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Research Progress of ANP, NPRA, and Cx43 in Gastric Cancer

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Abstract

The occurrence and development of gastric cancer are regulated by many factors and result from the joint action of many factors. Studies have shown that ANP, NPRA, and Cx43 play a vital role in the proliferation and migration of gastric cancer. This article reviews the relationship between Atrial natriuretic peptide (ANP), Atrial natriuretic peptide receptor A (NPRA), and Connexin43 (Cx43) with the occurrence and development of gastric cancer. The review aims to provide an effective reference value for scientific research and clinical treatment.

Keywords

ANP, NPRA, Cx43, Gastric Cancer, Research Progress

1. Introduction

Gastric cancer (GC) is a common malignant tumor of the digestive tract. According to the 2020 global cancer statistics released by the International Agency for Research on Cancer (IARC), GC ranks fifth in the incidence of malignant tumors and fourth in the mortality rate worldwide. In China, gastric cancer occupies third place in both the incidence and mortality of malignant tumors. Gastric cancer is a serious threat to people's lives and health. However, the pathogenesis of gastric cancer is still unclear [1].

With the continuous in-depth research on the biological mechanism of gastric cancer, Han *et al.* [2] found that multiple genes and signaling pathways jointly regulate the occurrence and development of gastric cancer. For example, atrial Natriuretic peptide (ANP), Natriuretic peptide receptor-a (NPRA), and Connexin43 (Cx43) play essential roles in the development and progression of gastric cancer. This article reviews the molecular structure and biological functions of

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ANP, NPRA, and Cx43 and their roles in the development and progression of gastric cancer.

2. ANP

2.1. Molecular Structure and Function of ANP

NPPA gene encodes for ANP protein, an active polypeptide of ANP composed of 28 amino acid residues. The right atrium secretes ANP during atrial stretching and hypertension caused by hypervolemia [3]. The NPPA gene contains three exons, which are transcribed and translated into a precursor of 151 amino acids, preproANP. In the process of transport, 25 amino acid signal peptides are removed to produce proANP (γ-ANP) of 126 amino acids, which is hydrolyzed into ANP by the transmembrane enzyme Corin during secretion [3]. ANP circulates in the blood and acts on various organs. The half-life of ANP is very short. In the human body, the half-life of ANP is 2 - 4 min after intravenous injection [4]. ANP has vasodilation, natriuretic, diuretic, cardiac, anti-fibrosis and anti-hypertrophy effects [3]. ANP functions by preferentially binding NPRA and increasing the amount of cGMP in target tissues [3].

2.2. Relationship between ANP and Tumor

Previous studies have confirmed the presence of ANP synthesis cells in the heart. In recent years, the study has found that ANP is expressed in the heart, not only in the brain, gastrointestinal tract, pancreas, ovary, salivary glands, and is also expressed in areas such as the submandibular gland, anti-inflammatory, participate in the immune substances metabolic regulation [5]. ANP plays an essential role in various kinds of cancer through multiple channels, and the mechanism associated with regulating these channels is complicated [5]. The exact mechanism is unclear due to the complex nature of the ANP regulation in various cancers [5]. Aconite is the processed product of aconite root, because it is attached to the aconite root and growth, so the name of aconite. Normoffine, one of the main active components of Aconite, can promote the release of cardiac peptide hormone ANP. ANP inhibits the growth of colon cancer of subcutaneously transplanted tumor, induce the apoptosis of tumor cells, and thus plays an antitumor effect [6]. Loss of ANP may significantly inhibit melanoma growth by inhibiting tumor cell proliferation and microvascular formation [7]. ANP inhibits the invasion and metastasis of lung cancer cells by inhibiting the expression of E-selectin induced by inflammation and inhibiting the adhesion between cancer cells and vascular endothelium [8]. ANP treatment can prevent cancer metastasis to a certain extent and significantly reduce the recurrence rate of cancer patients after surgery [9]. ANP inhibits the growth of tongue cancer cells SCC9 and SCC25 by inducing cell apoptosis through the mitochondrial pathway [10]. Compared with oral squamous cell carcinoma (OSCC), primary submandibular squamous cell carcinoma (SMG OSCC) is characterized by increased NPPA expression [5]. Perioperative low-dose human atrial natriuretic peptide (hANP)

administration is feasible and safe for patients with colorectal cancer [11]. Studies have shown that ANP-related polypeptide KTH-222 can inhibit human pancreatic tumor cells (MIA PACA-2 and HPAC) [12]. A study on breast cancer showed that ANP could significantly reduce the expression of p53 and promote the decline of cell proliferation [13]. The effect of ANP on its receptor NPRA in breast cancer cells has been studied and reported that the higher the concentration of ANP, the higher the expression of NPRA. This study indicates that ANP upregulates the expression of NPRA [13]. These studies conclude that the anti-proliferation ability of ANP may be caused by inhibiting growth-promoting signals of various protein kinases [13].

2.3. Relationship between ANP and Gastric Cancer

At present, there are few studies on ANP in gastric cancer. Zhang *et al.* [14] found in *in vitro* experiments that different concentrations of ANP had opposite effects on AGS gastric cancer cells. The study reported that a lower concentration of ANP promoted AGS gastric cancer cells proliferation while a higher concentration inhibited AGS gastric cancer cells proliferation. This result correlated with the fact that the lower concentration of ANP depended on the cGMP pathway, which upregulated the expression of voltage-dependent potassium channel KQT subfamily 1 (KCNQ1), whereas higher concentration had opposite effects. Li *et al.* [15] reported that at the cellular level, ANP could inhibit the proliferation of gastric cancer cell MGC-803, and the inhibitory effect became more evident with the increased concentration and time extension. At the tissue level, studies have shown that the higher the degree of tumor differentiation, the stronger the expression of ANP, and ANP can inhibit the invasion and metastasis of gastric cancer [15]. Hao *et al.* [16] used the immunohistochemical technique (IHC) to reveal the expression of ANP in human stomach tissue. The study reported that ANP expression is high in human non-cancerous stomach tissue but low in gastric cancer tissue. And with the decrease of gastric cancer differentiation, ANP gradually decreases, which is consistent with Li and Li, 2018 [15]. ANP may inhibit the proliferation, invasion, and metastasis of gastric cancer through BNP, PI3K/Akt, and Hedgehog signaling pathways [16] [17] [18].

It can be inferred from the above discussion that ANP has a comprehensive and extensive tumor inhibition effect. Given its advantages in the anticancer process, ANP has shown a good prospect in the field of gastric cancer inhibition.

3. NPRA

3.1. Molecular Structure and Function of NPRA

NPRA gene is located on chromosome 1Q21-22. It is a 135 kDa glycoprotein whose extracellular domain, the transmembrane domain, and intracellular domain consist of 441, 21, and 568 amino acid residues, respectively. NPRA is an important receptor of ANP. NPRA expresses ANP and BNP signals by increas-

ing second messenger cGMP and activating cGMP dependent protein kinases (PKG), which in turn upregulate the expression of genes encoding ion transporters and transcription factors, and these genes trigger a large number of physiological and pathophysiological functions in some target cells and tissues. These include cell growth, apoptosis, proliferation and inflammation [19]. mRNA of NPRA is expressed in the kidney, lung, fat, adrenal gland, brain, heart, testis, and vascular smooth muscle tissues [19]. However, recent studies have shown that the expression and signal transduction of NPRA is important for tumor growth [19]. In addition to being related to cardiovascular and renal effects, NPRA has also been proved to exist in various neuronal structures, cells, and cerebral vessels [20]. It is worth considering that animal studies have shown that it may regulate the integrity of the blood-brain barrier, inflammation, and memory function [20].

3.2. The Relationship between NPRA and Tumor

It was not until 1993 that researchers began studying NPRA's role in cancer. Ohsaki *et al.* [19] first found the expression of functional NPRAs in human small cell lung cancer cell line and Hela cells. Vesely *et al.* [19] further studied natriuretic peptide and cancer cell proliferation. They reported the expression of NPRA in various human cancer cells, including lung squamous cells, angiosarcoma, colonic cancer, prostate cancer, glioblastoma cells, medullary thyroid cancer, pancreatic adenocarcinoma, melanoma cells, breast cancer, ovarian cancer, kidney gland cancer cell, and small cell lung cancer cells. And in lung cancer, melanoma, ovarian and prostate cancer, the expression of NPRA is increased, so it may be a new anticancer target [19]. Qu *et al.* [21] found that NPRA expression is upregulated in breast cancer tissues, whereas inhibition of NPRA expression can reduce the proliferation, migration, and invasion of breast cancer cells. Moreover, the overexpression of NPRA can enhance the malignant behavior of breast cancer cells. Tan *et al.* [22] found that NPRA knockdown significantly reduced the invasion ability of HTR8/SVneo cells in human chorionic trophoblast cells. Nakao *et al.* [23] studied that the overexpression rate of NPRA in tongue squamous cell carcinoma was higher than that in normal oral epithelium, and NPRA was associated with VEGF expression level, invasion, and metastasis. NPRA may be a prognostic factor for tongue squamous cell carcinoma patients.

3.3. Relationship between NPRA and Gastric Cancer

Studies have shown that NPRA is expressed in gastric and esophageal cancer [19]. Li *et al.* [24] found in *in vivo* and *in vitro* studies that NPRA expression was related to tumor size and the disease stage of gastric cancer. Inhibition of NPRA can induce cell death and G2/M cell cycle arrest in a ROS-JNK-dependent manner, and further speculated that high concentration of ANP plays an anticancer role by reducing the expression level of NPRA [24]. Western blot analysis

showed that high ANP treatment could damage the expression of NPRA in gastric cancer cell SGC-7901 and BGC-823. Therefore, the anticancer effect of ANP does not conflict with the cancer-promoting properties of NPRA. NPRA knockdown affected AGS cell proliferation ability which was impaired, apoptosis increased, and invasion ability decreased, indicating NPRA knockdown significantly reduced voltage-gated outward K^+ current [25]. Our previous study revealed that NPRA gene silencing downregulates the expression of β-tubulin of cytoskeleton protein via regulation of the Akt/mTOR signaling pathway, thus inhibiting the proliferation and migration of gastric cancer cell MGC-803 [26]. NPRA not only plays the biological role of ANP but also in tumor genesis and development [23] [27]. Studies have shown that the expression of NPRA is positively correlated with the tumor size and pathological stage of gastric cancer, and inhibition of NPRA can lead to impaired proliferation and viability of gastric cancer cells *in vitro* and *in vivo*. Downregulation of the NPRA gene plays its antitumor role by decreasing mitochondrial function and increasing reactive oxygen species (ROS) [24].

As discussed above, there are few studies on the role of NPRA in gastric cancer, and its exact role in cell proliferation, migration, and NPRA mediated signal transduction still needs further research.

4. Cx43

4.1. Molecular Structure and Function of Cx43

Gap junctions are made up of proteins called connexins. Connexin (Cx) is a membrane protein with at least 21 members, of which Cx43 is the most studied. Cx43 protein is encoded by the gap junction protein alpha 1 (GJA1) gene and has a molecular weight of about 43 kDa. Cx43 contains nine domains, including four transmembrane segments, two extracellular rings, one amino-terminal, one cytoplasmic ring, and one carboxyl-terminal (CT) [28]. The transmembrane structure of Cx43 forms a half-channel on the cell membrane and gap junction intercellular communication (GJIC) between two adjacent cells, allowing passage of small molecules (ions, second messengers, and metabolites), antigens, and microRNAs [28]. Another important feature of the Cx43 is the long-chain CT; CT has a slender helical structure of 156 amino acids with many protein binding sites. Through these sites, Cx43 can interact with a variety of cytoplasmic and membrane proteins, affecting the permeability of gap junction channels and various other signaling pathways [29]. In addition, the nuclear localization of the C-terminal domain of Cx43 protein has been shown to regulate gene expression by binding to other protein chaperons. For example, Cx43 has been shown to downregulate the expression of transfer-related genes by interacting with b-catenin localized in the nucleus [30] [31]. Through the above important domains, Cx43 is involved in regulating the rhythm of heart beating, cell proliferation and migration, skin wound healing, corneal wound healing, and other functions [28].

4.2. The Relationship between Cx43 and Tumor

Because gap junctions in tumor cells are downregulated, there is less or no exchange of molecules between tumor cells compared to healthy cells. Studies have shown that Cx43 expression is reduced or completely lost in primary tumors such as breast cancer or melanoma [32] [33]. A study reported that the absence of Cx43-mediated Gap Junction (GJ) may also be due to cytoplasmic localization of Cx43, which is observed in both pancreatic and breast cancers [34]. Cx43 overexpression increased the sensitivity of breast cancer to tamoxifen (TAM). Cx43 loss promotes TAM insensitivity by regulating T47D TAM resistant and sensitive cells and epithelial-mesenchymal transformation (EMT) in xenografts. Thus, the therapeutic strategies to increase or maintain Cx43 function may help overcome TAM resistance [35]. Cx43 induces G1 cycle arrest of human breast cancer cell MCF-7, inhibits cell proliferation, migration and invasion, and inhibits chemotherapeutic resistance of MCF-7 cells [28]. In many GJ-deficient cancer cells, connexin overexpression leads to GJ recovery, thereby reducing or completely blocking cell proliferation [36] [37] In most cell models, the hypothesis that GJ has a role in tumor growth control via Cx43 was strengthened by the use of chemical inhibitors of GJ that reduced cell proliferation [29]. Cx43 has been reported to be involved in the migration of many cells, such as astrocytes. It has been reported that activation of β2-adrenergic receptor (beta2-AR) enhanced Cx43 protein levels in Glioblastoma multiforme (GBM) cells and human olfactory ensheathing cells (OECs) may be a promising method for GBM treatment in the future [38]. In the human U2OS cell line [39] [40], Cx43 expression was regulated through various mechanisms to drive OS cell proliferation [37]. The studies have demonstrated that Cx43 knockdown activates the Wnt/β-catenin signaling pathway, promotes U2OS cell proliferation, and inhibits apoptosis. In addition, these authors demonstrated that the anti-tumor activity of resveratrol on U2OS cells is realized by upregulation of Cx43 and inhibition of the Wnt/β-catenin signaling pathway [40]. Cx43 expression was decreased in neoplastic prostate tissue compared with normal tissue [41]. Currently, it is widely believed that Cx43 has an adverse effect on the growth of primary prostate cancer. Therefore, Cx43 is considered a tumor suppressor gene in the early stage of prostate cancer development, especially during primary tumor growth [42]. There have been more and more studies on Cx43 polypeptides in recent years. For example, TATCX43266-283, a CX43-based peptide, has been found to reduce the growth, invasion, and progression of glioblastoma, improve the survival rate of glioma-carrying mice with no toxicity to endogenous brain cells. These results suggest that the peptide can be used as a new clinical treatment for hypermalignant glioma [43]. We synthesized a bi-functional Cx43 analog peptide and bonded it to hyaluronic acid (HA) to generate a uniform bi-functional injectable hydrogel system (HA - JM2) that simultaneously inhibited tumor recurrence and promoted wound healing. Because HA-JM2 hydrogel can continuously release JM2 to control host inflammation and stimulate angiogenesis, it can accelerate wound healing in full-thickness skin defects. When HA-JM2 hydrogel was applied to

incomplete tumor defect, it inhibited tumor recurrence and stimulated skin wound healing [44]. Cx43 overexpression can inhibit the growth and progression of primary tumors, as reported in colorectal [45] and lung cancer [46]. In lung cancer, Cx43 reversed EMT in A549 lung adenocarcinoma. Overexpressed A549 cells showed epithelial morphology, with increased E-cadherin expression and decreased mesenchymal marker Vimentin, Slug, and Snail expression. In addition, the invasion and migration potential of Cx43 overexpressed A549 cells was reduced, providing evidence for the ability of Cx43 to reverse the EMT phenotype of A549 lung cancer cells [46]. This study provides a theoretical basis for the treatment of lung adenocarcinoma. Several studies have reported the involvement of Cx43 semitaxel in tumor growth. For example, blocking the Cx43 semitaxel (by targeting the extracellular ring of Cx43) antibodies can reduce the growth of rat C6 glioma cells [46]. In contrast, the Cx43 half channel plays an antitumor role in osteoblasts: ATP released by the half channel on osteoblasts stimulates paracrine signals and triggers an inflammatory cascade that prevents breast cancer cells from migrating and invading bone tissues [46]. Thus, these studies suggest that half channels on healthy cells have antitumor effects, while half channels on cancer cells promote tumor growth and migration.

4.3. The Relationship between Cx43 and Gastric Cancer

Cx43, as a tumor suppressor, was downregulated in gastric cancer. Li *et al.* [47] found that the ultrastructural damage of gap junction in gastric cancer tissue was apparent, and the damage was more severe in poorly differentiated tissues. Cx43 protein and mRNA expression were higher in healthy gastric tissues than in gastric cancer tissues. Also, the expression was higher in the highly differentiated group than the less differentiated group. Cx43-mediated GJ deficiency in gastric cancer may be caused by cytoplasmic localization of Cx43 [34]. The elimination of precancerous lesions of helicobacter pylori (HP) infected gastric can upregulate the expression of Cx43 at the glandular epithelial junction of gastric mucosa, thereby contributing to the recovery of GJIC function. Further studies found that HP promotes the expression of GATA-3, and GATA-3 can directly bind to the promoter region of the Cx43 gene to induce its expression inhibition [48]. The expression of Cx43 decreased with the progression of gastric mucosal lesions to precancerous lesions [48]. Zhang *et al.* [49] found that Cx43 was negatively correlated with phosphorylated cytoskeletal protein (P-Ezrin) in gastric cancer as p-Ezrin could phosphorylate Cx43 and destroy intercellular GJIC. Overexpression of Cx43 in gastric cancer cells enhances Gj, thereby increasing sensitivity to chemotherapy drugs [50]. The expression of Cx43 increased in advanced gastric cancer metastatic lesions. Immunohistochemical analysis of 117 gastric cancer samples showed that the decreased expression of Cx43 and E-cadherin contributed to the development of primary gastric cancer. However, increased Cx43 and E-cadherin expression contribute to lymph node metastasis [51] [52]. In the cohort of patients with lymph node metastasis, epithelial Cx43 expression is higher in primary gastric adenocarcinoma. The higher epithelial

Cx43 expression is associated with higher mortality. Thus, increased epithelial Cx43 expression may be used as a biomarker for gastric cancer prognosis [53]. Low expression of Cx43 predicts poor cancer-specific survival after gastric cancer surgery [54].

Substantial evidence suggests the role of Cx and Cx43 in human cancers, including gastric cancer. Cx43 has been shown to play an important role in the global incidence of cancer and cancer-related deaths. The present studies reveal many conflicting ideas that lack detailed research on specific cancer such as gastric cancer. Thus, more information and ongoing research are needed to explore and investigate the role of gap junctions and their conjunctive proteins, such as Cx43, in gastric cancer.

5. Summary and Outlook

From the above, it is not difficult to find that there are abnormal expressions of ANP, NPRA, and Cx43 in gastric cancer. There are many studies on individual factors in the occurrence and development of gastric cancer, but fewer studies on their correlation. The three may be related to the occurrence and development of gastric cancer. The interaction of ANP, NPRA and Cx43 with each other in cell signal transduction may jointly affect the occurrence, development, invasion, and metastasis of gastric cancer. These results will provide new ideas for our future research on the relationship between ANP, NPRA and Cx43 and their relationship with tumor growth.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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