Recent research advances in interleukin, microRNA and neuroendocrine tumor biomarkers (Review)

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Abstract. The incidence of neuroendocrine tumors (NETs) has been increasing in recent years and most cases are not easily detected in the early stages. The diagnostic modalities used for NETs are currently limited due to the small number of individuals with this type of disease. It is clear that patients exhibit chronic inflammation in the early stages, which leads to corresponding changes in inflammatory factors and in the tumor microenvironment. Among the numerous inflammatory factors, the interleukin (IL)-6 family has a clear association with tumor development and serves a role in most NETs. In addition, the IL-6 family, through various signaling pathways, can influence tumor progression. IL-6 is also involved in the upregulation and suppression of novel biomarkers of NETs. In terms of diagnosis, the specific elevation of inflammatory factors and the alterations in non-coding RNAs for different NETs is of great importance for the early differentiation of tumor types.

Contents

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1. Introduction

During flare-ups of chronic inflammatory diseases, humans are more susceptible to various types of cancer, including breast cancer, colorectal cancer, and gastric mucosal cancer. Tumor transformation caused by chronic inflammation accounts for 15% of the total cancer cases worldwide (1). Chronic inflammation is typically characterized by tissue damage, followed by cell proliferation and repair at the site of injury, where inflammatory factors are recruited. Among these factors, the significant increase in the interleukin (IL)-6 family of cytokines has been strongly linked to the progression and aggressiveness of tumors, particularly in relation to their staging and ability to invade surrounding tissues (2). Various cytokines within the IL-6 family, including IL-6, IL-11, IL-27, and IL-31, are known to accelerate tumor growth by influencing and modulating the tumor microenvironment (TME) (3). These inflammatory factors not only affect the occurrence and development of tumors but also constitute an integral part of the tumor microenvironment. The tumor microenvironment is a comprehensive concept, encompassing immune cell responses, activation, differentiation, and cytokine secretion. It can either promote or counteract tumor development and mediate disease validation and resistance, depending on the interference of specific cytokines (4). Neuroendocrine tumors (NETs) are a rare, heterogeneous disease characterized by the secretion of growth hormones (5). In NET cells, the signaling and activation of the STAT3/IL-6 axis are essential in driving tumor growth, supporting its survival, and influencing cellular differentiation (6,7). Therefore, the expression levels of the IL-6 family may vary among patients with NETs. This review provides an overview of the association between the IL-6 family and NETs over the past decade, categorizing and summarizing the role and impact of the IL-6 family in different types of NETs, and supplements the previous shortcomings of single tumor descriptions related to IL-6.

2. Tumor microenvironment

To understand the process and steps of tumor development, the tissue response surrounding the tumor must be included in the research scope, which encompasses circulation and metastasis. A tumor consists of a complex array of tissues, including the extracellular matrix (ECM), activated fibroblasts, chemokines, inflammatory factors, and blood and lymphatic vessels, all of which are collectively referred to as the TME (8). Inflammatory factors and other substances in the TME can activate downstream proteins or genes (9). In addition, various factors of the TME interact and influence each other, collectively promoting tumor progression or metastasis. Notably, the TME not only comprises normal tissues, but also dysregulated factors, such as microRNAs (miRNAs/miRs) in the vicinity of tumor tissues. miRNAs of tumor cell origin are closely associated with the production of immunologically heterogeneous TMEs and the loss of effector cells, and they are determinants of the immune outcome of cancer (10,11). These tumor cell-derived miRNAs can be seeded in different TME regions, and because miRNAs subtly suppress genes and preferentially inhibit dose-sensitive targets, they are key to immune-mediated tumor clearance (12,13). In the TME, miRNAs can promote gastric cancer cell immune escape by targeting granule 2 and activating the binding of zinc finger E-box to the homology box 1/programmed cell death ligand 1 (PD-L1) axis, which enhances the inhibitory effect of gastric malignant cells on T-cell activation (14). In the lung TME, lung tumor cells secrete miR-21/29 to target intracellular Toll-like receptor 8, which induces the secretion of NK-κB-mediated pro-inflammatory factors TNF-α and IL-6 to achieve tumor cell invasion (15). In colorectal tumors, miR-27 can alter tumor antigen presentation, and higher levels of miR-27 in colorectal cancer has been shown to reduce T-cell infiltration, which is associated with a poor prognosis after distant metastasis (16). It is now clear that miRNAs serve an important role in the TME; however, it is unclear whether they have a role in the tumor escape process. It has been shown that tumor cells secrete miRNA-rich exocrine vesicles, which are involved in signaling pathways, such as PTEN/AKT and suppressor of cytokine signaling 1 (SOCS1)/STAT1, inducing high PD-L1 expression in the TME and suppressing $CD8^+$ T cells, which can thus promote tumor immune escape and progression (17). Song *et al* (18) also demonstrated another way in which miRNAs disrupt antigen presentation by participating in the IFNγ-activated Janus kinase (JAK)/STAT signaling pathway in cancer cells, while also silencing SOCS1 and promoting the tumor escape process.

3. Neuroendocrine tumors

NETs are a group of heterogeneous malignant tumors that originate from cells with neuroendocrine features, dispersed across various organs and systems in the body (19,20). The most common site for NETs is the gastrointestinal tract, and the extensive cellular diversity reflects the heterogeneity of the disease itself (21). The pathogenic mechanisms of NETs vary depending on the original structure of the cells (22). These pathogenic processes may involve pathways such as enterochromaffin-like cell hyperplasia, gene mutations or chromosome loss, miRNA-assisted dissemination, the impact of lipids or saturated fatty acids on oxidative stress, and cross-talk or abnormal activation of signaling pathways (23-29). The present review mainly focuses on the mechanisms and novel insights into how inflammatory factors, including the IL-6 family, form NETs through signaling pathway cross-talk or abnormal activation.

4. IL-6 family and neuroendocrine tumors

Medullary thyroid carcinoma (MTC). MTC primarily arises from the parafollicular cells of the thyroid and accounts for 3-10% of global cases (30). Research has shown that dysregulation of the Hippo pathway is associated with the development of various tumors, including MTC (31). The Hippo pathway transmits both intracellular and extracellular signals to control cell migration, proliferation and differentiation (32). In mammals, two transcriptional co-activators, Yes-associated protein (YAP) and TAZ, have been identified; these can activate upstream phosphorylated kinases of the Hippo pathway to exert tumor-suppressive effects on the pathway (31-33). When YAP is dephosphorylated in tumor cells, it promotes the expression of YAP/TAZ, and while disrupting the Hippo pathway, YAP can also stimulate the activation of IL-6 in cancer cells (34,35). The abundant expression of IL-6 promotes tumor cell cycle progression and inhibits apoptosis. Moreover, IL-6 is involved in epithelial-mesenchymal transition (EMT) in tumor cells, a mechanism associated with cancer cell invasion and metastasis (35). IL-6 and EMT interact with the TME and the Hippo pathway, influencing the onset and spread of MTC (36). Research has demonstrated that miR-375 is significantly upregulated in MTC, whereas it is not highly expressed in other thyroid histopathologies, and that there is an association between miR-183 and miR-375 upregulation in MTC and lateral cervical lymph node metastasis and mortality. Notably, miR-375 causes YAP to be downregulated; therefore, it may be useful to assess how miR-375 functions in MTC, and whether it is also via the Hippo pathway (37) (Fig. 1).

Small cell lung cancer (SCLC). SCLC is classified as a type of pulmonary NET. Notably, SCLC is typically diagnosed at a late stage, making both diagnosis and treatment more challenging (38). Abnormal secretion of antidiuretic hormone is a prominent feature of SCLC, with paraneoplastic Cushing's syndrome being the second most common characteristic (39). It has also been observed that activation of STAT3 is common in SCLC cases (40). The results of a retrospective study have indicated that macrophage-derived factors, such as IL-6, are involved in the activation of STAT3 in SCLC cells (41). This suggests that IL-6 may stimulate the expression of STAT3, thereby influencing the proliferation or metastasis of SCLC. Furthermore, to investigate the specific heterogeneity of SCLC, Lu *et al* (42) conducted a study and revealed that the neuroendocrine marker expression in SCLC neuroendocrine cells co-cultured with fibroblasts was decreased, whereas neuroendocrine marker protein expression in SCLC cells cultured alone was increased. Furthermore, this previous study continued to explore the mechanism by which fibroblasts induce the reduction of neuroendocrine marker expression and demonstrated that the phosphorylation levels of JAK2/STAT3

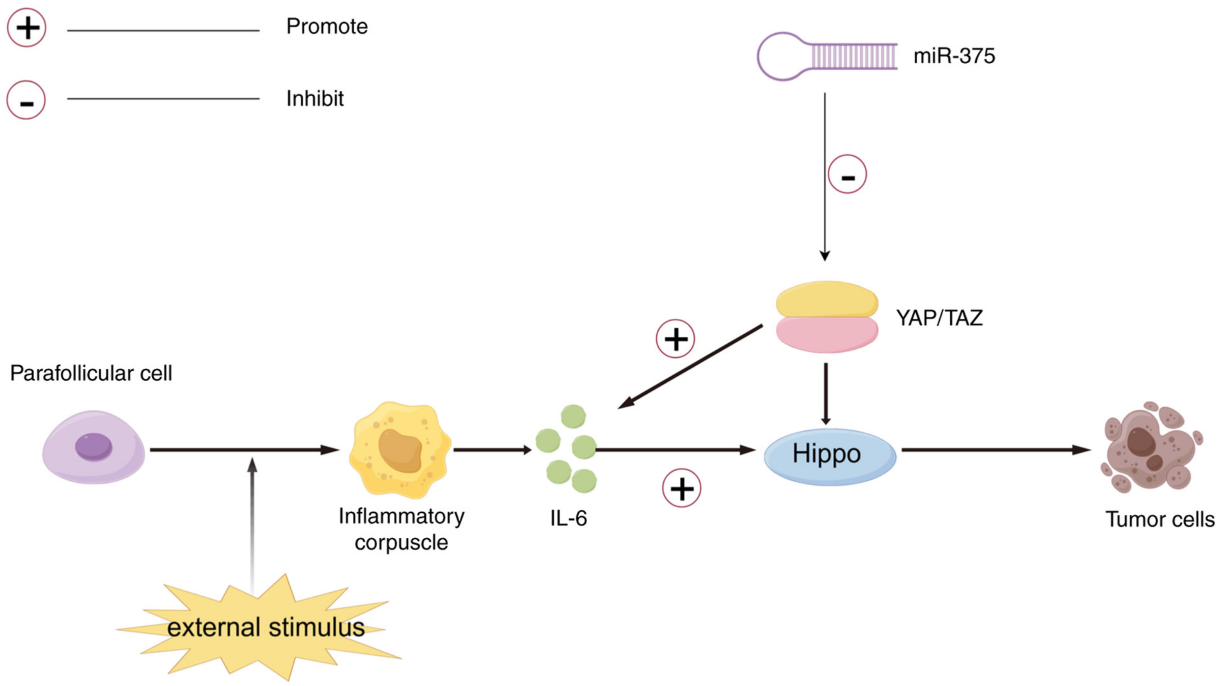

Figure 1. In thyroid medullary carcinoma, IL-6 and miR-375 jointly act on the Hippo pathway to promote the proliferation process of tumor cells. The figure was created using Figdraw 2.0 software (https://www.figdraw.com/static/index.html#/). IL-6, interleukin-6; miR-375, microRNA-375; YAP, Yes-associated protein.

in SCLC cells co-cultured with fibroblasts were elevated (42). Additionally, NOTCH signaling has been shown to serve a role in the reprogramming of biomarker phenotypes in SCLC, with c-MYC as a key upstream regulatory factor (43). Notably, it has been shown that IL-6 from fibroblasts indeed activates the JAK2/STAT3 pathway in SCLC cells, and phosphorylated STAT3 binds to and upregulates MYC expression upon fibroblast stimulation (42). In addition, the insulin-like growth factor 1 (IGF1)/IGF1R signaling axis can crosstalk with multiple pathways to affect the development of malignant tumors, in which IGF1R triggers the PI3K/AKT signaling pathway, driving the advancement of SCLC, whereas miR-377 enrichment can inhibit IGF1R and suppress SCLC metastasis (44) (Fig. 2).

Gastric neuroendocrine neoplasms (g-NENs). g-NENs are rare, accounting for only 5-23% of all gastrointestinal NETs (45). g-NENs are classified into four types, with Type I being the most common (45). These tumors are often multifocal, but the likelihood of distant lymph node metastasis is low, and the prognosis is generally favorable (46,47). In the gastrointestinal tract, inflammation is one of the mechanisms that creates a pro-TME. In tissues with carcinogenic mutations, the interaction between the tumor epithelial components, related fibroblasts and inflammatory factors create a tumor-promoting microenvironment, where cytokines are key in facilitating communication (48,49). The IL-6 family is known for its role in tumor growth and promotion. IL-6, produced by tumor-associated macrophages, creates conditions ideal for immune suppression and angiogenesis. In the STAT3 pathway, the IL-6 family is activated, stimulating the proliferation and survival of malignant tumors. The NF-κB pathway promotes tumor transcriptional proliferation and creates a suitable TME to stimulate tumor invasion (48,49). The diffuse endocrine system cells found in the gastric mucosa are the origin of g-NENs and are stimulated by chronic inflammation. When a patient has superficial gastritis or chronic atrophic gastritis, pro-inflammatory factors, such as IL-6 and related substances, mediate the neuroendocrine differentiation of tumor cells and the synthesis and secretion of gastrointestinal hormones (50). Chronic inflammation overstimulating gastric cells over a prolonged period of time leads to excessive proliferation and tumor transformation (51). It has been shown that miR-96 increases with the degree of G1-G3 differentiation in g-NEN cells. miR-96 also regulates the expression of the FoxO1 gene, which is a downstream target of the PI3K/AKT pathway involved in the pathophysiological process of cancer progression (52).

Gastrointestinal NETs. NETs can progress throughout the entire digestive tract, with the highest incidence observed in the small intestine (53). Small intestinal NETs originate from the enterochromaffin cells of the gastrointestinal tract. Because these tumors grow slowly, the majority of patients are diagnosed at later stages, with liver metastasis being the most prevalent type of metastasis. Additionally, small intestinal NETs can secrete excessive hormones, leading to carcinoid syndrome in 20% of patients (54-56). Research has indicated that these tumors express TNF-α and IL-17B cytokines, and the ECM also expresses TNF-α. Specifically, IL-17 partially activates downstream targets by triggering NF-κB and phosphorylated STAT3. Moreover, STAT3 binds to the SYP promoter, suggesting that the expression of IL-17 may correlate with SYP. Furthermore, IL-17 activates TNF-α-related signaling pathways (57-60). In addition, the IL-17 cytokine

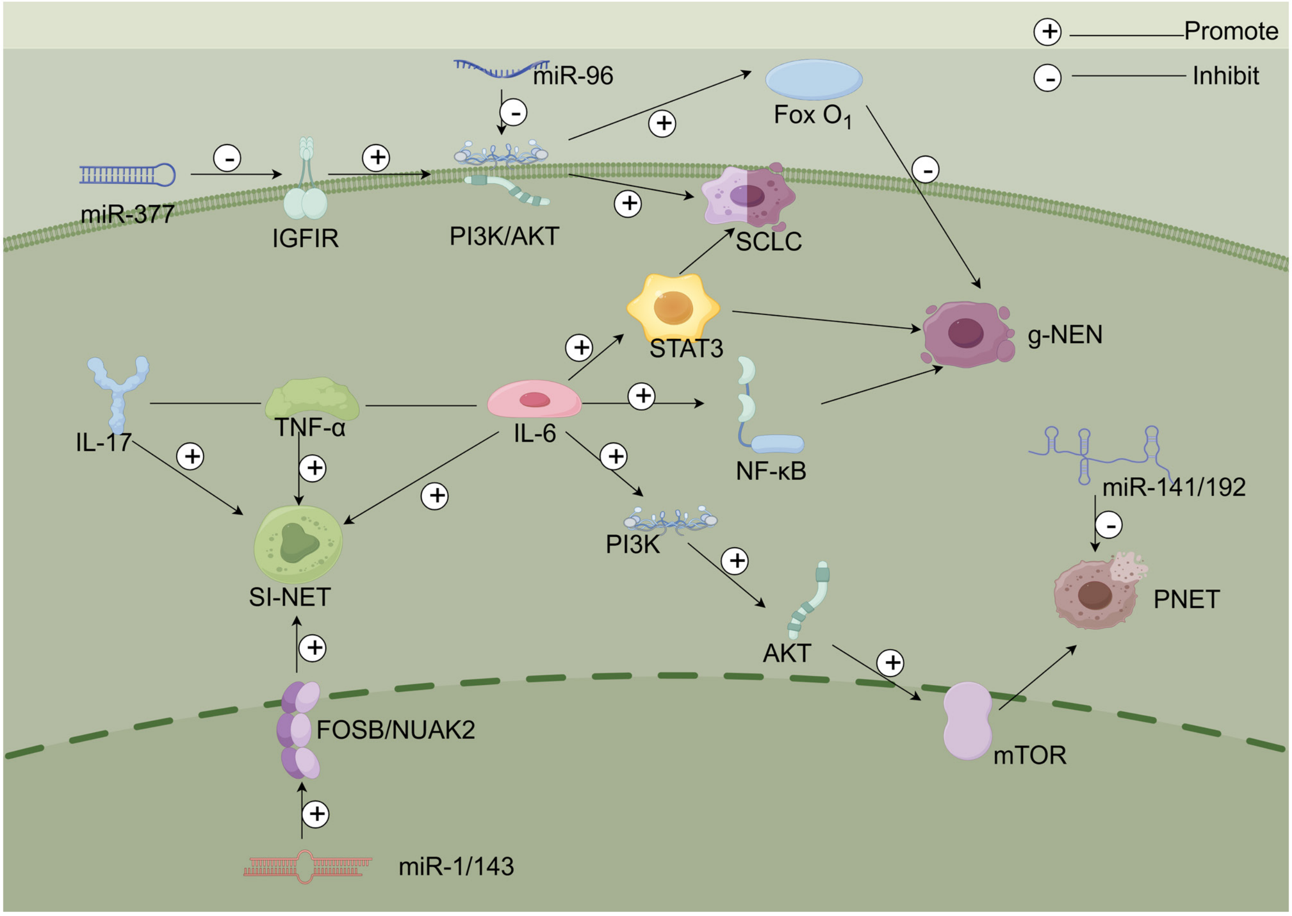

Figure 2. IL-6 and tumor-related microRNAs can interact and exert effects on tumors through various signaling pathways such as PI3K/AKT/mTOR, STAT3, and NF-κB, either in a coordinated or antagonistic manner. The figure was created using Figdraw 2.0 software (https://www.figdraw.com/static/index.html#/). IL, interleukin; miR, microRNA; PNET, pancreatic neuroendocrine tumors; g-NEN, gastric neuroendocrine neoplasm; SCLC, small cell lung cancer; IGF1R, insulin-like growth factor 1 receptor; SI-NET, neuroendocrine tumors of the small intestine.

synergizes with IL-6 and TNF-α to activate STAT3, promoting the growth of intestinal tumors (60).

Rectal NETs are the second most frequent type of NET after small intestinal NETs, accounting for 12-27% of all gastrointestinal NETs (61-63). Rectal NETs originate from neuroendocrine cells and their malignancy status can be uncertain, with some exhibiting neuroendocrine functions while others do not. The incidence of rectal NETs is higher than that of colonic NETs (64). Due to the low incidence and difficulty in detecting colorectal tumors, the mechanisms and treatment approaches remain to be explored, which may represent a novel direction for future discoveries.

In enteric NETs, miR-204-5p/miR-375 expression has been shown to be increased, whereas miR-1 and miR-143 expression has been revealed to be decreased. Furthermore, the reduced expression of miR-1 and miR-143 has been reported to activate the oncogenes FOSB and NUAK2, which in turn can enhance lymph node and liver metastasis in enteric NETs (52). Finally, sustained elevation of IL-6 promotes fribroblast proliferation and alters the expression of miRNAs that regulate various signaling pathways, contributing to the development of intestinal fibrosis; the most notable consequence of intestinal fibrosis is its effects on intestinal structure, impairing nutrient absorption and destroying the microflora, ultimately leading to malignant transformation (65).

Pancreatic NETs (PNETs). PNETs are rare tumors considered to arise from the pancreatic islet cells, which normally secrete insulin and glucagon (66). PNETs are highly heterogeneous tumors that exhibit a wide range of pathological features; they can be classified into different grades based on the Ki67 index, mitotic count and morphological characteristics (67). Although PNETs are categorized as well-differentiated or poorly differentiated, most of them are well-differentiated (68). While the gene mutation rate in PNETs is relatively low, there are mutations related to tumorigenesis and progression, such as those in the multiple endocrine neoplasia 1 (MEN1) and α-thalassemia/mental retardation syndrome X-linked (ATRX) genes and the mTOR pathway (69). Some studies have shown that genomic alterations in well-differentiated PNETs include changes in RNA expression after activation of the mTOR pathway, aneuploidy, and loss of MEN1 and MUTYH germline genes (28,70,71). According to previous studies, MEN1 is the most common mutation in PNETs, and 37% of cases have altered MEN1 gene expression. Furthermore, in PNETs, MEN1 is involved in mTOR signaling, histone modification and DNA repair damage, which determines cell fate (72-74). ATRX mutations cause disorders in chromatin remodeling and mitotic function during chromosome mitosis, and these abnormalities may lead to chromosomal mutations ultimately contributing to the development of PNETs (75). In addition, a recent study has shown that loss of ATRX/death domain associated protein and the presence of alternative lengthening of telomeres may serve as predictors of distant metastasis, and are associated with poorer overall survival and relapse-free survival in non-functional PNETs measuring ≤2.0-cm (76). The association between patients with PNETs and mutations in mTOR signaling-related genes is high, and these mutations lead to upregulation of mTOR activity, which is closely linked to poor prognosis and aggressive tumor behavior in patients with PNETs (72,77).

MEN1 encodes menin, a nuclear protein that is involved in chromatin remodeling during DNA replication, functioning as a scaffold to regulate gene transcription. In addition, menin is an important component of the histone methyltransferase complex. When the MEN1 gene is mutated, DNA replication and chromosome division are affected, which can lead to a disrupted state of cytokinesis and differentiation. In a validation set of 68 PNET cases, mutations in the MEN1 gene were identified in 30 cases, suggesting MEN1 as a major driver of PNET development. In addition, 12 of the 68 cases harbored mutations in the ATRX gene, which encodes a protein located in the structural domain of the helicase enzyme. Notably, the activity of the helicase enzyme is altered when ATRX is mutated, which is also a major factor affecting PNET (78). Research has shown that MEN1 also serves a role in regulating mTOR signaling. mTOR has a regulatory role in lipid peroxidation and ferroptosis, and MEN1 overexpression has been shown to inhibit the mTOR signaling pathway. At the same time, mTOR regulates lipid peroxidation and ferroptosis in PNET; thus, MEN1 inhibits the mTOR signaling pathway, as well as lipid peroxidation and ferroptosis, in PNET. In addition, mTOR, as a signaling hub, serves an important role in regulating amino acid, glucose, nucleotide, fatty acid and lipid metabolism. When MEN1 is upregulated and inhibits mTOR, it also has an effect on basic cellular metabolism and energy conversion, which is one of the major reasons for the occurrence of PNETs (78).

These aforementioned mutations can be targeted for PNET treatment, particularly in cases where MEN1 mutations occur. In low-grade, intermediate-stage PNETs, mTOR pathway inhibitors can serve as potential therapeutic targets (78). According to Li *et al* (79), IL-6 can act as an upstream factor to enhance activation of the PI3K/AKT/mTOR pathway. Therefore, it may be hypothesized that IL-6 or other inflammatory factors could directly or indirectly influence mTOR, modulating the expression of this signaling pathway and thereby achieving therapeutic effects on PNETs. Moreover, single nucleotide polymorphisms (SNPs) in genes encoding regulatory cytokines may have a role in promoting or inhibiting the development and progression of PNETs. Karakaxas *et al* (80) reported that an SNP in the IL-1β gene, rs16944, appears to be associated with PNETs. In another study, the characteristics of functional and non-functional PNETs were revealed to be associated with differences in an IL-6 SNP, described as rs1800795. Compared with patients with functional PNETs, those with non-functional PNETs exhibited higher serum levels of IL-6, and a positive correlation between IL-6 levels and IL-6 gene polymorphisms was observed exclusively in patients with non-functional PNETs (80,81). Thus, IL-6 not only influences tumor development through signaling pathways or the TME, but may also directly affect tumor cells through its own encoded nucleotide sequence, impacting progression of the tumor.

Evidence has suggested that changes in macrophage subtypes in the TME serve an important role in tumor progression and metastasis. Heterogeneity of macrophage phenotypes has been observed in tumor-associated macrophages (TAMs) of various malignancies; however, $CD163^+$ TAMs may be the major population, and in PNETs, a previous study has shown that higher $CD163^+$ cell counts are associated with lymph node metastasis, perineural invasion and lymphovascular invasion, suggesting that $CD163^+$ TAMs are an indicator of poor prognosis. Furthermore, $CD163^+$ macrophages are associated with poor disease-free survival and disease-specific survival in PNETs (82). In PNETs, PIWI-interacting RNA-hsa-30937 can promote CD276 upregulation in macrophages via the PTEN/AKT pathway, and CD276 suppresses T-cell antitumor immunity; this results in fewer antitumor cells in the TME, leading to a homeostatic bias towards pro-tumor characteristics (83). In addition to this, when hypoxia occurs, TAMs in the TME undergo M2-like polarization, and the M2-polarized macrophages promote the formation of pre-metastatic ecological niches and facilitate the metastasis of pancreatic NENs through the release of MMP2, which is a pro-carcinogenic alteration of the TME (84). Furthermore, miR-141 has been shown to exert tumor-suppressive effects in various types of cancer, including pancreatic cancer. By contrast, the role of the miR-192/194 family in cancer remains intricate and controversial, with findings suggesting both oncogenic and tumor-suppressive effects. Specifically, miR-192 has been found to suppress tumor angiogenesis, whereas miR-194 inhibits cancer cell proliferation, migration and metastasis, and promotes apoptosis (85).

Pituitary NETs (PitNETs). PitNETs are among the most common brain tumors, accounting for 10-25% of all brain tumors. Most patients with these tumors can be treated with surgery or medications (86). A notable factor influencing the development of PitNETs is the TME, which is crucial in mediating the interaction between the tumor and the host immune response (87,88). PitNETs are typically characterized by a high degree of macrophage infiltration within the pituitary gland (68-70). Studies have confirmed the presence of both M1 and M2 macrophages in estrogen-induced PitNETs, with the expression levels of the M2 polarization factor IL-4 being significantly higher than normal (89-91). Therefore, tumor-associated macrophages in the TME may influence tumor initiation and progression through cytokines and other factors. In addition to tumor progression driven by the TME, M2-like macrophages secrete C-C motif chemokine ligand 17 (CCL17), which enhances the invasive ability of tumor cells through the CCL17/CCR4/mTOR axis (92). IL-6 can also interact with the mTOR pathway to induce PD-L1 (93). Thus, PitNETs can be broadly categorized into two types, according to their progression: One is driven by the interaction between the TME and the tumor, and the other involves the participation of cytokines, such as IL-6 or other factors, that activate or suppress related signaling pathways, influencing tumor progression. Wang *et al* revealed that miR-134 expression is reduced in PitNETs, and its target gene vascular endothelial growth factor A (VEGFA) is upregulated, accompanied by an increase in tumor invasiveness. Further research has shown that miR-134 may inhibit tumor development by suppressing VEGFA expression. Regarding the mechanism, VEGFA expression is related to the PI3K/AKT signaling pathway and miR-134 is an important component of this signaling pathway. Therefore, upregulation of miR-134 may inhibit PI3K by activating downstream VEGFA, thus resulting in tumor suppression (94).

5. Relevance of novel biomarkers

miRNA expression profiles can be used as practical biomarkers for the diagnosis and prognosis of NETs, providing sufficient information for appropriate patient care and management (95-99). It has been reported that there is a direct link between miR-31 and advanced disease stage and poor survival. miR-31 is also highly expressed in patients with advanced breast and gastrointestinal cancers, where it is correlated with poor prognosis, and miR-31 interacts with downstream target genes, thus enhancing the likelihood of tumors to spread (100). Upregulation of miR-21 has been shown to be significantly associated with advanced clinical stage, lymph node involvement and survival in breast cancer. Furthermore, reduced expression of miR-126/335 has been linked to cancer metastasis (101).

Notably, various miRNA families have been investigated as potential diagnostic biomarkers. Upregulation of miR-21/200/210/182 has been associated with lung tumor progression, and miR-30/451 has been linked with heterogeneous tumor behavior (102). Furthermore, not only do miRNAs serve as diagnostic biomarkers for lung cancer detection, but they also play a role in prognosis and treatment (103). In breast cancer, miR-21 downregulation and the miR-32-5p/TOB1 axis could negatively regulate the progression of triple-negative breast cancer cells by inhibiting the expression of the oncogene TOB1. In osteosarcoma, it was shown that HNF1A-AS1 binds to miR-32-5p to regulate the expression of high mobility group box 1-induced apoptosis, and prevents the proliferation, migration and invasion of osteosarcoma cells. In retinoblastoma, miR-32 was revealed to be upregulated and to competitively bind to long non-coding RNAs to regulate retinoblastoma signaling pathways. miR-32 upregulation significantly inhibited the proliferation, migration and invasion of ovarian cancer cells through the regulation of the target gene B and T lymphocyte attenuator. In colorectal and lung cancers, downregulation of miR-32 expression was also associated with tumor prognosis and progression (104). However, in terms of the sensitivity and specificity of miRNAs, it is unclear as to whether their diagnostic role in tumors is highly specific. It may be possible to use double or multiple tracers of numerous miRNAs in the same tumor, which could improve the diagnostic value.

Another challenge is that the aforementioned miRNAs identified in laboratory screenings, cannot currently be extracted from clinical pathology samples, making it unclear how to effectively apply miRNAs as biomarkers in clinical practice. In a study from a clinical perspective, Maués *et al* (105) employed a method to detect miRNAs in the normal human platelet small RNA-sequencing data sourced from the GSE61856 repository. Their research identified a new set of miRNAs (miR-486-5p, miR-92a-3p, miR-103a-3p, miR-151a-3p, miR-181a-5p and miR-221-3p) that exhibited sensitive expression patterns due to biological changes in platelets during storage. These miRNAs could act as potential indicators for assessing the quality and viability of platelet concentrates during storage (106).

In colorectal cancer, miR-1228 and miR-16 are considered suitable biomarkers (107). In diseases caused by human papillomavirus (HPV), miR-3654, miR-647 and miR-1914 were demonstrated to be downregulated, whereas miR-612 was shown to be upregulated in HPV-induced warts (108). The identified miRNA characteristics of miR-181b-5p, miR-200b-3p, miR-200c-3p and miR-203a-3p in inflammatory breast cancer, could be used individually to distinguish between patients with inflammatory breast cancer and non-inflammatory breast cancer (109). In pancreatic endocrine tumors, the expression of specific miRNAs can distinguish tumor cells from normal pancreatic tissue. For example, in PNETs, miR-144/21/193b is expressed, miR-103/107 is upregulated and miR-155 is underexpressed, while normal pancreatic cells do not specifically express these miRNAs (95,110,111). Furthermore, miRNAs not only aid in distinguishing between different tumors but also provide prognostic information. Upregulation of miR-21/642/196a has been shown to possess a positive correlation with Ki-67 (a proliferation marker), and miR-210 can indicate the likelihood of liver metastasis (112,113). In addition, in small intestinal NETs, miR-7-5p, miR-182, miR-183 and miR-96-5p have been demonstrated to be expressed at higher levels than in normal tissue (110). In g-NENs, miR-222 was shown to be upregulated, whereas in appendiceal NETs, miR-96 was underexpressed and miR-133a was upregulated. In colorectal NETs, miR-186 was shown to be underexpressed, and in rectal NETs, miR-885-5p was upregulated (114-117). Current studies have suggested that miRNAs exhibit differential expression and may serve as tumor markers to improve the detection, staging, grading and identification of distant metastasis of NETs. However, whether miRNAs can independently serve as biomarkers to reflect tumor status requires further investigation.

It is known that the IL family can function as upstream factors or downstream targets of miRNAs, affecting their differential expression, and the post-transcriptional regulatory mechanisms of IL-6 expression have been extensively studied. The majority of these regulatory factors have been shown to inhibit IL-6 expression by binding to the 3' untranslated region of the mRNA, leading to its degradation (118). However, further exploration is required to determine whether miRNAs are upregulated when chronic inflammation or the TME leads to IL-6 upregulation, as well as to assess which miRNAs will be upregulated and whether these IL-6-induced miRNAs could serve as biomarkers for NETs. After immune activation, serum IL-6 levels rapidly rise under the influence of cytokines, Toll-like receptor agonists, prostaglandins and other stress signals. At this time, certain miRNAs will regulate IL-6 gene expression (119). The present review aimed to only address the interaction between IL-6 and miRNAs. Considering the upstream and downstream genes or signaling pathways, it has been shown that miRNA interference with IL-6 expression is influenced by certain molecules and the JAK/STAT signaling pathway. It has been established that miR-34 and miR-218 are tumor suppressors, and when miR-34 is silenced, the incidence of colitis-associated intestinal tumors in mice increases, with these tumors typically being larger and characterized by increased IL-6 receptor expression and STAT3 activation (120,121). Other miRNAs have also been shown to target STAT3 (122). STAT3 activation regulates the IL-6 cytokine family, promoting tumor development, influencing cell cycle progression and driving tumor invasion (119). By contrast, negative regulators of the JAK/STAT cascade are also inhibited by miRNA-mediated suppression. miR-155 and miR-19 have been shown to target SOCS1 and SOCS3, thus inhibiting the JAK/STAT signaling pathway (123,124). IL-6 was shown to enhance cell adhesion in human endothelial cells through the inhibition of miR-126-3p (125). MiR-1254 enhanced proteasome stability in rectal tumors by activating the IL-6/STAT3 pathway (126). MiR-892c increased IL-6 expression and promoted macrophage polarization (127). MiR-30c has been shown to target IL-6 in mesenchymal stem cells, offering a novel approach for the treatment of colon cancer (128). The IL-6/miR-30d axis may also impact chemotherapy resistance in colorectal cancer (129). In summary, the relationship between IL-6 and microRNAs remains to be fully elucidated. Therefore, based on the aforementioned findings, it may be inferred that miRNAs and IL-6 cytokine pathways regulate each other.

Whether the increase in IL-6-induced miRNAs can be used as a tumor biomarker to assess disease requires further research. Currently, it is clear that in chronic inflammation, there is a close relationship between inflammatory factors, miRNAs and signaling pathways. To study miRNAs as tumor biomarkers, it is necessary to consider the upstream and downstream signaling pathways, rather than evaluating them in isolation. According to research, the levels of serum IL-6 are increased with the decrease in survival rates for late-stage tumors. This signifies that in patients with advanced tumors, serum IL-6 is elevated, and the increase in IL-6 levels has been reported to be due to the activation of upstream epithelial growth factor receptor (EGFR) through the NF-κB pathway, with the elevation of EGFR being caused by the amplification of the malignant tumor gene malignant T-cell amplified sequence 1 (MCT-1) (130,131). Through the analysis of cytokine arrays and cancer stem cells, it has been reported that miR-34a antagonizes MCT-1, and high expression of MCT-1 reduces miR-34a. miR-34a is a non-coding RNA that has been shown to inhibit the progression of cancer cells. In essence, high expression of miR-34a leads to reduced levels of MCT-1/EGRF/NF-κB/IL-6 (132). Therefore, using MCT-1 antagonists or increasing the expression of miR-34a, may represent a combined strategy for treating malignant tumors. As to whether miR-34a inhibits the expression of IL-6, thereby affecting tumor progression, it is known that IL-6 can activate the signal transduction of transcription factors and the activation of the STAT family, with STAT3 located within the cell. Once phosphorylated and activated, STAT3 can translocate to the nucleus and bind to the promoter regions of target genes, including miR-21. Researchers have verified this through *in vitro* experiments in mouse cells, showing that phosphorylated STAT3 is expressed at higher levels in cells treated with IL-6, leading to an increase in the expression levels of miR-21. Additionally, previous CUT&RUN sequencing experiments have confirmed that IL-6 regulates the expression of miR-21 in ectopic mesenchymal cells through phosphorylated STAT3 (133-135).

The aforementioned findings describe the advantages of miRNAs as biomarkers; however, they do not address the sensitivity and specificity of miRNAs in distinguishing between different types of NETs. Kanavarioti *et al* (136) measured the copy numbers of five miRNAs, let-7b, miR-15b, miR-21, miR-375 and miR-141, in both healthy and cancerous samples, and demonstrated the equivalence of serum and urine for testing these miRNAs. Among these miRNAs, miR-141, miR-21 and miR-375 showed a specific increase in expression in breast cancer, prostate cancer and pancreatic cancer. By comparing the corresponding miRNA copy numbers with serum from healthy males (cat. no. H6914; Sigma-Aldrich KGaA), the data were divided into healthy and cancer samples, showing no overlap, indicating that there were zero false negatives and zero false positives, resulting in sensitivity, specificity, positive predictive and negative predictive values all equal to 1. This unprecedented distinction preliminarily validates each miRNA (miR-21, miR-375 and miR-141) as biomarkers for these three types of cancer (136).

6. Interplay between miRNAs and signaling pathways in neuroendocrine tumors: Functional roles and implications

According to relevant research, miR-375 exerts its influence on tumors by targeting the expression of SNAIL1 (137). In addition, miR-375 has been shown to inhibit g-NENs through the Wnt/β-catenin pathway (138). miR-3614-5p targets various components of the TGF-β signaling pathway to induce the progression of pulmonary NETs (138). Furthermore, miR-128-3p has been shown to have an impact on inducing mesenchymal cell transformation via Wnt/β-catenin and TGF-β in lung cancer (139). Soldevilla *et al* (140) revealed that the downstream targets and epigenetic regulation of gastrointestinal PNETs are achieved through the PI3K/AKT and TNF-α/NF-κB signaling pathways, respectively. Peng *et al* (141) revealed that various phenotypes of miRNA are involved in the progression of NETs, such as pituitary tumors, through the Wnt/β-catenin and SNHG6/miR-994/RAB11A axes.

7. Conclusion

NETs, a type of malignant tumor, are often difficult to detect due to their subtle behavior. In the early stages of NETs, changes are typically limited to alterations in endocrine hormone levels. However, chronic inflammation is also present at this stage, leading to elevated levels of inflammatory factors. IL-6, one such factor, is expressed in various types of NETs. Additionally, miRNAs, which serve as tumor markers, can degrade elevated IL-6 levels. As a result, rising IL-6 levels may reflexively induce the upregulation of specific miRNAs, suggesting a potential target for further research. IL-6 expression varies across different NETs and is known to exert its effects through the JAK/STAT signaling pathway. Nevertheless, the precise role of the JAK/STAT pathway in different NET subtypes remains unclear. Therefore, the relationship between IL-6, miRNAs, signaling pathways and NETs warrants further investigation.

Although IL-6 and miRNAs are currently major focal points in the research of mechanisms related to tumors, how to effectively implement their specific roles in clinical practice to facilitate diagnosis and treatment is essential for guiding future research directions. It is suggested not to solely rely on pathological findings to understand the aforementioned mechanisms, but also apply the expedited results of molecular mechanism experiments to the advancement of clinical practice, which may establish a pioneering area of focus. Recent evidence has suggested that IL-6 can intervene in pancreatic cancer through the miR-455/IGF1R axis (142). The aforementioned study confirmed that IGF1R is the target gene of miR-455 in pancreatic cancer cells, and that IL-6 significantly decreases the expression of miR-455 in these cells. miR-455 was found to inhibit pancreatic cancer progression by downregulating IGF1R, while IL-6 downregulates miR-455 and upregulates IGF1R (142). A proposed therapeutic approach for pancreatic cancer involves inhibiting the high expression of IL-6 and the overexpression of miR-455 in pancreatic cancer cells. Additionally, miR-375 induces the downregulation of YAP in medullary thyroid carcinoma (37). YAP, a key component of the Hippo signaling pathway, not only contributes to tumor progression but also promotes IL-6 expression (34,35). This establishes a link between miR-375, IL-6, and medullary thyroid carcinoma, offering new insights into potential treatment approaches. The enrichment of miR-377 in SCLC has been shown to inhibit the IGF1R pathway, thereby suppressing SCLC cell metastasis (44). IL-6 stimulates STAT3 activation to promote SCLC cell metastasis, and crosstalk has been observed between the STAT3 and IGF1R signaling pathways (143). Additionally, an indirect relationship has been identified between IL-6 and miR-377, which represents a novel research focus in SCLC. miR-96 is involved in the PI3K/AKT pathway and plays a role in gastric NET progression, while IL-6 activation of the STAT3 pathway promotes tumor cell proliferation (48). Furthermore crosstalk has also been observed between the STAT3 and PI3K/AKT pathways (144). In gastrointestinal NETs, it has been shown that elevated expression of IL-6 induces changes in fibroblast activity and miRNA levels, which regulate signaling pathways that ultimately affect intestinal structure and lead to malignant metaplasia (65). PNETs and PitNETs share similar mechanisms, with specific miRNAs and IL-6 acting on signaling pathways that crosstalk with each other, collectively playing a role in tumor development. In the future, it will be assessed which miRNAs target downstream IL-6 through various signaling pathways or competing endogenous RNA networks. In addition, an aim is set to verify which signaling pathway is associated with this, as well as to specifically determine the mechanism by which miRNAs achieve targeting of downstream genes to affect tumorigenesis and development. At present, there are limitations in the clinical use of IL-6/miRNAs as biomarkers, because the changes in protein or RNA expression levels cannot be assessed in real time in the clinic, and the current pathological technology cannot extract and distinguish which specific IL will be elevated in time, which leads to a lack of specificity. Furthermore, as molecules in the TME, IL-6 and miRNAs also influence downstream genes. In addition, as molecules in the TME, it remains unclear whether crosstalk occurs between their downstream or upstream effects, which may affect the specificity of these biomarkers. Currently, the clinical application of IL-6 and miRNAs as biomarkers for NENs faces several technical bottlenecks. First, there are challenges with specificity and timeliness in detection: Serum IL-6 levels can be easily influenced by non-tumor factors such as infection and stress, while assessing tissue-specific miRNA expression requires a biopsy, and real-time quantitative analysis is difficult with existing pathological techniques. Second, the complexity of the molecular network presents challenges: The synergistic effects of IL-6 and other cytokines (such as IL-1β and TNF-α) in the tumor microenvironment, along with the crosstalk of miRNAs on multiple signaling pathways, may limit the diagnostic efficacy of using a single molecular marker. Therefore, future studies should integrate multi-omics technologies (such as transcriptomics and proteomics) to construct a regulatory network of 'inflammatory factors-miRNA-signaling pathways' specific to NENs and verify the therapeutic value of key molecular nodes through animal models. Additionally, the development of liquid biopsy-based dynamic monitoring technologies for miRNA/IL-6 (including digital PCR and flow cytokine assays) will offer novel directions for the early detection and individualized treatment of NENs.

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Authors' contributions

XG and SY developed the framework and drafted the manuscript, contributing to the overall structure and conceptualization of the review. CC and DL revised the content of the manuscript and handled the correspondence with the editor. SY generated the figures and performed the final review of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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