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The role of corticotropin-releasing hormone (CRH) family in tumors

Minireview

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The corticotropin-releasing hormone (CRH) family is widely distributed among the central nervous system and peripheral tissues, such as the digestive, cardiovascular, immune, reproductive, endocrine systems. The CRH family members are widely involved in the regulation of human cell biological processes, immune response, and regulation of inflammatory processes that can affect the occurrence and development of tumors. At present, CRH family members and their receptors can be detected in many tumor tissues, and some people think that members of the CRH family may be potential tumor treatment targets as they can affect cellular processes, such as proliferation, migration, invasion, and apoptosis. However currently, there is no systematic introduction to the relationship between the CRH family and various tumors. This review introduces the molecular regulation of the CRH family in tumor formation and seeks further targeted therapy.

Key words: CRH family, cancer, targeted therapy, mechanism

Structure and function of CRH family proteins

CRH family is a family of peptide hormones, whose members include corticotropin-releasing hormone (CRH), urocortin 1 (UCN1), urocortin 2 (UCN2), and urocortin 3 (UCN3). The family of receptors includes CRHR1, CRHR2, and the corticotropin-releasing hormone binding protein (CRHBP) [1]. In 1981, researchers isolated CRH from the sheep hypothalamus, as a 41-amino acid peptide that is released by hypothalamic neuroendocrine cells and activates the stress response. CRH is widely expressed in the central nervous system, such as the hippocampus, amygdala, and striatal nucleus [2, 3]. In 1995, researchers discovered the presence of UCN1 in the rat brain [4]. UCN1 is a 41 amino acid peptide [1], and is expressed in the center and periphery subsequently, such as brain, cerebellum, hippocampus, heart, adrenal gland, skeletal muscle, etc. [5, 6]. UCN2 and UCN3 were isolated from the rat midbrain, and are both 38 amino acid peptides [7]. The expression of UCN1 and UCN2 can be detected in the center and periphery, UCN2 has been detected in the brain, hypothalamus, brainstem, pituitary, heart, placenta, stomach, skin, ovary, uterus, etc. [6]. UCN3 is expressed in the hypothalamus, adrenal gland, heart, and kidney [8]. CRH and UCNS have a high sequence homology [1]. The protein receptors CRHR1 and CRHR2 of this family belong to the B1 family of G protein-coupled receptors. CRHR1 is mainly located in the central nervous system and plays an important role in the hypothalamic-pituitary-adrenal axis (HPA), while the CRHR2 receptor is mostly expressed in the peripheral region [9]. CRHR1 receptor is a protein composed of 415 amino acids, compared with UCN2 and UCN3, CRH and UCN1 have a higher affinity for CRHR1. CRHR2 receptor is a protein composed of 431 amino acids and UCN2 and UCN 3 are the selective ligands of CRHR2. The binding capacity of the CRHR2 receptor to UCN1 is stronger than CRH [10]. CRHBP is a 37 kDa glycoprotein identified from plasma [11], and is expressed in large amounts of the central nervous system and also expressed in peripheral tissues, especially in the human pituitary, liver, and placenta. Compared with the CRH receptor, the CRHBP binding protein has a higher affinity for CRH. CRHBP combines with CRH to form a dimer, which can remove CRH from blood, thus affecting the binding efficiency of CRH and its related receptors [12]. CRH family members act

on systemic tissues and target organs through their receptors and play an important role in maintaining homeostasis *in vivo* [13]. They are involved in the physiological and pathological regulation of multiple systems, such as the nervous system and digestive system [14]. CRH family members play a key role both in the center and periphery. In the center, CRH family members are the key activators of the HPA axis. They stimulate the release of adrenocorticotrophin hormone (ACTH) in the anterior pituitary, and ACTH can further cause changes in autonomous behavior [15]. At present, the CRH family has been widely studied in regulating stress-induced autonomic behavior changes. In peripheral tissues, the effects of CRH on various systems have also aroused great interest, for example, studies have found that CRH/CRHR1 can promote the growth of endogenous and inflammatory blood vessels in the intestine, while UCN3/CRHR2 has the opposite effect [12]. UCNs and their receptors are involved in regulating the function of the HPA axis, thyroid axis and affect the pathophysiology of the reproductive system, gastrointestinal tract, pancreas, and other organs. For example, intracerebroventricular injection of UCN1 can induce increased cortisol secretion. Compared with CRH, UCN1 has a lower stimulating activity on the HPA axis. UCN1/CRHR1 regulates thyroid blood flows and calcitonin secretion [16]. In the gastrointestinal tract, when UCN2/CRHR2 is activated, gastric motility is inhibited, while CRH/CRHR1 activation promotes colon motility [12]. In this review, we mainly discuss the relationship between CRH and various tumors in the periphery, summarizing its clinicopathological characteristics and related mechanisms, as shown in Tables 1 and 2 and Figure 1 to explore the clinical value of the CRH family members.

When the homeostasis of the body is destroyed, the CRH family members participate in coordinating the stress response. When the response is not controlled, the imbalance of homeostasis is further aggravated, which is related

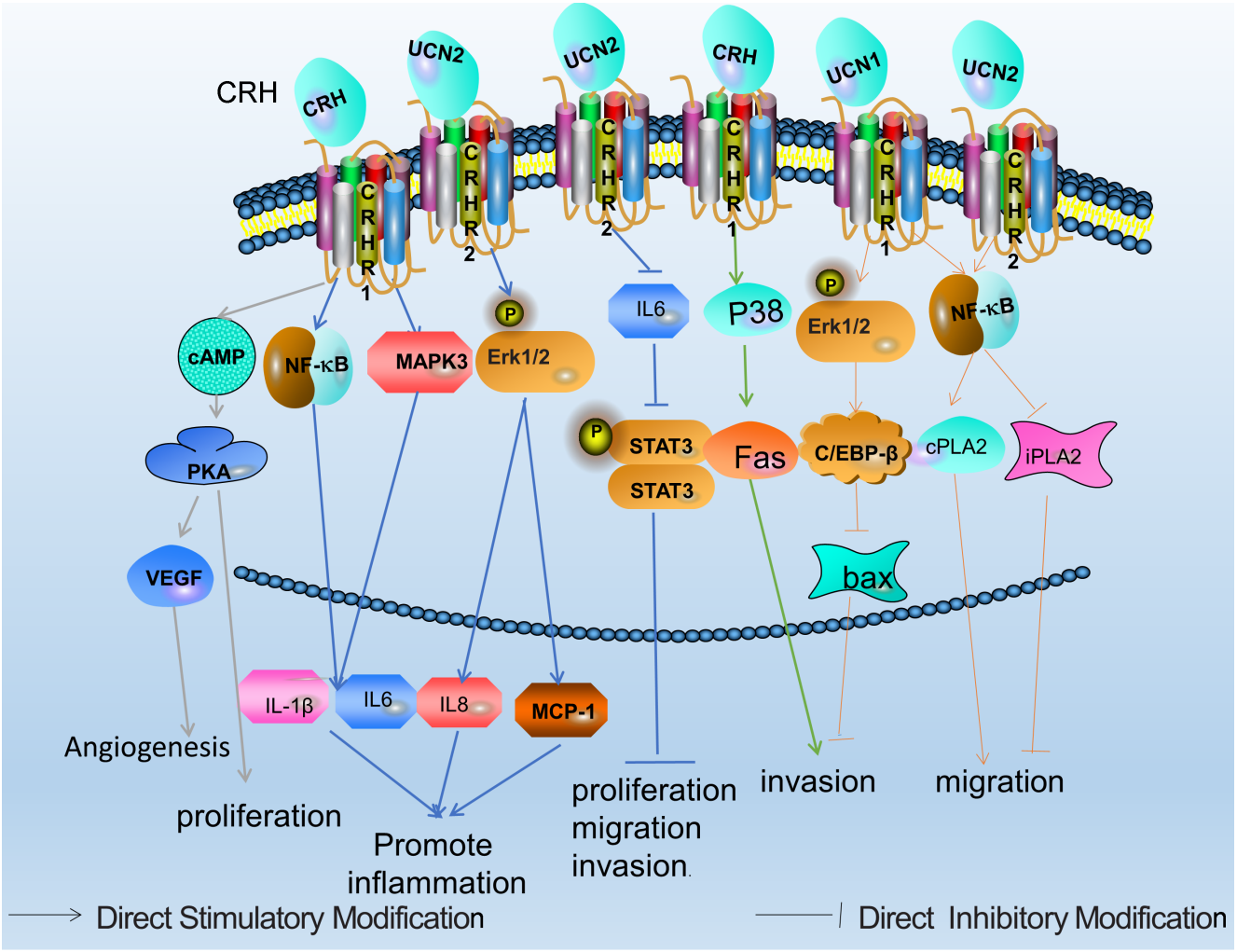

Figure 1. Mechanism of action of corticotropin-releasing hormone (CRH) in tumors.

Table 1. Composition and expression sites of CRH family proteins.

Protein name	Alias	Chromosome location	Amino acid composition	Expression site
corticotropin-releasing hormone	CRH	8q13.1	41	nervous system, placenta, intestine, stomach, ovary, uterus, breast
urocortin 1	UCN1	2p23.3	40	brain, cerebellum, hippocampus, heart, adrenal gland, skeletal muscle
urocortin 2	UCN2	3p21.31	38	brain, hypothalamus, brainstem, pituitary, heart, placenta, stomach, skin, ovary, uterus
urocortin 3	UCN3	3p21.31	38	hypothalamus, adrenal gland, heart, and kidney
CRH receptor 1	CRHR1	17q21.31	415	nervous system, liver, intestine, ovary, uterus, breast
CRH receptor 2	CRHR2	7p14.3	431	esophagus, stomach, liver, intestine, ovary, breast, kidney
corticotropin-releasing hormone binding protein	CRHBP	5q13.3	–	nervous system, liver, placenta, kidney, uterus

Table 2. Function and clinical significance of CRH family proteins in various human cancers.

Cancer types	Expression	Function role	Clinicopathological features
Colorectal cancer	CRH, UCN1, CRHR1 upregulated CRHR2 downregulated	CRH/CRHR1 promotes cell proliferation and anti-apoptosis; UCN2/CRHR2 inhibits proliferation, migration, invasion; UCN2/CRHR3 promotes migration	CRH/CRHR1 promotes blood vessel formation; UCN2/CRHR2 mediates the immune escape and accelerates tumor progression
Hepatocellular carcinoma	CRHBP downregulated	UCN1/CRHR2 inhibits proliferation; UCN/CRHR1 promotes migration through cPLA2; UCN/CRHR2 on iPLA2 inhibits migration; UCN1/CRHR1 inhibits apoptosis	UCN/CRHR1 inhibits angiogenesis and tumor growth, the content of CRHBP is negatively correlated with advanced tumor stage and survival rate
Glioma	CRH, CRHR1 upregulated	CRH/CRHR1 inhibits cell proliferation and promotes apoptosis	CRHR1 content is positively correlated with tumor TNM staging
Ovarian cancer	CRH upregulated	CRH/CRHR1 promotes apoptosis	CRH content is positively correlated with tumor TNM staging; CRH/CRHR1 promotes blood vessel formation.
Endometrial carcinoma	–	CRH/CRHR1 inhibits cell proliferation and promotes cell migration and invasion; UCN/ CRHR2 inhibits cell migration	CRHR2 content is positively correlated with tumor TNM staging
Breast cancer	–	CRH, UCN activates receptors to inhibit EMT	CRH family inhibits tumor development by inhibiting EMT
Kidney cancer	UCN3 downregulated CRHBP downregulated	CRHBP overexpression inhibits cell proliferation, migration, invasion, and apoptosis	UCN3/CRHR2 reduces blood vessel formation, the content of CRHBP is negatively correlated with advanced tumor stage and metastasis ability

to the pathogenesis of various diseases [17]. When the CRH family members activate CRHR, the structural conformation of CRHR changes and then interacts with G protein to further activate various signaling pathways [18]. In most cells, the CRH family members produce biological effects by activating the cAMP/PKA/CREB pathway. After ligand-receptor interaction, intracellular cAMP-dependent signal transduction cascade can be initiated, resulting in protein kinase A (PKA) in the cytoplasm to modify the target protein after translation, and regulate gene transcription through the activation of cAMP response element binding protein in the nucleus, thereby increasing the expression of downstream target genes [19]. Studies have confirmed that CRH/CRHR can activate the cAMP/PKA/p38 MAPK signaling pathway, and the activation of ERK plays an important role in cell proliferation [20]. The activation of this pathway can also induce the release of vascular endothelial growth factor (VEGF) in human mast cells [21]. CRH family members can also regulate the expression and activity of NOS (the enzyme of NO formation *in vivo*), resulting in the change of cGMP content of cells. The activation of the NO/cGMP signaling pathway plays an important role in the activation of peripheral arteries [22].

The relationship between CRH and various tumors

Colorectal cancer. Colorectal cancer is the fourth leading cause of cancer deaths worldwide, it is a heterogeneous disease caused by many factors [23]. The researchers have found that CRH and UCN2 are expressed in the submucosa of the ileum, myenteric plexus, and hidden nerve fibers in the lamina propria [24]. Moreover, CRH can be locally produced

in human colon chromaffin cells. Human colon chromaffin cells are a kind of special secretory cells in the gastrointestinal tract, which contain secretin, cholecystokinin, and 5-hydroxytryptamine (5-HT), and 5-HT can promote the secretion of water, electrolytes, and promote the peristalsis of the colon [25]. CRHR1 receptor is mainly located in macrophages in the lamina propria of the human colon. Macrophages play an important role in the interaction between the innate immune system, microorganisms, and their products [21]. Studies have found that CRHR2 is reduced in colon cancer tissues compared with normal [26]. It has been reported that there is a certain link between irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and colon cancer, as chronic stress makes the human body tolerate the immune system, which can produce IBS and IBD. IBS may be the cause of colorectal cancer and IBD can promote the occurrence and development of colon cancer [27]. CRH has been found to play an important role in the association of these diseases [27]. Under peripheral chronic stress conditions, the activation of CRH/CRHR1 can promote the release of TNF-α and protease. TNF-α and protease can destroy the tight junction mechanism of neighboring cells, and the destruction of the epithelial barrier can trigger the dysfunction of intestinal epithelial barrier function and increase the permeability of the epithelial barrier, which further leads to microbial infiltration and translocation [28]. In the central nervous system, CRH activates parasympathetic neurons and stimulates intestinal motor neurons to release acetylcholine, which could accelerate colonic transportation, thereby triggering and enhancing colonic inflammation [29]. In a study of patients with ulcerative colitis, the authors found that the expression of the CRHR1 receptor and UCN1 in macrophages of the lamina propria was upregulated [30]. Further research confirmed that CRH/UCN1 could promote the progression of ulcerative colitis after CRHR1 was activated [31]. Under pathological conditions, UCN1 acting on CRHR1 can destroy the VE-cadherin-β-catenin complex, thus increasing the permeability of intestinal epithelium and destroying the integrity of the epithelial barrier, thereby enhancing the progression of colon disease [32]. In summary, we can conclude that CRH/UCN1 activates CRHR1 to mediate the occurrence and development of colorectal inflammation, mainly through increasing the permeability of the intestinal epithelium and promoting the release of inflammatory factors.

Chronic inflammation is one of the main causes of tumor formation and development. It has been reported that CRH and UCN2 can promote the occurrence and development of colitis by acting on the corresponding receptors [33]. The research found that the expression of Fas/FasL in normal colonic epithelial tissues was higher than that in colorectal cancer tissues, and we can speculate that colorectal cancers may produce immune escape by downregulating Fas/FasL [34]. Further research has found that the downregulation of Fas/FasL is related to the loss of CRHR2. In colorectal cancer, UCN2/CRHR2 induces Fas production in a dose-dependent manner of UCN2. The signal transduction of UCN2/CRHR2 regulates the expression of Fas through miR-7/YY1. The increased expression of UCN2/CRHR2 can reverse the Fas-mediated immune escape in colorectal cancer cells [35]. The combination of CRH and CRHR1 activates the MAPK and ERK/NF-KB signaling pathways that can induce immune cells to release inflammatory factors, such as IL-1β and IL-6 [36]. In an *in vitro* cell study, it was verified that UCN 2 can stimulate ERK1/2 phosphorylation in the CRHR2-expressing cells, thereby causing the expression of IL-8 and MCP-1 to increase, and MCP-1 is an important pro-inflammatory factor [37]. It can be concluded that members of the CRH family induce immune cells to release inflammatory factors by activating related pathways that could accelerate the progression of IBD.

The CRH protein family has an impact on the proliferation, migration, invasion, and apoptosis of colon cancer. In a cell study on colon cancer, it was found that UCN2/CRHR2 can inhibit the proliferation, migration, and invasion induced by the IL-6/STAT3 signaling pathway. Compared with normal tissues, the CRHR2 expression is reduced in colon cancer tissues, therefore, the inhibitory effect of UCN2/CRHR2 on cell biological processes is reduced [26]. In the mouse model of colitis-related cancer, the CRHR2 expression in tumor tissues was significantly reduced or even disappeared. UCN2/CRHR2 signal transduction can hinder the metastatic ability of colon cancer cells and negatively regulate the growth of colon cancer [38], however, the combination of UCN3 and CRHR2 can activate the Src/ERK/FAK pathway, which can promote the migration and invasion of colorectal cancer [39]. Angiogenesis is the basis of tumor occurrence and development, and vascular endothelial growth factor VEGF is an effective inducer of angiogenesis. CRH induces the VEGF release from human mast cells by activating the cAMP/PKA/p38 MAPK signaling pathway [40]. The overexpression of CRH in tumor epithelial cells can stimulate the chemotaxis of endothelium and further increase the formation of blood vessels [41].

According to the above description, it was concluded that the high expression of CRH/CRHR1 can promote the development of colon cancer. Therefore, it has been proposed that the high expression of CRH/CRHR1 can be used as a new therapeutic target for the prevention and treatment of colon cancer.

Hepatocellular carcinoma. In the world, hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths [42]. HCC is a malignant disease developed from chronic liver diseases caused by many factors, such as infectious, lifestyle, and so on [43]. At present, radiotherapy, chemotherapy, and surgery are the main treatments, however, the prognosis of patients with liver cancer is poor due to the recurrence and metastasis of liver cells [44]. Under normal and pathological conditions, the CRH family peptides are expressed in the liver. UCN1, CRHR1, and CRHR2 receptor

proteins were found in the cytoplasm and cell membranes of hepatocytes, blood vessels, and bile ducts [45]. UCN1, CRHR1, CRHR2, and CRHBP transcripts are present in highly purified Kupffer cells (KCs) in the liver. KCs are essential for antigen-specific immune responses [45]. When the liver is stimulated, UCN1 can produce a local immune response by autocrine or paracrine manner to protect the liver from harmful stimulation, for example, CRHR1 and CRHR2 mediated lipopolysaccharide can inhibit the production of tumor necrosis factor (TNF) [46]. In malignant liver tumors, the combination of UCN1 and CRHR1 receptors can affect cell growth factors and immune processes, thus affecting the occurrence and development of liver cancer [47]. In *in vivo* experimental studies, it was found that UCN1 inhibited the growth of hepatocellular carcinoma in nude mice and reduced tumor microvessel density [48]. Therefore, it has been suggested that the anti-tumor effect of UCN/CRHR1 may provide a new direction for the treatment of hepatocellular carcinoma.

It has been found that CRH family members can affect liver proliferation, migration, invasion, and apoptosis. In the study of two liver cancer lines SMMC-7721 and HepG2, it was found that UCN1/CRHR2 could inhibit cell proliferation [48]. UCN can affect the migration of liver cancer cells through cPLA2 and iPLA2. UCN/CRHR1 can increase the expression of cPLA2 through the NF-KB pathway, and the high expression of cPLA2 can promote the migration of hepatoma cells. On the contrary, the effect of UCN/CRHR2 on iPLA2 inhibits the migration of tumor cells [49]. PLA2 is an active enzyme protein, existing in almost all nucleated cells, and is composed of calcium-dependent secretory sPLA2, cellular cPLA2, and calcium-independent iPLA2. PLA2 plays an important role in maintaining homeostasis [50]. In a study on the rat pheochromocytoma PC12 cell line, it was found that CRH/CRHR1 activates the p38 mitogen-activated protein kinase [51]. The activated p38 mediates the production of the Fas ligand, and the Fas ligand-mediated apoptosis is crucial in the pathogenesis of some liver diseases, such as chronic viral hepatitis and acute liver failure. Under hypoxic conditions, UCN1/CRHR1 on hepatocytes activates p-ERK 1/2, which activates C/EBP-β to downregulate the apoptotic gene Bax [36], thereby inhibiting the apoptosis.

CRHBP is expressed in brain, placenta, liver, kidney and other tissues and organs, which is closely related to the occurrence and development of tumors [11]. The latest study found that CRHBP gene expression was significantly reduced in patients with liver cancer [52], and was confirmed that liver cancer patients with low expression of CRHBP have shorter survival time than patients with high expression of CRHBP [11]. The above results speculate that CRHBP can inhibit the occurrence and development of hepatocellular carcinoma. In liver cancer tissues, the expression of CRHBP may be used as an indicator of clinical prognosis and a potential therapeutic target.

Glioma. Glioma is the most common primary tumor in the brain and spinal cord. Histological diagnosis and malignant grade are the "gold standard" for its diagnosis and treatment. The current treatment methods are mainly radiotherapy, chemotherapy, and surgery [53]. At present, the treatment success rate and overall survival rate of patients with glioma are low, so it is very important to find the molecular markers to improve the diagnosis and treatment effect [54]. Under normal and pathological conditions, CRH and its receptor CRHR1 are expressed in the brain tissue. Compared with normal brain tissues, the expression of CRHR1 in gliomas is significantly increased and positively correlated with tumor grade [55]. In the animal model of glioma, after artificially giving CRH to treat glioma, it was found that CRH has anti-tumor therapeutic effects similar to steroids, but the toxicity and negative effects of CRH are lower [56], which provides a new basis for clinical targeted therapy in the future.

An experimental study found that compared with the control group, the expression of p53 in the CRH-treated glioma cells was significantly increased [55]. The activation of the p53 signaling pathway can regulate the expression of various genes, including cell proliferation, cell cycle, and apoptosis, and it also plays an important role in the inhibition of angiogenesis and DNA repair, which is very important for the treatment of tumor [57]. In human glioma U87 cells, CRH inhibits cell proliferation and induces apoptosis through the p53 signaling pathway [55]. Histone acetyltransferase inhibitor II (HATI II) activates the p53 signaling pathway and can induce apoptosis and inhibit the proliferation of glioma cells through the caspase pathway [58]. In glioma, whether CRH affects proliferation and apoptosis through the caspase pathway remains to be further studied.

Ovarian cancer. Globally, ovarian cancer is the sixth most common cancer among women and is the main cause of death from gynecological cancer. Ovarian cancer is also the fifth leading cause of cancer-related deaths [59]. Due to the lack of effective early detection, the prognosis of ovarian cancer patients is poor, the current treatment methods are mainly surgical resection, chemotherapy, and radiotherapy [60]. CRH was found in the ovarian cortex, stromal cells, and follicular fluid of the human ovary, and the receptors CRHR1 and CRHR2 are located in the corpus luteum [61]. In ovarian tissue, CRH can regulate the production of ovarian steroids [62]. It has been verified that the higher the expression of CRH and FasL, the higher the advanced stage of ovarian cancer. CRH/CRHR1 can act on extravillous trophoblast cells (EVT), which can cause the upregulation of the expression of the pro-apoptotic molecule FasL in ovarian cancer cells [63]. FasL can kill the activated immune cells of the human body, thus resisting the immune response in tumor cells. Therefore, CRH can resist the immune response by upregulating the expression of FasL, thereby promoting the occurrence and development of ovarian cancer. At present, there is no obvious evidence that CRH is related to the proliferation of ovarian cancer, but the upregulation of FasL

mediated the PBL apoptotic ability [64]. CRHR1 antagonists reduction of the immune defense in ovarian tumors has been proposed, which provides novel ideas for the treatment of ovarian cancer.

Endometrial carcinoma. Among gynecological tumors, endometrial carcinoma is one of the most common tumors, surgical resection and radiotherapy are the main treatment methods [65]. CRH and UCN are both expressed in the normal uterus and endometrial carcinoma, CRHR1 and CRHR 2 are expressed in the cytoplasm of normal endometrial cells. CRH and UCN have the function of promoting the differentiation of progesterone-like cells in the uterus [66]. In endometrial carcinoma with progesterone receptor expression, the expression of CRHR1 is increased, which may indicate that the expression of CRHR1 is related to the degree of tumor differentiation. It was further found that progesterone can stimulate the expression and production of CRH through the cAMP pathway [67]. A study found that the expression of CRHR2 was higher with the increase of tumor grade indicating that the content of CRHR2 predicted the prognosis of the tumor [68]. In endometrial carcinoma, CRH and UCN can also affect its proliferation, migration, and invasion, in the human endometrial cancer cells ISK, CRH/CRHR1 can inhibit cell proliferation through the cAMP-PKA signaling pathway [69]. At the same time, CRH can inhibit the proliferation of tumor cells, promote the migration and invasion of tumor cells by increasing the levels of matrix metalloproteinase (MMP)-2 and MMP-9, but UCN1/CRHR2 can inhibit cell migration [70]. The CRH family has a greater impact on female reproductive system cancers. Through further research, we are looking forward to finding corresponding targets to intervene in the occurrence and development of tumors.

Breast cancer. Globally, breast cancer is the most common cancer in women and the second leading cause of cancer death. Breast cancer incidence rate increases with age [71]. It is considered that early breast cancer can be cured, mainly targeted therapy of anti-human epidermal growth factor 2 (ErbB2), endocrine therapy, and chemotherapy [72]. The presence of CRH family members was detected in the biopsy of breast cancer patients. It has been found that when stimulated by transforming growth factor β1 (TGF-β1), CRH and its receptor CRHR1/CRHR2 can increase the expression of E-cadherin and decrease the expression of N-cadherin [73]. The mechanism study showed that UCN binding with CRHR1/CRHR2 can increase the expression level of Smad7, which could inhibit the activation of Smad2/3 induced by TGF-β1 and weaken the upregulation of Snail 1 and Slug by TGF-β1 [74]. Therefore, we can conclude that UCN/CRHR1 and UCN/CRHR2 can inhibit the EMT conversion in breast cancer patients, and UCN may be a potential therapeutic target for breast cancer patients.

Kidney cancer. Renal cell carcinoma is the most common renal solid tumor in the kidney [75]. UCN3 is found in the kidney under both physiological and pathological conditions, mainly located in renal tubular epithelial cells [76]. UCN3 reduces the production of VEGF by binding to its receptor CRHR2, thereby reducing the formation of blood vessels [77]. In kidney cancer patients, the content of VEGF in renal cells is significantly increased, the combination of VEGF inhibitors and immunotherapy is currently being explored for the treatment of kidney cancer patients [78]. In patients with kidney cancer, the expression of UCN3 in serum and urine was significantly lower than the normal level, which may be a biologic marker for early diagnosis of renal cell carcinoma [79]. CRHBP, another member of this family, is also involved in the occurrence and development of kidney cancer. CRHBP is found in normal glomeruli and podocytes, its expression in tumor tissues is significantly reduced and the degree of CRHBP reduction is positively correlated with tumor stage and metastasis ability [76]. Overexpression of CRHBP can inhibit the proliferation, migration, and invasion of renal cell carcinoma. CRHBP-activated NF-KB signaling pathway can mediate the occurrence of renal inflammation. CRHBP also activates the mitochondrial apoptosis pathway mediated by the p53 signaling pathway and promotes the apoptosis of renal cancer cells. Therefore, these results suggest that CRHBP can inhibit the occurrence and development of renal cell carcinoma [80]. In a study on clear cell renal cell carcinoma, it was also found that the protein expression of CRHBP was significantly reduced [81]. It is currently speculated that CRHBP has an inhibitory effect on the occurrence and development of renal cancer, but its mechanism of action needs to be further studied.

Conclusion and future perspectives

More and more research has found that the abnormal expression of the CRH family members is related to the occurrence and development of various tumors. In different tumor tissues, the CRH family members have tissue specificity. The abnormal expression of these family members can affect many cell functions, such as proliferation, migration, invasion, and apoptosis. The family members also affect the abnormal activation of many important pathways, thus affecting the occurrence and development of tumors. Although the relationship between abnormal expression of CRH family members and various tumors has been shown in preliminary studies, the detailed mechanism of its relationship with tumor occurrence and development still needs further research to explore its further clinical value. We expect that with the additional study of the mechanism of the CRH family members on related tumors, the molecular targeted therapy of the CRH family members may provide a new direction for the diagnosis and treatment of tumors, which will bring more hope for the prevention and diagnosis of cancer in the future.

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