and an incomplete basement membrane, and are not distinguished by venules, capillaries or arterioles.

It is known that signaling pathways regulated by PTHrP in CRC-derived cell lines may be involved in angiogenesis [39] (Calvo N. et al., 2014). In a recent study, Calvo N. et al. [47] examined whether PTHrP regulates the expression of proangiogenic factors in Caco-2 and HCT 116 cell lines to evaluate the effect of this cytokine on angiogenesis associated with tumor progression. The authors observed that PTHrP increases messenger RNA levels of VEGF, HIF-1α, and matrix metalloproteinase 9 through the ERK1/2 and PI3K/Akt signaling pathways in both cell lines, and also revealed increased levels of VEGF in PTHrP-treated HCT116 xenograft tumors compared with control tumors. These findings were complemented by the presence of cells forming structures with the characteristics of newly formed vessels and staining positive for a cluster of endothelial markers of vascular differentiation [47].The ability to quantitatively distinguish between tumor neovascularization and pre-existing vessels is important because these data provide more accurate information when assessing tumor angiogenesis. Overall, these results represent represents the first evidence related to the mechanism of action of PTHrP that leads to its proangiogenic effects in CRC.

The presented results suggest an interaction between tumor cells and their microenvironment through proangiogenic factors. In this regard, Calvo N. et al. [47] further assessed the molecular crosstalk between tumor cells and endothelial cells. For this purpose, conditioned media from the Caco-2 and HCT 116 CRC cell lines were used, and the HMEC-1 cell line was also included as a model of endothelial cells. Conditioned medium from both colorectal cancer cell lines exposed to PTHrP was found to increase cell number, migration, and tube formation in HMEC-1 endothelial cells, whereas a neutralizing anti-VEGF antibody decreased this response. In addition, pre-incubation of conditioned media with an anti-VEGF antibody reduced their stimulatory effect on endothelial cells [47]. This indicates that PTHrP increases the expression of VEGF in Caco-2 cells and HCT116 cells, followed by its release into the culture medium. This factor, in turn, has a proangiogenic effect on endothelial cells. These data have expanded the understanding of the mechanism of action of PTHrP, since this cytokine acts not only directly on CRC cells, but also exerts its effects by acting as an intermediary between the tumor and its microenvironment.

Participation of PTHrP in the formation of chemoresistance of colorectal cancer cells

The above data suggest that PTHrP may be involved in other events related to CRC cell behavior. Most people with metastatic CRC eventually experience clinical failure (that is, recurrence or disease progression). Chemoresistance is a common cause of treatment failure in patients with colorectal cancer. Failure to respond to first-line treatment makes them potential candidates for second-line systemic therapy. It is known that several mechanisms are involved in drug resistance in tumor cells. Regarding recent evidence, the EMT program, induction of cancer stem cell properties and angiogenesis are highlighted as key events in this process [48].

Currently, the two chemotherapeutic agents approved as first- and second-line palliative agents for CRC are oxaliplatin and irinotecan [49]. One of the drugs most commonly used as first- and second-line chemotherapy for advanced or recurrent CRC is irinotecan (also known as CPT-11, a topoisomerase I inhibitor that targets tumor cell topoisomerase in the S phase of the cell cycle). The availability of irinotecan has radically changed both the first- and second-line treatment of advanced CRC compared to the era when the only treatment option for advanced disease was 5-fluorouracil (5-FU) [50]. The combination of CPT-11 with other drugs significantly increases survival in patients who do not respond to initial treatment. In addition, CPT-11-based drug combination therapy increased the overall tumor response rate and improved quality of life in patients compared with single drug therapy [51].

Despite these available drugs, chemoresistance is a common cause of treatment failure in patients with CRC. It is known that PTHrP can mediate

chemoresistance in tumor cell lines derived from prostate and osteosarcoma [52,33]. A recent study examined the involvement of PTHrP in the development of chemoresistance to drugs commonly used in CRC therapy [44]. To answer the question of whether PTHrP could be a major factor in the observed chemoresistance to CPT-11, the Caco-2 and HCT116 cell lines were treated with PTHrP followed by CPT-11 (10 μM). The authors found that exogenous addition of PTHrP attenuated the cytotoxic effect in both cell lines. These results suggested that PTHrP promotes chemoresistance of CRC cells to CPT-11 [44]. The response of tumor cells to this drug under the influence of PTHrP involves the ERK signaling pathway [33]. Studies conducted by Paillas S. et al. [53] showed that the p38 MAPK pathway also modulates the sensitivity of CRC cells to CPT-11. Other investigators have reported that activation of ERK 1/2 MAPK in the HCT116 cell line may induce resistance to other antitumor agents such as oxaliplatin [54].

Many pharmacotherapeutic strategies have been tested in the treatment of CRC. Oxaliplatin is another drug commonly used for this purpose, and it exerts its cytotoxic effects through different mechanisms towards CPT-11. The combination of CPT-11 and oxaliplatin is commonly used to improve the effectiveness of adjuvant therapy [51]. Doxorubicin is another chemotherapy agent that has been effective in the treatment of advanced CRC. However, side effects associated with its use at high doses and the development of chemoresistance pose a major challenge to effective treatment [55,56]. It was shown that treatment of HCT116 cells with PTHrP attenuated the cytotoxicity induced by oxaliplatin and doxorubicin. This indicates that PTHrP promotes resistance to various types of cytotoxic agents. It is possible that the mechanisms triggered by this cytokine alter the specific targets or signaling of these drugs.

A subsequent study demonstrated the involvement of the Met receptor pathway in the aggressive behavior of CRC cells induced by PTHrP [57]. Met is a receptor with tyrosine kinase activity, expressed in normal tissues and involved in various physiological processes such as embryonic development and wound healing [58]. Met is aberrantly activated in many types of human malignancies, and its dysregulated activity correlates with aggressive tumor features such as abnormal proliferation and survival, leading to tumor growth, local invasion, and metastasis. Over expression of Met or its dysregulation can lead to malignant transformation of cells and contributes to the development and progression of various types of cancer, including colorectal tumors [59,60]. Moreover, this receptor is over expressed and/or can be aberrantly activated by several mechanisms in CRC cells, causing tumor development and progression [41,61]. Moreover, Met dysregulation is also associated with drug resistance in colorectal cancer cells [62]. Several studies have demonstrated over expression of this receptor in tumor tissue of patients with CRC. In this regard, Met inhibition is being widely investigated as an adjunct to conventional therapy [63,64]. PTHrP-induced Met signaling pathway is involved in cellular events associated with aggressive behavior of human HCT116 cells. PTHrP attenuates the cytotoxic effect of CPT-11, oxaliplatin or doxorubicin in human HCT116 cells via the Met signaling pathway.

It is assumed that the expression and activity of Met are regulated by signaling pathways triggered by the binding of PTHrP to the PTHR1 receptor [57]. The authors observed that exogenous PTHrP modulates Met protein and gene expression in HCT116 cells. In CRC, the Met signaling pathway is associated with tumor evolution, as well as resistance to chemotherapeutic drugs [59]. Currently, inhibition of this receptor is being widely studied as an adjunctive therapy to traditional CRC treatments [63]. Use of the Met kinase inhibitor SU11274 along with CPT-11, oxaliplatin, and doxorubicin increases the sensitivity of CRC cells to these drugs, suggesting the involvement of Met in PTHrP-induced chemoresistance. SU11274 prevents Met activation because it is an ATP-competitive inhibitor of Met catalytic activity [65]. The fact that there was a significant reduction in HCT116 cell viability and migration in the presence of a Met

inhibitor, as well as a reversal of the induction of the mesenchymal phenotype even in the presence of PTHrP, indicates that Met is primarily involved in the molecular mechanisms that are involved in these cellular responses to PTHrP. . *In vitro* studies suggested the existence of a mechanism based on the action of PTHrP on the regulation of Met gene expression, as well as its activation through Src kinase and the MAPKs pathway [57]. Once activated, Met signaling leads to molecular changes in tumor cells that promote chemoresistance to CPT-11, oxaliplatin, or doxorubicin. It is likely that activation of Met expression is also involved in the induction of events associated with aggressive behavior of CRC cells. To date, *in vitro* observations indicate that binding of PTHrP to its receptor, PTHR1, contributes to the regulation of Met gene expression as well as its activation through the Src kinase and MAPKs pathway. Once activated, Met signaling leads to molecular changes in tumor cells that promote events associated with aggressive behavior of CRC cells. PTHrP has been shown in vivo to modulate the expression of markers associated with tumor progression (including Met), as well as its own receptor.

Effect of PTHrP on the modulation of the epithelial-mesenchymal transition program and other events associated with tumor invasion

The evidence that PTHrP promotes chemoresistance in CRC cells and the angiogenesis associated with these tumor cells has provided a logical prerequisite for studies of the involvement of this multipotent cytokine also in other events associated with tumor progression. The process of invasion requires the acquisition of characteristics by tumor cells and the presence of various environmental factors that are involved in extracellular matrix remodeling, such as matrix metalloproteinases (MMPs). It was previously found that MMP-7 is over expressed in 80% of patients with CRC [66]. Novoa Díaz M.B. et al. [44] also found in *in vitro* experiments that PTHrP treatment caused an increase in MMP-7 transcription in CRC cells. The same study examined the effect of PTHrP on morphological changes in CRC cells associated with tumor progression, including the role of PTHrP in the process of epithelial-mesenchymal transition (EMT), which is considered an important step in the development of various tumors. During EMT, epithelial cells reduce intercellular adhesion and acquire mesenchymal properties that increase their ability to migrate and invade, recognized characteristics of tumor cells [67].

Carriere P. et al. [68] obtained results that allowed us to state that PTHrP modulates the expression of factors and promotes morphological changes associated with EMT in the HCT116 cell line derived from CRC. PTHrP increased the expression of the protein SPARC (secreted protein acidicrichincystein), which regulates the proliferation and interactions of matrix cells. SPARC is involved in EMT in HCT116 cells but not in Caco-2 cells. PTHrP also increased SPARC expression and its subsequent release from HMEC-1 endothelial cells. Conditioned medium of PTHrP-treated HMEC-1 cells induced early changes associated with EMT in HCT116 cells. Moreover, treatment of SPARC cells with HCT116 enhanced PTHrP modulation of E-cadher in expression and cell migration. These results suggest a novel effect of PTHrP on CRC progression involving the microenvironment in modulating EMT-related events. It was also shown that key molecular mechanisms associated with the EMT observed in this cell line in response to PTHrP were not detected in the more differentiated and less aggressive Caco-2 cells. The difference in the response of both CRC-derived cell lines suggests a new mechanism of action of PTHrP, where its effect depends on the different aggressiveness of the cell line.

The study also showed that PTHrP is involved in a paracrine manner in events associated with the aggressive behavior of CRC cells. The fact that this cytokine establishes a connection between CRC cells and HMEC endothelial cells through molecular factors promoting tumor-associated angiogenesis provided the basis for analyzing how PTHrP promotes the interaction between the tumor cell and cells from its microenvironment. Recent work

has demonstrated that this cytokine acts on endothelial cells to promote the release of factors that contribute to the EMT program in CRC-derived cells [68]. Analysis of the influence of PTHrP on the EMT program, as well as other programs associated with malignant progression, including the initiation of cancer stem cells (CSCs), indicates that the EMT program is closely related to the phenotype of CSCs, regulating their characteristics [9]. In CRC-derived cells, PTHrP modulates the protein expression of cell surface markers widely associated with colon CSCs, possibly participating in the initiation and reprogramming of this cell subpopulation. Taking all these results into account, the authors stated that PTHrP is involved in the modulation of several events associated with the aggressive phenotype of colorectal tumor cells. The action of autocrine and paracrine factors originating from the tumor and its stroma may contribute to a number of events that contribute to the phenotypic and genetic heterogeneity of tumor cells, influencing the effectiveness of currently used treatments.

CONCLUSION

Analysis of literature data presenting the results of studies on the role of PTHrP in the development of CRC allowed us to state that the main attention of scientists was focused on studying the following events: survival, cell cycle progression and proliferation, migration, chemoresistance, tumor-associated angiogenesis, the transition program from epithelium to mesenchyme, as well as events associated with the induction of cancer stem cell signatures. PTHrP in CRC cells has been found to promote survival, cell cycle progression, proliferation, migration, and chemoresistance, and to modulate the expression of markers associated with invasion, angiogenesis, epithelial-to-mesenchymal transition, and cancer stem cell features. PTHrP administration has been shown to increase the expression of several markers associated with oncogenic events. Facts have been established indicating the participation of PTHrP in the acquisition of an aggressive phenotype by CRC cells, and the molecular mechanisms involved in these processes have been described. Through its action on CRC cells and their microenvironment, this protein promotes interactions between cells from the tumor niche, promoting aggressive tumor behavior. PTHrP has been shown to induce events associated with the progression of CRC not only through its direct effect on intestinal cells, but also through its influence on cells in the tumor microenvironment, promoting the development of molecular and morphological changes in tumor cells. PTHrP and its effectors may be involved in tumorigenesis and/or disease progression of CRC and may also influence the success of chemotherapy treatment. The evidence presented in this review lays the foundation for subsequent studies examining the clinical applicability of existing information.

AUTHORS CONTRIBUTION

Concept and design of the study: *Anatoly N. Kurzanov, Vladimir M. Durleshter*
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