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REVIEW

Erythropoietin-induced hepatocyte receptor A2 regulates effect of pyroptosis on gastrointestinal colorectal cancer occurrence and metastasis resistance

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Abstract

Erythropoietin-induced hepatocyte receptor A2 (EphA2) is a receptor tyrosine kinase that plays a key role in the development and progression of a variety of tumors. This article reviews the expression of EphA2 in gastrointestinal (GI) colorectal cancer (CRC) and its regulation of pyroptosis. Pyroptosis is a form of programmed cell death that plays an important role in tumor suppression. Studies have shown that EphA2 regulates pyrodeath through various signaling pathways, affecting the occurrence, development and metastasis of GI CRC. The overexpression of EphA2 is closely related to the aggressiveness and metastasis of GI CRC, and the inhibition of EphA2 can induce pyrodeath and improve the sensitivity of cancer cells to treatment. In addition, EphA2 regulates intercellular communication and the microenvironment through interactions with other cytokines and receptors, further influencing cancer progression. The role of EphA2 in GI CRC and its underlying mechanisms provide us with new perspectives and potential therapeutic targets, which have important implications for future cancer treatment.

Key Words: Colorectal cancer; Pyroptosis; Erythropoietin-induced hepatocyte receptor A2; Tumor metastasis; Drug resistance

Core Tip: This study investigated the expression of erythropoietin-induced hepatocyte receptor A2 (EphA2) in gastrointestinal (GI) colorectal cancer (CRC) and the mechanism by which EphA2 regulates pyroptosis. By reviewing the relevant literature, we found that EphA2 regulates pyroptosis through a variety of signaling pathways (such as the phosphatidylinositol 3 kinase/protein kinase B and Ras/mitogen-activated protein kinase pathways), thereby affecting the survival, proliferation and metastasis of cancer cells. The abnormal expression of EphA2 is closely related to the malignant behavior of GI CRC, and EphA2 further regulates the tumor microenvironment and immune response through interactions with inflammatory factors (such as tumor necrosis factor-α and interferon-γ). Studies have shown that targeting EphA2 can induce pyrodeath in cells, improve the sensitivity of cancer cells to treatment, and subsequently inhibit the occurrence and metastasis of tumors. Therefore, an in-depth understanding of the molecular mechanism by which EphA2 regulates pyrodeath provides new ideas and potential targets for the treatment of GI CRC.

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INTRODUCTION

Erythropoietin-induced hepatocyte receptor (Eph) is the largest receptor tyrosine kinase (RTK) family in the spinal cord animal genome[1-4]. According to their extracellular structure, Eph ligands can be divided into two categories: A (EPHA1-A8 and EphA10) and B (EphB1-B4 and EphB6), and EPH ligands can also be divided into two categories: Ephrin A1-5 and Ephrin B1-3. EphA2 has received increasing attention due to its role in regulating the progression and prognosis of malignant tumors[5]. The *EphA2* gene is located in band 6 of the short arm 3 region of human chromosome 1 and has been shown to be a region that is often altered in cancer. EphA2 was discovered in 1990 during the screening of HeLa cell cDNA libraries and was originally called epithelial cell kinase because EphA2 is expressed in most epithelial cells[6-8]. The EphA2 receptor is a type I transmembrane protein composed of 976 amino acid polypeptides, and its structure is usually conserved[9]. It includes an N-terminal extracellular region, a transmembrane region and a C-terminal intracellular region[10-12]. The extracellular region consists of a ligand-binding domain at the N-terminus, a Sushi domain, a cysteine-rich domain, and two fibronectin III repeats (FN III)[13-15]. The intracellular portion consists of a near-membrane tyrosine kinase domain, followed by a tyrosine kinase domain, an S-adenosylmethionine (SAM) domain, and a PDZ-binding motif at the C-terminus, and the following is a timeline summary of EphA2-related research and findings (Figure 1).

Gastrointestinal (GI) colorectal cancer (CRC) is one of the most common and lethal malignancies in the world. The molecular mechanisms of its occurrence and metastasis are complex and diverse. EphA2, as a RTK, has been found to be closely related to the progression of CRC in recent years. Specifically, EphA2 regulates cell pyrodeath by activating signaling pathways such as phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), thereby affecting the proliferation, migration and invasion of tumor cells. In addition, experimental studies have shown that high expression of EphA2 is associated with poor prognosis of CRC, and inhibition of EphA2 can significantly reduce tumor growth and metastasis. These studies reveal the key role of EphA2 in CRC and provide an important theoretical basis for developing new treatment strategies.

EPHA2 SIGNAL CHARACTERISTICS

EphA2 can interact with any of the eight ligands of Eprin class A but has a particular preference for Ephrin A1[16-18]. Unlike classical RTKs, which usually only mediate one-way transmission, cells expressing EphA2 receptors can transmit forward signals from Ephrin A1 to Ephrin A1 during intercellular contact, while cells expressing Ephrin A1 receive reverse signals from EphA2 to Ephrin A1[19]. This bidirectional signaling pathway, also known as the ephrin A1-EphA2 pathway, can cause signal transduction on the cell surface, regulating cell activity and cell-cell interactions[20-24]. This signaling pathway plays an important role in regulating the growth and metastasis of malignant tumors and the proliferation and invasion of cancer cells[25]. Many downstream signaling pathways are related to Ephrin-Eph complexes[26-30]. For example, EphA2 can activate the PI3K/Akt signaling pathway and subsequently inhibit cell apoptosis[31]. EphA2 can also activate the MAPK signaling pathway, which is closely related to cell proliferation, metastasis, invasion and other processes[32-36]. The interaction of EphA2 with epidermal growth factor receptor (EGFR) can activate signaling pathways such as the EGFR/Akt and EGFR/MAPK pathways, thus promoting cell proliferation and migration[37-40]. In conclusion, the signal transduction pathway of EphA2 involves multiple molecules and pathways, and this complex regulatory network plays an important role in the growth, metastasis, invasion and other processes of CRC[41-45].

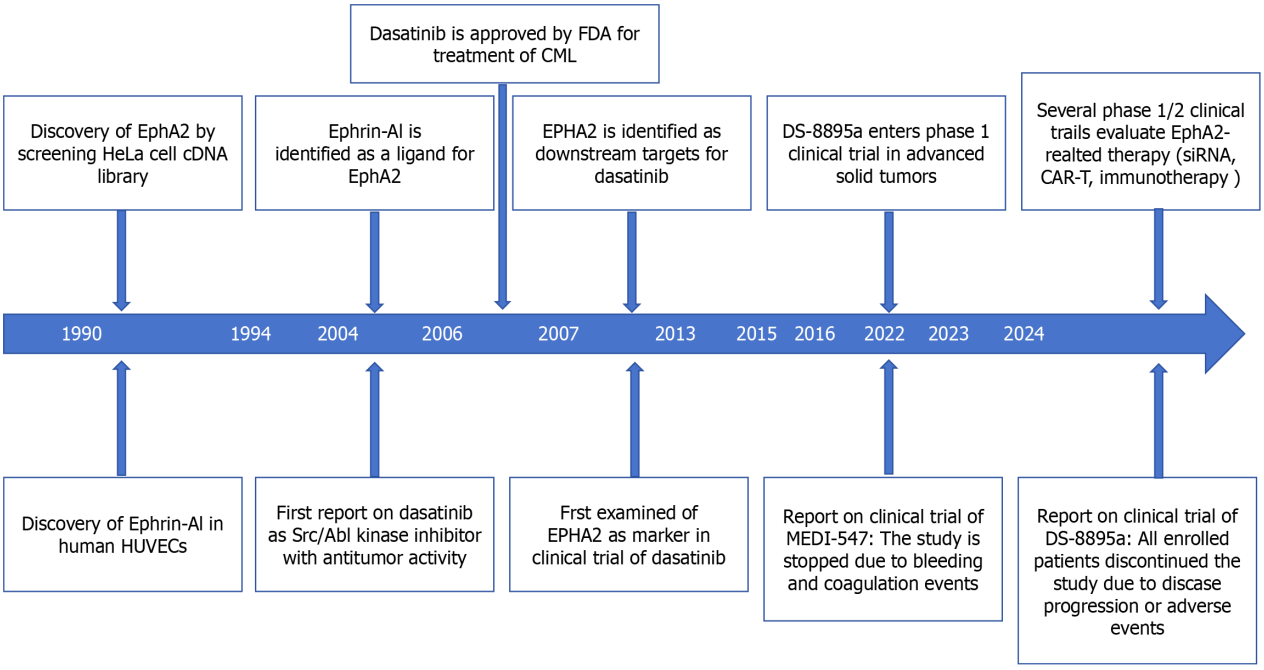

Figure 1 Timeline summary of erythropoietin-induced hepatocyte receptor A2-related research. Created by the BioRender. EphA2: Erythropoietin-induced hepatocyte receptor A; FDA: Food and Drug Administration; CML: Chronic myeloid leukemia; siRNA: Small interfering RNA; CAR-T: Chimeric antigen receptor T-cell therapy; HUVECs: Human umbilical vein endothelial cells.

THE ROLE AND CLINICAL PROGRESS OF EPHA2 IN TUMORIGENESIS AND DEVELOPMENT

Eph receptors are the largest RTK family in vertebrates and have a single transmembrane structure[46]. Fourteen Eph receptors and 8 Eph ligands have been identified. In recent years, as research has progressed, Eph receptors such as EphA2 have been found to be closely related to the occurrence, development and drug resistance of tumors[47-50]. EphA2 is a 130 kDa transmembrane glycoprotein composed of 976 amino acid residues[51]. Due to its multiple phosphorylation sites, EPHA2 exerts different functions, so its biological effects are very complex, and EPHA2 plays a bidirectional role in the occurrence and development of tumors[52-55]. Structurally, the extracellular segment of EphA2 has ligand-binding domains, EGF-like domains and FN-III repeats[56]. The intracellular near-membrane regions Y588 and Y594 are phosphorylated when ligands are bound to extracellular regions, activating classical ligand-dependent pathways[57]. The tyrosine kinase domain contains two phosphorylation sites, Y735 and Y772, which can interact with the p85 regulatory subunit of PI3K. The intracellular terminal SAM structure contains the phosphorylable site S897[58-60]. It is regulated by intracellular kinases and performs nonclassical functions that are not dependent on ligands (Table 1).

Overview of the classical and nonclassical signaling pathways of EphA2

The classical signaling pathway of EphA2 begins with the binding of EphA2 to ephrin, which is expressed on the cell surface but not in the free form[61-64]. Therefore, receptor ligand binding not only activated the downstream signal of the receptor but also negatively affected the expression of the ligand in the intracellular signaling pathway. After binding with ligands, self-phosphorylation of the EphA2 intracellular near-membrane regions Y588 and Y594 occurs, initiating the phosphorylation cascade and recruiting intracellular effector molecules[65]. GTPase activating protein, guanylic acid exchange factor, FAK, Src, p85, *etc.*, can interact with this activated form of EphA2 to regulate cell proliferation, apoptosis, adhesion, migration, and morphological development[66-70]. According to previous reports, the classical signaling pathway of EphA2 mainly plays a role in cancer inhibition (Figure 2).

EphA2 is associated with cell survival and proliferation

EphA2 regulates cell proliferation in normal epithelial tissues but is highly expressed in breast cancer, lung cancer and CRC[71]. Several glioma-related studies have reported the role of RSK-EphA2 pathway activation in regulating cell proliferation and its association with poor prognosis[72-75]. Knockdown of EphA2 or interference with EphA2 through microRNA (miRNA) can inhibit EGF-dependent cell proliferation, while overexpression of the EphA2S897A mutant does not cause abnormal cell proliferation, suggesting that the regulation of proliferation by EphA2 is ligand independent[76]. Some studies reported that EphrinA1 combined with EphA2 inhibited the proliferation and metastasis of breast cancer cells and that Y594 and Y588 phosphorylation and S897 dephosphorylation occurred[77-80]. EphrinA1 expression decreased significantly in breast cancer tissues[81]. These results suggest that the ligand-dependent classical EphA2 pathway plays a major role in cancer inhibition and antagonizes nonclassical functions. Previously reported EphA2-mediated regulation of cell proliferation may affect the cell cycle by decreasing p27KIP1 and inhibiting the Cdk2/CycinE1/2 complex[82]. EphA2 can also interact with FAK, HER2 and a variety of cytokines to promote proliferation and

Table 1 Summary of various erythropoietin-induced hepatocyte receptor and their implicated roles depending on cancer type

Cancer type	Eph receptor	Aberrant function	Role of Eph receptor
Colorectal cancer	EphA1	Overexpressed in early stages; low expression in later stages	Tumour suppressive
	EphA2	Overexpressed in early stages; low expression in later stages	Tumour suppressive
	EphA3	Low expression	Tumour suppressive
	EphA4	Overexpressed	Tumour promoting
	EphA7	Low expression	Tumour suppressive
	EphB2	Overexpressed in early stages; low expression in later stages	Tumour suppressive
	EphB3	Overexpressed in early stages; low expression in later stages	Tumour suppressive
	EphB4	Overexpressed	Tumour promoting
	EphB6	Low expression	Tumour suppressive

Eph: Erythropoietin-induced hepatocyte.

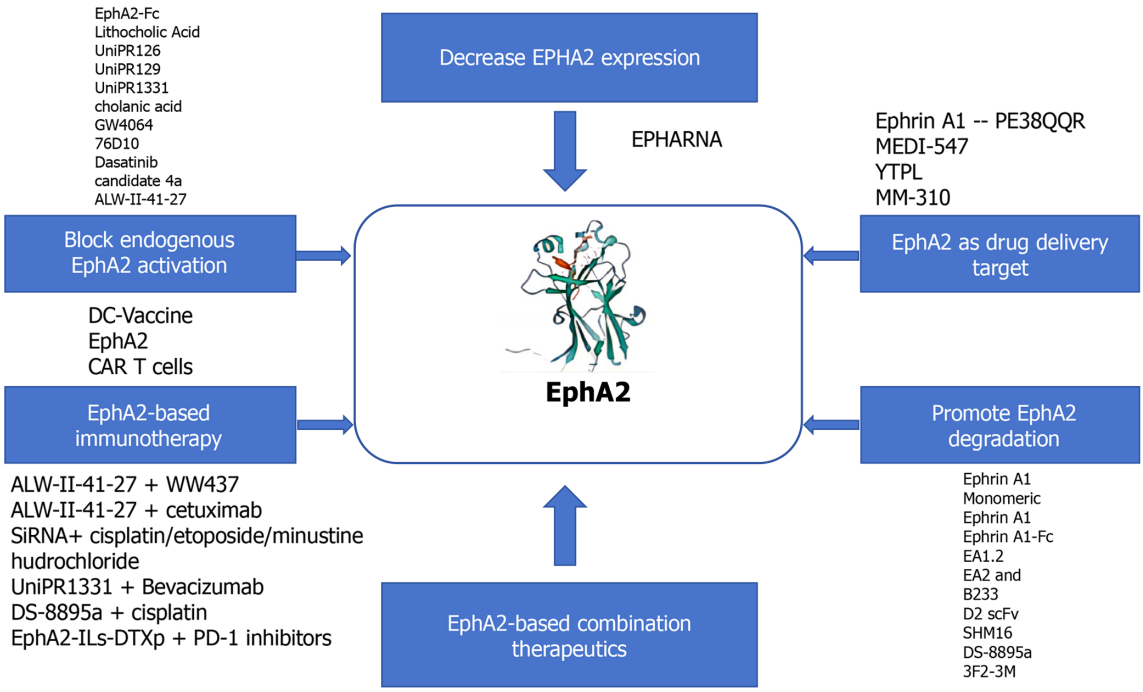

Figure 2 Overview of the signaling pathways affected by erythropoietin-induced hepatocyte receptor A2. Created by the BioRender. EphA2: Erythropoietin-induced hepatocyte receptor A.

metastasis.

EphA2 and cell migration

The most widely studied nonclassical pathway of EphA2 is its involvement in cell motility and morphological development[83-85]. A variety of cytokines can phosphorylate EphA2 expressed in cellular pseudopods at S897 through RSK1/2 to regulate cell migration and allow cells to move to the side of high-concentration chemokines[86-90]. For example, RSK1/2 phosphorylates EphA2 (S897) to promote invasion and metastasis in the MDA-MB-231 cell line. It has also been reported that tropomyosin-associated kinase A activates SRC-mediated cell migration *via* the AKT-EphA2 (S897) pathway[91]. Treatment of cells with RSK inhibitors or EphA2-targeting miRNA200a reduced cell motility, while overexpression of the EphA25897A mutant did not restore cell migration after downregulation, suggesting that RSK activates the EphA2S897 site to regulate cell motility[92-95]. Immunohistochemistry showed that RSK inhibition not only decreased pEphA2 S897 staining intensity but also disrupted EphA2 distribution in cells, indicating that RSK also regulated the phosphorylation of EphA2 and its intracellular localization. In addition, EphB6 inhibited the migration-promoting effect of EphA2, and EphA2 and EphB6 expression was often negatively correlated in tissues, suggesting the existence of a common upstream regulatory mechanism[96]. Chemokines such as nerve growth factor precursors phosphorylate EphA2 S897 *via* AKT, thereby activating SRC-mediated cell migration[97].

EphA2 regulates the effect of pyroptosis

Pyroptosis is a form of inflammatory programmed cell death that, unlike cell necrosis, plays a key role in tumor suppression and the immune response. Studies have shown that EphA2 regulates pyrodeath through a variety of signaling pathways. For example, EphA2 can activate the PI3K/AKT and Ras/MAPK signaling pathways, which are commonly associated with cell survival and antiapoptotic mechanisms. However, under specific physiological or pathological conditions, the overexpression or abnormal activation of EphA2 can lead to pyroptosis, thereby inhibiting the growth and spread of cancer cells. Binding of EphA2 to its ligand triggers a series of downstream signal transduction events that promote the release of intracellular inflammatory response factors, such as interleukin (IL)-1β and IL-18, thus initiating the pyroptosis process.

In addition, the interaction of EphA2 with other cytokines and receptors is also an important mechanism regulating pyrodeath. EphA2 can synergize with inflammatory factors such as tumor necrosis factor-α and interferon-γ to enhance pyroptotic signal transduction. These interactions not only affect the survival of the cancer cells themselves but also alter the tumor microenvironment and enhance the ability of immune cells to recognize and clear cancer cells.

In GI CRC, EPHA2-regulated pyroptosis has dual effects on cancer initiation and metastasis. On the one hand, EPHA2-mediated pyroptosis can limit the growth and metastasis of cancer cells and improve therapeutic efficacy. On the other hand, abnormal EphA2 expression and signaling may cause cancer cells to evade pyrodeath and increase drug resistance and metastasis. Therefore, a thorough understanding of the regulatory mechanism of EphA2 in pyroptosis is highly important for the development of new therapeutic strategies. In summary, EphA2 regulates pyroptosis through a variety of complex signaling pathways and interactions and plays a key role in the occurrence, development and metastasis resistance of GI CRC.

EPHA2 PROMOTES THE DEVELOPMENT AND METASTASIS OF CRC

CRC is a highly complex disease whose pathological features involve abnormal changes in multiple biological processes, including cell proliferation, differentiation, apoptosis, cycle regulation, migration and invasion, and angiogenesis[98-100]. These biological processes interact and together drive the onset and development of cancer[101-103]. Serum EphA2 levels are greater in patients with advanced TNM, deeply invasive tumors, multiple lymph node metastases, and distant metastases[104]. The abundance of 21 RTKSs and reported that the expression levels of some RTKSs, including EphA2, were closely related to liver metastasis and the prognosis of CRC patients[105-110]. In conclusion, EphA2 plays a crucial role in the development and metastasis of CRC, and its mechanism of action involves several biological processes, such as angiogenesis, epithelial-to-mesenchymal transition (EMT) and intracellular signal transduction (Figure 3).

EphA2 promotes angiogenesis

Neovascularization plays an important role in the development and metastasis of CRC[111-114]. Tumor cells release large amounts of vascular endothelial growth factor (VEGF) in harsh environments, stimulating angiogenesis to meet the oxygen and nutrient requirements for tumor growth[115]. The formation of blood vessels and lymphatic vessels can also provide pathways for metastasis, which can promote hematologic or lymphatic metastasis of tumors[116-120]. EphA2 is an important factor that promotes vascular mimicry, and its mechanism of action mainly involves the regulation of the VE-cadherin/EphA2 pathway in vascular endothelial cells. Serum EphA2, VEGF-A and carcinoembryonic antigen levels in CRC patients were significantly greater than those in controls, and serum EphA2 levels were positively correlated with VEGF-A content. One study revealed a close relationship between EphA2 and VEGF[121]. The level of N6-methyl-adenosine methylation of EphA2 and VEGF-A in CRC was significantly greater than that in normal tissues. This modification allows its messenger RNA to be stabilized and translated[122-125]. Thus, the protein expression of EphA2 and VEGF-A is synergistically upregulated, and this process is caused by insulin-like growth factor 2 (IGF2) mRNA binding protein 2/3. With the activation of IGF2BP2/3, EphA2 and VFGRA promote the formation of intravascular structures in tumor blast cells through the PI3K/Akt and ERK1/2 pathways to promote tumor growth and development [126-130]. EphA2 is a functional receptor for growth factor progranulin (PGRN). In EPHA2-deficient endothelial cells, the role of PGRN in promoting endothelial cell angiogenesis is significantly weakened. EphA2 plays a promoting role in angiogenesis and promotes the development and metastasis of CRC[131-134].

EphA2 promotes EMT

EMT is a complex process involving cytoskeletal and phenotypic changes. During EMT, epithelial cells gradually lose their characteristic cell-cell connections and epithelial cell morphology and gradually acquire the morphological and biological characteristics of mesenchymal cells[135]. EMT can increase the migration and invasion ability of CRC cells so that they can more easily metastasize and spread to other tissues and organs[136]. EphA2 regulates EMT in CRC by downregulating the expression of epithelial E-cadherin, thereby reducing intercellular adhesion and enhancing cell metastasis[137]. SW480 cell line, the phosphorylation of EphA2 was reduced through the Akt-EphA2 pathway, resulting in a significant increase in E-cadherin. The inhibition of EphA2 phosphorylation was also significantly associated with low vimentin expression[138-140]. Further studies revealed that EphA2 promotes EMT through the Notch and Snail signaling pathways, thereby enhancing the invasion and migration ability of the CRC cell line LoVo. Further studies revealed that EphA2 promotes EMT through the Notch and Snail signaling pathways, thereby enhancing the invasion and migration ability of the CRC cell line LoVo[141-145].

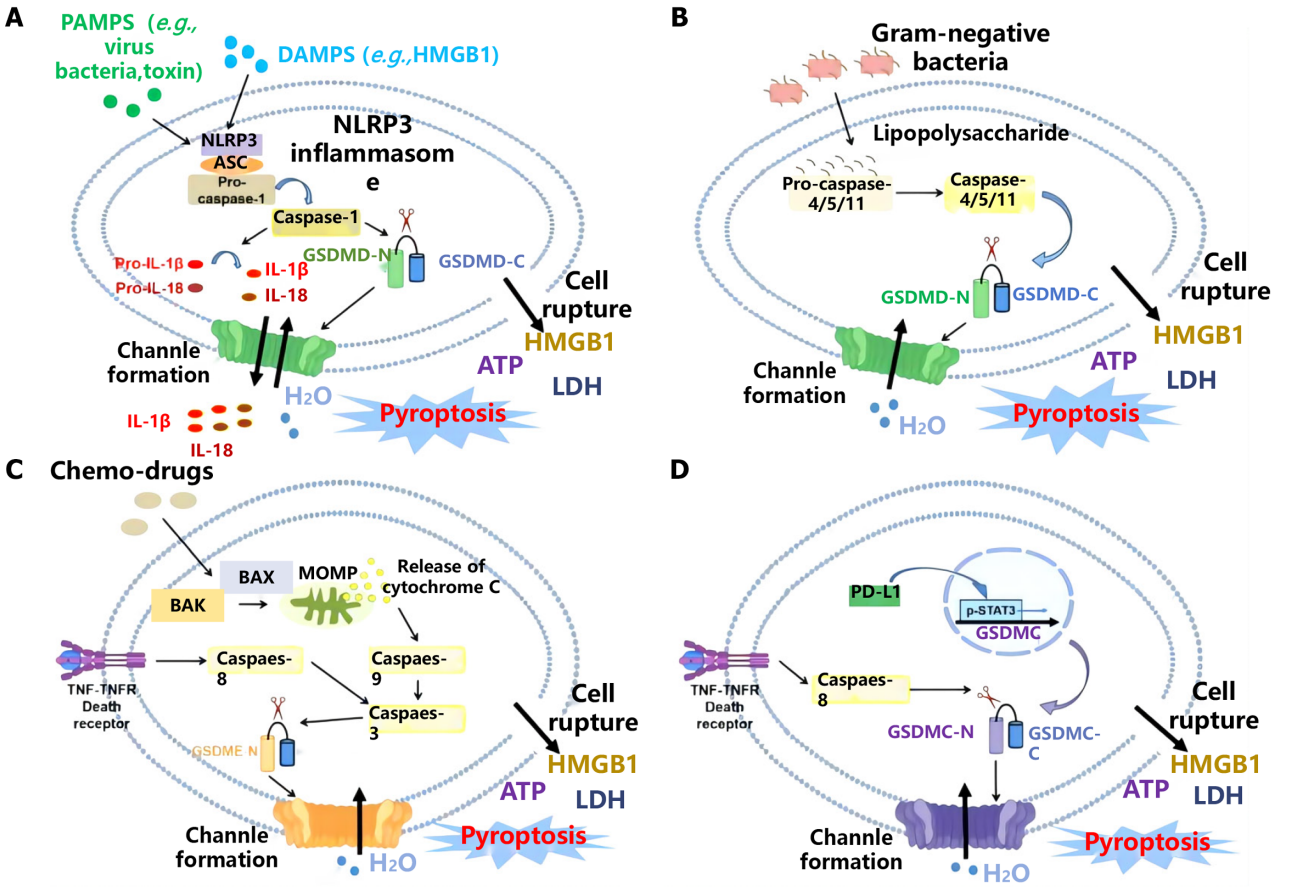

Figure 3 Analysis of signal transduction pathways related to erythropoietin-induced hepatocyte receptor A2 and pyroptosis. Created by the BioRender. A: Pathogen-associated molecular patterns and damage-associated molecular patterns; B: Gram-negative bacteria; C: Chemo-drugs; D: Channle formation. PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; HMGB1: High mobility group box 1; NLRP: NOD-like receptor protein; ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain; IL: Interleukin; GSDMD: Gasdermin D; LDH: Lactate dehydrogenase; MOMP: Mitochondrial outer membrane permeabilization; TNF: Tumor necrosis factor; PD-L1: Programmed death-ligand 1.

EphA2 affects intracellular signal transduction

EphA2 not only promotes the development and metastasis of CRC by directly affecting cell biological processes such as cell adhesion, migration and invasion but also regulates the growth, apoptosis and metastasis of CRC cells by affecting a variety of intracellular signaling pathways and gene regulation[146-148]. PGRN can form a complex with EphA2 on the surface of the tumor cell membrane, thereby activating the EphA2 signaling pathway[149]. This signaling pathway promotes the proliferation and development of tumor cells through the EphA2-mediated activation of Akt and MAPK. Cui *et al*[126] showed that EPHA2-superenhancer promotes tumor progression by recruiting FOSL2 and TCF7 L2 to activate the expression of the target gene EphA2. The deletion of EPHA2-superenhancer promoted apoptosis, inhibited cell growth and enhanced cell invasion by blocking the PI3K/Akt and Wnt/β-catenin pathways in HCT-116 cells. Liu *et al*[128] showed that the upregulation of Smad4 inhibits EphA2 phosphorylation by blocking the PI3K/Akt/EphA2 axis, thus weakening the migration and invasion ability of CRC cells. In conclusion, EphA2 is an important regulatory factor that is closely related to various biological processes related to CRC development and metastasis.

ROLE OF EPHA2 IN DRUG RESISTANCE IN CRC

In addition to promoting the proliferation, invasion and angiogenesis of CRC cells, a series of studies in recent years have shown that EphA2 is closely related to chemotherapy resistance and targeted therapy resistance in CRC[150-154]. Drug resistance occurs in tumor cells through a series of ways to reduce their sensitivity to drugs, resulting in reduced or ineffective therapeutic effects, which is still the primary problem of treatment (Figure 4).

EphA2 and chemotherapy resistance in CRC

The protein and mRNA expression levels of EphA2 in drug-resistant CRC cells were significantly greater than those in their parental cells and gradually increased with increasing chemotherapeutic drug concentration[155-160]. When EphA2 expression is disrupted in drug-resistant cells, the sensitivity of these cells to chemotherapy drugs is significantly increased[161]. Yao *et al*[11] showed that EphA2, which is equivalent to that in the CRC parent strain HCT8, is overex-

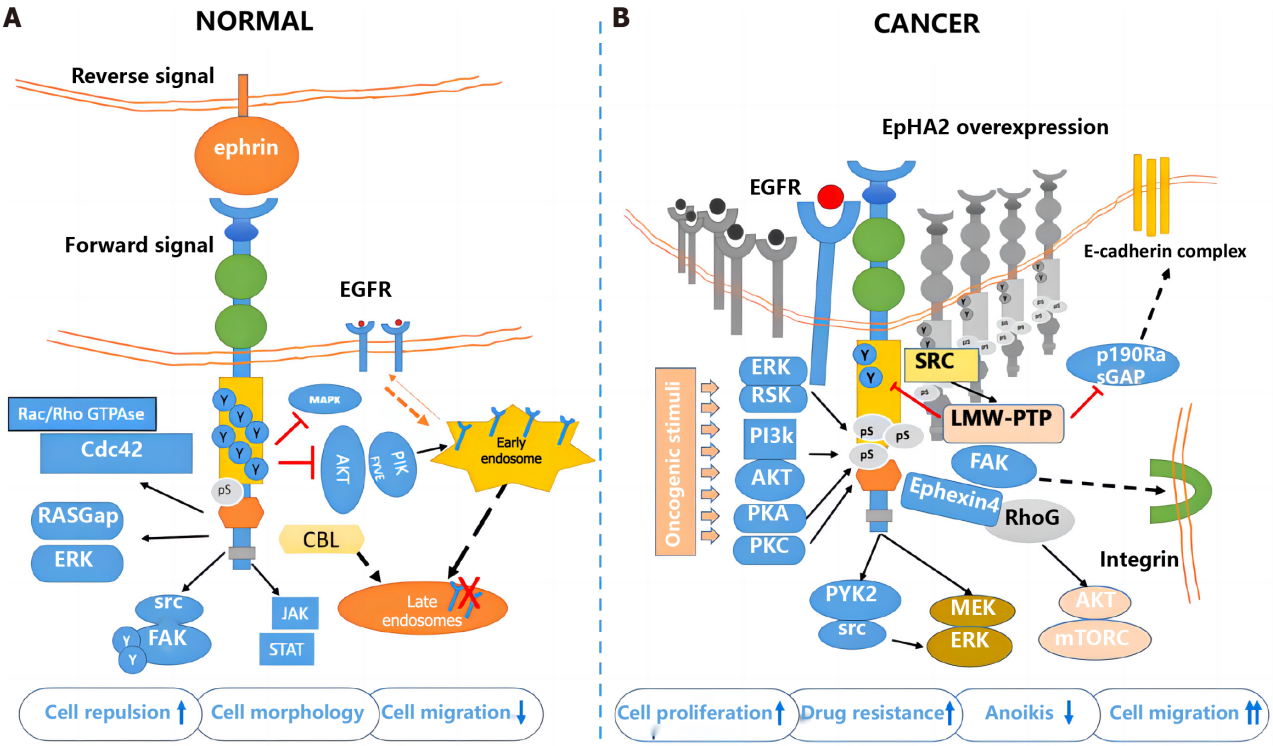

Figure 4 The role of erythropoietin-induced hepatocyte receptor A2 in the development of colorectal cancer. Created by the BioRender. A: Normal group; B: Cancer group. EphA2: Erythropoietin-induced hepatocyte receptor A; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; AKT: Protein kinase B; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase; CBL: Casitas B-lineage lymphoma; STAT: Signal transducer and activator of transcription; SRC: Proto-oncogene tyrosine-protein kinase Src; mTOR: Mechanistic target of rapamycin; GAP: GTPase-activating protein.

pressed in 5-fluorouracil/cisplatin (5-Fu/DDP)-resistant cell lines and mediates the resistance of CRC cells to chemotherapy, which is closely related to long noncoding RNAs. LINC02418 upregulates EphA2 expression through competitive binding of miR-372-3p, thereby promoting CRC chemotherapy resistance to 5-Fu/DDP. This study revealed the potential mechanism of 5-FU/DDP resistance in CRC through the LINC02418/miR-372-3p/EphA2 axis. At the same time, treatment with ALW-II-41-27 can significantly improve the chemotherapy sensitivity of CRC-resistant cells, reduce cell proliferation, promote cell apoptosis, and block the cell cycle in the G2/M phase, indicating that inhibition of EphA2 kinase activity can have a series of effects on the function of drug-resistant cells, increasing the sensitivity of drug-resistant cells to chemotherapy drugs[162-166]. EphA2 also promotes the differentiation of cancer stem cells in CRC. Cancer stem cells are a subgroup of cancer cells with strong adaptability that enable them to survive chemotherapy drugs and promote tumor recurrence and metastasis, which is closely related to chemotherapy resistance[167-170]. When EphA2 binds to PGRN or is activated by IGF2BP2/3, the mammalian target of rapamycin (mTOR) pathway of PI3K-Akt-rapamycin is activated, and the activation of this pathway promotes the survival and anti-apoptosis of cells[171-173]. Therefore, in the treatment of cancer, the mTOR pathway is activated. The activation of this pathway often leads to the occurrence of chemotherapy resistance, so inhibiting the interaction between EphA2 and its upstream molecules or blocking the PI3K-Akt-mTOR pathway may be one of the strategies for preventing chemotherapy resistance (Figure 5).

Resistance of CRC cells to targeted therapy by EphA2

Using transcriptomic sequencing technology (RNA-seq), high basal EphA2 expression was associated with resistance to regorafenib in metastatic CRC patients. Martini *et al*[9] showed that high EphA2 expression in CRC tissues leads to increased cetuximab (CET) resistance in cancer cells, and high EphA2 levels are significantly correlated with poor progression-free survival. Moreover, by combining CET with ALW-II-41-27 (an EphA2 kinase inhibitor), the sensitivity of tumor cells to chemotherapy drugs can be significantly enhanced, reversing primary and acquired resistance to CET[174-176]. CET is a monoclonal antibody that acts on CRC cells and binds to EGFR, thereby inhibiting the EGFR signaling pathway and preventing cancer cell growth and spread. According to the results of differential proteomic analysis, the EphA2 protein was significantly upregulated in drug-resistant cells, highlighting the role of EphA2 in KRAS mutation-acquired CET resistance in metastatic CRC. Studies have shown that the expression status of *EphA2*/*Efna1*/*EGFR* genes is closely related to the response of CRC patients to CET treatment, and the expression of these genes is not related to the genetic status of KRAS, which contradicts the findings of previous studies and needs further research[177]. Specifically, in CRC patients, progression-free survival in patients with high EphA2 expression under CET treatment is significantly lower than that in patients with low EphA2 expression, while in patients with high EGFR and EphA2 expression, the shortening of progression-free survival duration with CET suggests that EphA2 may play a role in circumventing CET's inhibition of the EGFR pathway and that patients with abnormal *EphA2* gene expression are more likely to show resistance to CET and have less effective treatment. Further studies have shown that the Akt signaling pathway can

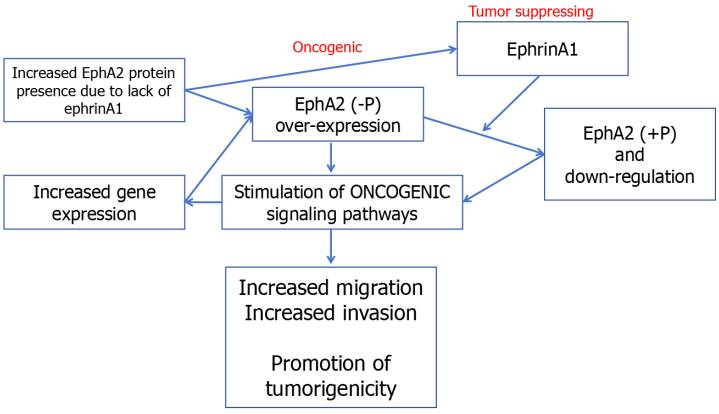

Figure 5 Erythropoietin-induced hepatocyte receptor A2 expression in colorectal cancer. Created by the BioRender. EphA2: Erythropoietin-induced hepatocyte receptor A.

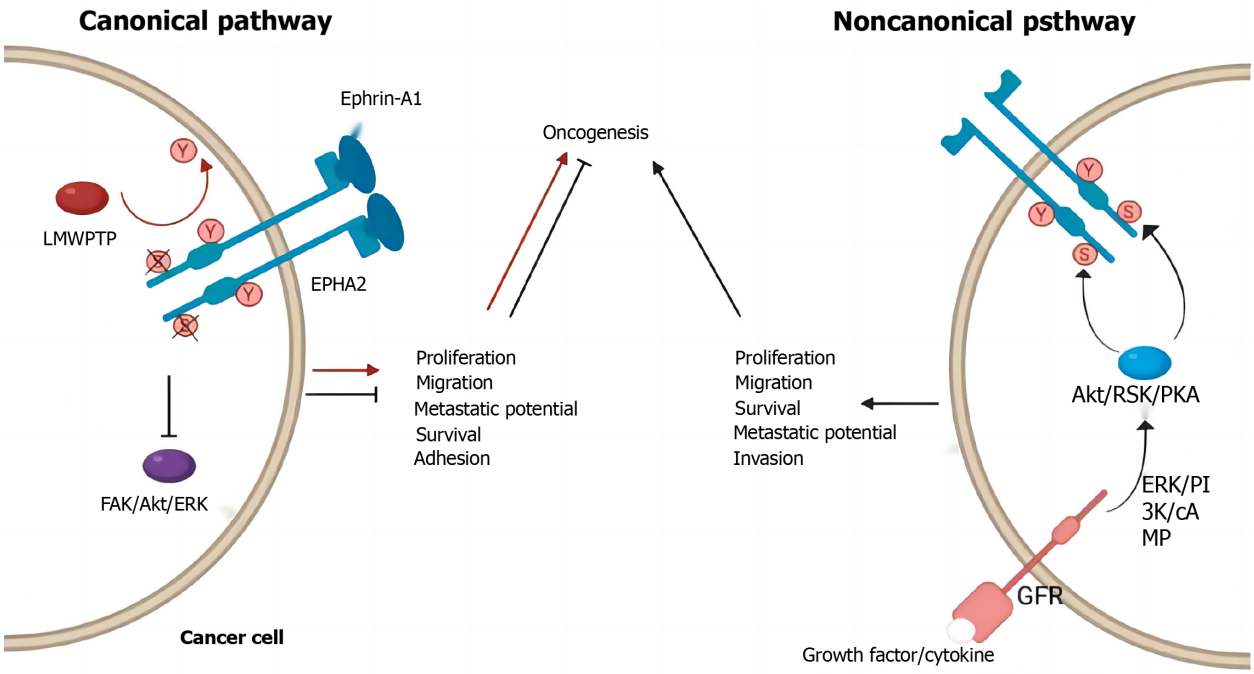

Figure 6 Canonical and noncanonical erythropoietin-induced hepatocyte receptor A2 pathway components in cancer cells. Created by the BioRender. EphA2: Erythropoietin-induced hepatocyte receptor A2; ERK: Extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; GFR: Glomerular filtration rate.

promote the interaction of EphA2 with EGFR and Ephexin1, thereby activating the Ephexin1 signaling pathway[178-180]. Akt promotes the interaction between EGFR and Ephexin1 by inducing EphA2 phosphorylation at Ser897, thereby promoting the development of CRC and resistance to CET. In general, EphA2 can enhance drug resistance in CRC cells by interacting with a variety of signaling pathways. These studies suggest that EphA2 is an important regulator of CRC resistance (Figure 6).

Relationship between EphA2 protein expression and invasion and microangiogenesis in CRC

RTKs are responsible for the transmission of external stimulus signals to the nucleus[181]. The *EPH* gene family, which is a key component of the signal transduction pathway that is involved in cell effects, is the largest member of the newly discovered RTK family and is widely expressed in cells of epithelial origin. Its structure includes an amino terminal extracellular ligand binding region, a transmembrane domain and an intracellular enzyme domain[182]. *EphA2* was the first gene found to have tyrosine kinase activity in the family. EphrinA1 can bind to the EphrinA1 ligand through the extracellular ligand binding region to form a receptor-ligand complex, which activates the cytoplasmic tyrosine phosphatase and leads to self-phosphorylation and tyrosine phosphorylation of a large number of downstream intracellular substrate protein molecules[183]. These pathways participate in cell growth, migration and differentiation activities and play important roles in embryonic development, blood vessel formation, tumor formation and so on. Studies have shown that EphA2 is highly expressed in many tumor tissues, including breast cancer, colon cancer,

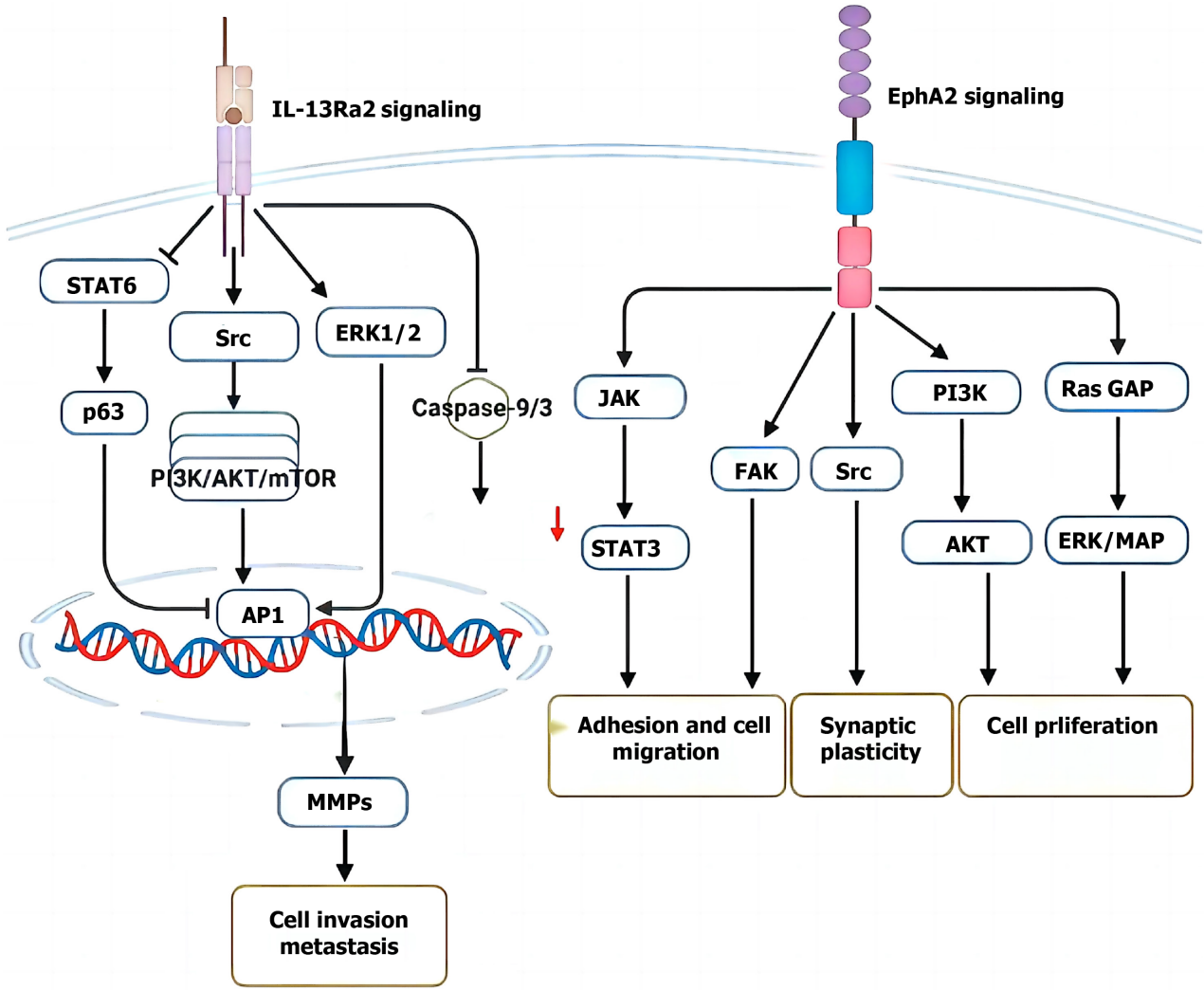

Figure 7 Erythropoietin-induced hepatocyte receptor A2 signaling in colorectal cancer cell invasion and metastasis. Created by the BioRender. EphA2: Erythropoietin-induced hepatocyte receptor A2; IL: Interleukin; STAT6: Signal transducer and activator of transcription 6; ERK1/2: Extracellular signal-regulated kinase 1/2; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; mTOR: Mechanistic target of rapamycin; AP1: Activator protein 1; MMPs: Matrix metalloproteinases; JAK: Janus kinase; GAP: GTPase-activating protein.

esophageal cancer, prostate cancer, *etc.*, especially in highly invasive tumor cells (Figure 7).

Since the hypothesis that tumor growth can be slowed by inhibiting tumor nutrient vessels was proposed by Folkman in the early 1970s, a large number of studies[184-186] have shown that angiogenesis is a prerequisite for tumor growth and metastasis. The microvascular density (MVD) of tumors is an important indicator of the biological behavior of malignant tumors. The so-called MVD refers to the small blood vessel count performed on the most densely populated part of the tumor blood vessels. As the gold standard for evaluating tumor angiogenesis, the MVD can reflect the tumor's ability to induce angiogenesis and is closely related to malignant behavior and tumor recurrence and metastasis. The MVD reflects the inevitable relationship between the intensity of tumor angiogenesis and tumor aggressiveness and can be used as an indicator to judge the prognosis of patients with CRC for clinical reference[187]. A study showed that the MVD was greater in patients with CRC and could predict that the tumor is more aggressive and has a poor prognosis [188]. Tumor angiogenesis is regulated by many factors, among which Eph RTK family members are central regulators of angiogenesis. Our results showed that in addition to EphA2 expression in CRC cells, EphA2 was also expressed in microvascular endothelial cells in tumors, and tumors with high EphA2 expression had a greater MVD, suggesting that EphA2 may affect the invasion and metastasis of CRC cells by regulating tumor angiogenesis.

CONCLUSION

As a key RTK, EphA2 plays a crucial role in the occurrence, development and metastasis of GI CRC by regulating cell pyrodeath. It regulates the initiation and execution of pyrodeath through various signaling pathways and interactions with other cytokines, thus affecting the survival and spread of cancer cells. Abnormal expression of EphA2 not only promotes cancer invasion and metastasis but also may lead to treatment resistance. However, by targeting EphA2 and its related signaling pathways, it is expected to induce pyrodeath in cells, inhibit tumor growth, and enhance therapeutic

efficacy. Therefore, further study of the mechanism by which EphA2 regulates pyroptosis will provide new strategies and potential targets for the treatment of GI CRC.

FOOTNOTES

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