

Research advances of secretory proteins in malignant tumors

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Abstract

Secretory proteins in tumor tissues are important components of the tumor microenvironment. Secretory proteins act on tumor cells or stromal cells or mediate interactions between tumor cells and stromal cells, thereby affecting tumor progression and clinical treatment efficacy. In this paper, recent research advances in secretory proteins in malignant tumors are reviewed.

Keywords: Secretory protein; tumor microenvironment; stromal cells; tumor progression; drug resistance

Submitted Aug 26, 2020. Accepted for publication Jan 05, 2021.

doi: 10.21147/j.issn.1000-9604.2021.01.12

View this article at: <https://doi.org/10.21147/j.issn.1000-9604.2021.01.12>

Introduction

Secretory proteins can be produced by tumor cells or stromal cells. Secretory proteins from tumor cells may act on tumor cells through autocrine or paracrine mechanisms and may also act on stromal cells. Secretory proteins produced by stromal cells may mediate the regulation of stromal cells on tumor cells. As important components of the tumor microenvironment, secretory proteins promote or inhibit tumor progression and affect sensitivity to cancer therapy.

Secretory proteins mediate regulation between tumor cells

Tumor cells may secrete growth factors, glycoproteins, inflammatory cytokines, enzymes and exosomes, which can act on the cells that produce them or adjacent tumor cells. There are an increasing number of studies on regulation between tumor cells mediated by secretory proteins, and this regulation has been found to be involved in an increasing number of cancer types, including lung cancer,

breast cancer, colorectal cancer, glioma, ovarian cancer, osteosarcoma, pancreatic cancer, etc.

Enhancement of tumor cell proliferation, stemness and survival by tumor cell-secreted proteins

Intercellular communication is important for maintaining cell proliferation, stemness and survival. Secretory proteins are important mediators of intercellular signal transduction between tumor cells.

The secretory protein regenerating islet-derived protein IV (Reg IV) is a member of the Reg multigene family that activates epidermal growth factor receptor (EGFR)/AKT/AP-1 signaling to increase the expression of Bcl-2, Bcl-XL and Survivin, thereby promoting the proliferation of colorectal adenocarcinoma cells (1). Secreted Meprin α , an astacin-type metalloprotease with proteolytic enzyme activity, promotes epidermal growth factor (EGF) and transforming growth factor alpha (TGF- α) shedding from the plasma membrane and releasing into the extracellular matrix (ECM), thereby promoting the proliferation and migration of colorectal cancer cells by activating the

EGFR/ERK1/2 pathway (2). Similarly, rhomboid domain-containing protein 1 (RHBDD1), a rhomboid intramembrane serine protease, interacts with proTGF- α to induce cleavage and a disintegrin and metalloproteinase (ADAM)-independent secretion of TGF- α and subsequent activation of the EGFR/Raf/MEK/ERK pathway to promote the proliferation and growth of colorectal cancer cells (3). The M2 isoform of pyruvate kinase (PKM2) promotes the proliferation of triple-negative breast cancer cells by inducing EGFR phosphorylation (4).

Secreted interleukin-8 (IL-8) stimulates ovarian cancer cell proliferation and alters cell cycle distribution by increasing cyclin D1 and cyclin B1 expression as well as activating the phosphatidylinositol 3-kinase (PI3K)/AKT and Raf/MEK/ERK pathways (5). Autocrine parathyroid hormone-related protein (PTHrP) promotes the proliferation and growth of intrahepatic cholangiocarcinoma cells by activating both the ERK/ATF-2/cyclin D1 and JNK/ATF-2/cyclin D1 pathways (6). In cervical cancer, expression and secretion of growth/differentiation factor 15 (GDF15) gradually increases with tumor progression, and GDF15 acts on the cell membrane receptor ErbB2 to activate PI3K/AKT and mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK) signaling, which upregulates cyclin D1 and cyclin E1 and downregulates p21 to promote tumor cell proliferation (7). Annexin A1 (ANXA1) highly expressed and secreted by triple-negative breast cancer cells enhances the proliferation, survival and invasive capacity of breast cancer cells through the ANXA1/FPR1 pathway (8). Progranulin (PGRN) increases proliferation and promotes the dedifferentiation of breast cancer stem cells via the receptor Sortilin (9).

The autocrine/paracrine insulin-like growth factor 2 (IGF2)/IGF1R cycle plays an important role in maintaining proliferation and the stem cell-like characteristics induced by the fusion gene *CD74-NRG1* in non-small cell lung cancer (NSCLC) (10). The receptor protein KIT is highly expressed in colon cancer under hypoxic conditions, and stem cell factor (SCF) secreted from differentiated tumor cells binds to KIT on undifferentiated stem-like tumor cells to maintain their proliferation and clonogenic capacity (11). Autotaxin secreted by ovarian cancer stem cells promotes the secretion of lysophosphatidic acid (LPA), which in turn maintains cellular proliferation and stemness through LPA/LPAR1/AKT1 signaling (12).

Heat shock protein HSP 90- α (Hsp90 α) secreted by

breast cancer cells overexpressing hypoxia-inducible factor 1- α (HIF-1 α) protects tumor cells from hypoxia-induced cell death by directly activating LRP1/AKT signaling (13). HSP90 binds to and stabilizes the protein kinase D2 (PRKD2) in human cancer cells. Inhibition of HSP90 triggers the degradation of PRKD2, promoting apoptosis in cancer cells. The ectopic expression of PRKD2 partially restores HIF-1 α and secretes vascular endothelial growth factor A (VEGFA) levels in hypoxic cancer cells, protecting cancer cells treated with HSP90 inhibitors from apoptosis effects and restoring the formation of blood vessel (14). The autocrine-paracrine loop of tumor necrosis factor α (TNF α) participates in the constitutive activation of transcription factors NF- κ B and YY1 in prostate cancer cells, resulting in the inhibition of Fas expression and cancer cell resistance to FasL-induced apoptosis (15). C-C motif chemokine ligands (CCLs) contribute to the resistance of prostate cancer cells to castration through an autocrine manner. The CCL2/CCR2 pathway reduces the cleavages of caspase-3 and poly ADP-ribose polymerase (PARP) to decrease the apoptosis of cancer cells induced by cabazitaxel. Blockade of CCL2/CCR2 pathway combined with cabazitaxel may be a potential strategy for the treatment of castration-resistant prostate cancer (16).

Promoting effect of secretory proteins from tumor cells on tumor cell motility and metastasis

Secretory proteins also play important roles in tumor cell invasion, migration and tumor metastasis.

PKM2 secreted by lung cancer cells directly acts on integrin β 1 to activate the FAK/SRC/ERK axis, thereby upregulating the expression of matrix metalloproteinase-9 (MMP-9) and promoting lung cancer metastasis (17). The lung cancer cell secreted glycoprotein signal peptide, CUB and EGF-like domain-containing protein 3 (SCUBE3) is cleaved by matrix metalloproteinase-2 (MMP-2) and MMP-9 into an N-terminal EGF-like domain and a C-terminal CUB domain. Both SCUBE3 and the CUB domain can bind to TGFBR2 on the surface of cancer cells and further activate TGFBR1 to phosphorylate mothers against decapentaplegic homolog 2/3 (SMAD2/3) and then promote the transcription of Snail, Slug, plasminogen activator inhibitor-1 (PAI-1), MMP-2, MMP-9 and VEGF, thereby enhancing the epithelial mesenchymal transition (EMT), invasion and metastasis of the cells (18). IL-8 also promotes the invasion of ovarian cancer cells by upregulating the expression of MMP-2 and MMP-9 (5).

EGFRvIII-positive cells in glioblastoma (GBM) secrete epidermal growth factor-like protein 7 (EGFL7) and further promote the expression of EGFL7 in EGFR wild-type (EGFRwt) cell by directly activating the EGFR pathway and enhancing the invasion and migration of EGFRwt cells (19). Secreted EGFL7 from pituitary adenomas promotes the migration and invasion of tumor cells by activating the EGFR pathway (20). Angiotensin II (ANG II) secreted by ovarian cancer cells triggers classic AGTR1 signaling and transactivates EGFR signaling to promote tumor metastasis (21). Lysyl oxidase (LOX) is secreted as an inactive precursor enzyme, and this secreted precursor is cleaved into mature active LOX by extracellular metalloproteinases such as bone morphogenetic protein 1 (BMP1). Mature LOX activates the secreted protease high-temperature requirement A serine peptidase 1 (HTRA1) to degrade transforming growth factor- β 1 (TGF- β 1), and this reduction in TGF- β 1 levels in the tumor microenvironment causes cancer cells to secrete matrilin-2 (MATN-2). Increased extracellular MATN2 captures EGFR on the surface of tumor cells and facilitates its activation by EGF, ultimately promoting tumor progression (22).

Serglycin (SRGN) is overexpressed in NSCLC cells and secreted into the tumor microenvironment in a highly glycosylated form. SRGN binds to CD44 on the surface of cancer cells to promote the activation of SRC and subsequent phosphorylation of Paxillin, leading to the dissociation of the Paxillin/FAK adhesion complex, and accelerating focal adhesion turnover. At the same time, SRGN promotes the activation of Ras-related C3 botulinum toxin substrate 1 (RAC1) and cell division control protein 42 homolog (CDC42) to enhance cytoskeletal reorganization, eventually enhancing the migratory ability of cancer cells (23). Other secretory proteins promoting tumor cell invasion and migration include Galectin-8 secreted from GBM (24), glucose-6-phosphate isomerase (GPI) secreted from glioma cells (25), and IL-1 β secreted from pancreatic cancer cells with high CD133 expression (26).

Secretory proteins that act as tumor suppressors

In addition to protumorigenic signals, secreted proteins may also mediate tumor suppressive signals through autocrine or paracrine mechanisms. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-long is a PTEN variant with an N-terminus 173 amino acids longer

than PTEN due to the utilization of different initiation codons during *PTEN* gene translation. It is a secretory and membrane-permeable lipid phosphatase. PTEN-long inhibits the PI3K pathway in tumor cells, inducing cell death *in vitro* and *in vivo* (27).

Secreted frizzled related protein 1 (SFRP1) binds to Wnt on lung cancer cells and inactivates Wnt signaling, leading to the downregulation of Wnt-related genes (*CCND1*, *c-Jun*, *VEGF* and *c-Myc*) and stemness-related genes (*ABCG2*, *Nanog*, *Notch1* and *Oct4*) and ultimately reducing the stem-like properties of cancer cells. The secretion of SFRP1 could be promoted by Rab-37, and low expression of Rab-37 and SFRP1 might predict a poor prognosis for patients with lung cancer (28).

The secretory protein CCN family member 2 (CCN2) from oral cancer cells acts on $\alpha\beta$ 5 integrin and inhibits FAK/PI3K/AKT signaling to reduce the binding of c-Jun to the AP-1 site of the COX-2 promoter region, downregulate the expression of COX-2 and inhibit the migration of cancer cells (29).

Macrophage migration inhibitory factor (MIF) is a secretory protein expressed in multiple types of cells, such as tumor cells, monocytes, macrophages, T lymphocytes, B lymphocytes, eosinophils, mast cells, basophils, and neutrophils. O-GlcNAcylated MIF in the tumor microenvironment competitively binds to EGFR and thereby blocks EGF-induced EGFR activation and the phosphorylation of ERK and c-Jun, leading to the inhibition of tumorigenesis. Ligand-binding or mutant EGFR can activate the EGFR pathway to enhance the secretion of MMP-13, which degrades extracellular MIF and eliminates the negative regulation of EGFR by MIF (30).

In breast cancer, insulin-like growth factor-binding protein 3 (IGFBP-3) secreted by trastuzumab-sensitive tumor cells reduces the IGFBP-2-stimulated activation of ErbB-2 in autocrine and paracrine manners, resulting in the inhibition of tumor cell growth (31). In triple-negative breast cancer, the secretory protein tubulointerstitial nephritis antigen-like 1 (TINAGL1) inactivates integrin/FAK and EGFR signaling, inhibiting tumor progression and metastasis (32).

Follistatin-like protein 1 (FSTL1) secreted by lung adenocarcinoma cells directly binds to the precursor of osteopontin (OPN) to inhibit its activation, thereby inhibiting the invasion and migration of cancer cells. Integrin or CD44 neutralizing antibodies could reverse the

migration promoting effect caused by FSTL1 neutralizing antibodies (33).

Effect of stromal cell-derived secretory proteins on tumor cells

Cancer-associated fibroblasts (CAFs)

CAFs are one of the key components of the tumor microenvironment. CAFs promote tumorigenesis and progression by acting on tumor cells via direct contact or through secretion of various soluble factors (34). CAF-derived microfibrillar-associated protein 5 (MFAP5) in oral squamous cell carcinoma promotes the growth and migration of tumor cells by activating both the MAPK and AKT pathways (35). IGF2 secreted by CAFs interacts with the receptor IGF1R on colon cancer cells to enhance PI3K/AKT signaling, which inhibits cell apoptosis and accelerates tumor progression (36). CAF-derived CCL2, CCL5, CCL7 and C-X-C motif chemokine 16 (CXCL16) synergistically activate both the Hedgehog and TGF- β pathways to promote the metastasis of hepatocellular carcinoma (37). CXCL1 secreted by CAFs confers radiotherapy resistance to esophageal squamous cancer cells by enhancing their DNA damage repair capacity in a ROS-dependent manner (38). CAFs in breast cancer secrete TGF- α , TGF- β 1, IL-32, and IL-1 β . Of those, TGF- α promotes cancer cell proliferation through the EGFR, AKT, and ERK pathways. Paracrine TGF- β 1 stimulates cancer cells to increase the phosphorylation of SMAD2/3/4, which indirectly induces the transcription of lncRNA HOTAIR. HOTAIR promotes cell invasion via the repression of E-cadherin and induction of β -catenin. IL-32 enhances the invasion and migration of tumor cells through integrin β 3/P38MAPK signaling (39-41). The interaction of paracrine IL-1 β with its receptor IL-1R1 on cancer cells induces the migration and invasion of those cells by upregulating PTGES, COX-2, RAGE and ABCG2 (42).

Mesenchymal stem cells (MSCs)

In tumor tissues, cancer cells recruit mesenchymal stem cells and activate them into tumor-derived MSCs. Activated MSCs produce various secretory factors to promote tumor growth and progression through endocrine or paracrine pathways. Granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted by MSCs from pancreatic ductal adenocarcinoma (PDAC) acts on the

receptors CSF2R α and CSF2R β on PDAC cells to promote their survival, invasion and EMT (43). Gastric cancer (GC)-derived MSCs secrete IL-8 to stimulate the activation of AKT or ERK1/2 signaling, promoting cancer progression (44). Tumor exosome-like vesicle-educated MSCs produce IL-6 to promote the tumorigenicity of osteosarcoma cells (45) as well as the proliferation, migration and invasion of colorectal cancer cells (46). MSC-derived TGF- β upregulates Snail expression and induces EMT in melanoma cells (47). In acute myeloid leukemia (AML) patients, CXCL8 from bone marrow mesenchymal stromal cells binds to the receptor CXCR2 on AML cells and promotes the survival and proliferation of cancer cells by activating the PI3K/AKT pathway (48).

Macrophages

Macrophages can be polarized into classically activated (M1 macrophages) or alternatively activated (M2 macrophages) phenotypes. M2 macrophages promote the migration, invasion, and EMT of gallbladder cancer cells by secreting CCL18 to activate the PI3K/AKT pathway (49). Tumor-associated macrophage (TAM)-secreted MMP-9 activates the PI3K/AKT/Snail pathway and promotes tumor metastasis by inducing EMT in GC cells (50).

At metastatic sites, TAM-secreted IL-35 binds to the IL-35 receptor and reverses EMT in cancer cells by activating the JAK2/STAT6/GATA3 pathway, thereby promoting metastatic colonization (51).

Stellate cells

When organs are damaged by inflammation or mechanical stimulation, pancreatic stellate cells (PSCs) and hepatic stellate cells (HSCs) that are normally resting can be activated to participate in pancreatic fibrosis, liver fibrosis or other pathological changes through hyperproliferation and remodeling of ECM. The interaction between PSCs and pancreatic cancer cells not only promotes tumor progression but also maintains the activation of PSCs, thereby establishing a vicious cycle that exacerbates tumorigenesis and induces drug resistance. Leukemia inhibitory factor (LIF) is a crucial paracrine factor from activated PSCs, and it promotes the progression and chemoresistance of PDAC through LIFR and its coreceptor GP130-mediated activation of STAT3 in cancer cells (52). Activated PSCs also promote the invasion and migration of pancreatic cancer cells by producing the paracrine factors OPN, IL-6 and stromal cell-derived

factor 1 (SDF-1; also known as CXCL12) to activate OPN/integrin $\alpha\beta_3$, IL-6/IL-6R/JAK/STAT3 and SDF-1/CXCR4 signaling, respectively. In addition, OPN can promote stem cell-like properties in pancreatic cancer cells (53-55).

PSCs secrete hepatocyte growth factor (HGF) to activate the HGF/c-MET/YAP/HIF-1 α pathway, enhancing the stemness potential and glycolysis in pancreatic cancer cells (56). Secretion of HGF by HSCs promotes invasion and migration of hepatocellular carcinoma cells by increasing Snail expression via HGF/c-MET signaling (57). HSC-derived cartilage oligomeric matrix protein (COMP) binds to its receptor CD36 on cancer cells and plays a crucial role in hepatocellular carcinoma proliferation, invasion and migration through the MEK/ERK and PI3K/AKT pathways (58).

TGF- β from activated HSCs could further activate resting HSCs, inducing them to secrete TGF- β and metalloproteinases-1 (TIMP-1). TGF- β enhances the survival and invasion of hepatocellular carcinoma cells. TIMP-1 acts on CD63 to activate FAK signaling in hepatocellular carcinoma cells, promoting their survival, proliferation and invasiveness, as well as tumor progression (59).

Adipocytes

Adipocyte-derived resistin enhances the expression of VEGF in ovarian epithelial cancer cells by increasing PI3K/AKT-dependent phosphorylation of the transcription factor SP1, thereby stimulating angiogenesis in cancer (60). Leptin secreted by adipocytes acts through specific Ob-R receptors and induces PKM2 expression in cancer cells via PI3K/AKT signaling, thereby promoting breast cancer metastasis (61). In triple-negative breast cancer, CXCL1 secreted by adipose-derived stem cells mediates the downregulation of miR-106a to increase the expression of the drug transporter ABCG2, resulting in doxorubicin resistance in breast cancer (62).

Endothelial cells

IL-8 secreted by endothelial cells promotes the initial growth of melanoma cells both *in vitro* and *in vivo* (63). In GC, CXCL1 from tumor-associated lymphatic endothelial cells activates integrin β_1 /FAK/AKT signaling to upregulate the expression of MMP-2 and MMP-9 in cancer cells thus aiding their entry into the lymphatic system and promoting cancer cell lymph node metastasis (64).

Crosstalk between tumor cells and stromal cells mediated by secretory proteins

Proteins secreted from tumor cells can also promote the progression of tumors by modifying stromal cells. For example, in glioma, OPN acts on the endothelial cell receptor $\alpha\beta_3$ to activate the PI3K/AKT/eNOS/NO signaling pathway, promoting tumor progression via the induction of angiogenesis (65). Angiopoietin secreted by breast cancer cells acts on endothelial cells to promote tumor metastasis by inducing angiogenesis, which involves the downregulation of miR-542-3p by decreasing the activity of the transcription factors CEBPB and POU2F1 (66). Breast cancer cell-derived PAI-1 binds to LRP1 on the membrane of adipocytes to enhance PLOD2 expression by activating the PI3K/AKT-FOXP1 pathway, and PLOD2 further induces the linear organization of adipocyte-derived collagen, which promotes the invasion and migration of tumor cells (67). PAI-1 secreted by metastatic ovarian cancer cells induces the formation of cancer-associated mesothelial cells to accelerate the peritoneal dissemination of tumor cells (68). Soluble SCF secreted by hepatocellular carcinoma cells is capable of promoting angiogenesis and cancer metastasis (69). Tissue transglutaminase (TGM2) secreted by pancreatic ductal adenocarcinoma cells stimulates fibroblast activation and proliferation and collagen crosslinking to remodel the surrounding matrix, and the resulting dense desmoplastic stroma promotes cancer cell proliferation and tumor growth by activating YAP/TAZ signaling in cancer cells (70). Tumor-derived IL-1 β acts on human mesenchymal stem cells and converts them into skeletal CAFs, which changes the bone matrix and promotes early prostate cancer cell colonization of bone metastasis sites (71). EGF derived from colon cancer cells activates the EGFR/PI3K/AKT/mTOR pathway to promote the polarization of tumor-associated macrophages to M2 macrophages that contribute to tumor progression (72). Galectin-3-binding protein (LGALS3BP) induces tumor cell production of VEGF by activating the PI3K/AKT pathway, and it can also directly stimulate the tubulogenesis of endothelial cells in a galectin-3-dependent, VEGF-independent manner (73).

Some secreted molecules derived from tumor cells help tumor cells escape immune surveillance by affecting the function and activity of specific immune cells. For example, in melanoma, VEGF and TGF- β secreted by tumor cells suppress the recruitment and function of antigen-

presenting cells (APCs), such as dendritic cells (DCs). Chemokines from tumor cells bind to receptors on the surface of regulatory cells (Tregs) to recruit them, and tumor cells subsequently nurture the recruited Treg cells by secreting TGF- β and immunosuppressive metabolites. Tumor-infiltrating Treg cells prevent the activation of effector T cells in various ways and exert an immunosuppressive effect. Tumor cells, by secreting GM-CSF, IL-6 and miRNA-loaded exosomes, also recruit and transform myeloid-derived suppressor cells (MDSCs) to suppress the immune response (74,75). In addition, secreted fibrinogen-like protein 1 (FGL1) is upregulated in NSCLC, melanoma and colon cancer, and it inhibits the activity of antigen-specific T cells by binding to lymphocyte activation gene 3 (LAG-3) on the surface of T cells (76).

Communication and crosstalk between cancer cells and stromal cells may also take place in more complex ways. For example, HGF and IL-6 produced by activated bone marrow-derived myofibroblasts (BMFs) bind to their receptors MET and IL-6R and activate STAT3 signaling in GC cells to induce sphere formation; HGF and IL-6 also stimulate cancer cells to secrete TGF- β 1. IL-6 activates BMFs in an autocrine manner to promote HGF production, and tumor cell-derived TGF- β 1 reciprocally activates BMFs, forming a positive feedback loop that induces the stemness of tumor cells, promoting tumor progression (77). During castration therapy for prostate cancer, the androgen receptor inhibitor enzalutamide induces prostate cancer cell expression and secretion of high mobility group box 1 (HMGB1); extracellular HMGB1 recruits and activates TAMs to secrete IL-6, promoting the neuroendocrine differentiation of tumor cells. Differentiated tumor cells secrete a variety of active substances to enhance the proliferative and antiapoptotic capacity of cancer cells, promoting tumor growth. Secretory IL-6 further stimulates the transcription of HMGB1 in cancer cells, thereby forming a positive feedback loop to enhance tumor resistance to enzalutamide (78). TNF- α secreted by metastatic ovarian cancer cells acts on omental stromal fibroblasts to activate NF- κ B signaling, which induces the expression and secretion of TGF- α , and secreted TGF- α activates the EGFR pathway in ovarian cancer cells to promote metastatic colonization (79). In breast cancer, tumor cells can secrete CXCL14, which binds to its cognate receptor GPR85 on mammary fibroblasts and activates them via the ERK1/2, AKT, and neddylation pathways; in return, activated fibroblasts induce the EMT of tumor cells through CCL17/

CCR4 paracrine signaling, promoting breast cancer progression (80).

Roles of secretory proteins in antitumor therapy

Secretory proteins and chemotherapy

Most studies on secretory proteins and chemotherapy are concerned with resistance to chemotherapeutic drugs, and some have explored possible approaches to overcome drug resistance. Many proteins secreted from tumor or stromal cells are associated with the sensitivity to chemotherapeutic drugs. SRGN is upregulated in chemoresistant breast cancer cells, and secreted SRGN enhances YAP expression by activating the integrin α -5 (ITGA5)/FAK/CREB pathway, leading to cancer cell resistance to chemotherapy, such as 5-fluorouracil (5-FU) treatment (81). In nasopharyngeal carcinomas, extracellular SRGN induces the expression of the tumor cell membrane coreceptor CD44 by activating MAPK/ β -catenin signaling, thereby maintaining tumor cell self-renewal capacity and leading to resistance to cisplatin and 5-FU (82). IL-6 induces ovarian cancer cell resistance to tamoxifen via ER isoforms and SRC-1 (83). Flagellin binds to and activates the receptor TLR5 to increase the expression of IL-6, and IL-6-mediated autocrine or paracrine signaling leads to multiple myeloma cell resistance to doxorubicin (84). CCL2 secreted by cisplatin-resistant GC cells not only maintains resistance to cisplatin in the secreting cells by activating the PI3K/AKT/mTOR axis but also confers such resistance to sensitive cancer cells (85). Autocrine CCL2/CCR2 signaling induces prostate cancer cell resistance to cabazitaxel (16). High CCN2 expression enhances the survival of glioma cells by inducing the expression of antiapoptotic proteins (BCL-XL, Survivin and Flip) and leads to resistance to multiple drugs, including bortezomib and temozolomide (86). CCN2 promotes osteosarcoma resistance to doxorubicin by increasing ABCG2 expression via activation of the α 6 β 1 integrin receptor (87). OPN secreted by hepatocellular carcinoma cells binds to integrin α v β 3, promoting cell survival and resistance to chemotherapy drugs (88). Matrix gla protein (MGP) secreted by ovarian cancer cells induces cancer cell resistance to paclitaxel and topotecan by enhancing the interaction between cells and the ECM (89). Secreted macrophage inhibitory cytokine-1 (MIC-1) protein from prostate cancer cells confers EMT characteristics and enhanced invasive ability to cells, which leads to the tumor

cell resistance to docetaxel (90). Basic fibroblast growth factor (bFGF) secreted by chondrosarcoma cells could promote the expression of XRCC5 in tumor cells, resulting in doxorubicin resistance (91). Additionally, in chondrosarcoma, secretory amphiregulin (AR) is highly expressed in tumor cells with strong migratory ability or drug resistance, and exogenous recombinant AR promotes cell migration and resistance to doxorubicin by activating the MAPK pathway (92). In hematologic malignancies, macrophage inflammatory protein-1 α (MIP-1 α) secreted from myeloma cells binds to the receptor proteins CCR1 and CCR5 to activate the ERK1/2, AKT, and mTOR pathways, promoting the survival, growth, and resistance of multiple myeloma cells to melphalan and bortezomib (93-95). Sonic hedgehog (SHH) secreted by myeloma cells promotes survival via autocrine signaling and enhances the resistance of CD138+ myeloma cells to bortezomib and melphalan. Combinational treatment with bortezomib or melphalan and SHH-neutralizing antibodies has displayed synergistic inhibitory effects (96). Interacting protein 1 (RIP1) is required in necroptosis. In colorectal cancer, nuclear factor κ B (NF- κ B) and RIP1 kinase drive the production of TNF- α , and pan-caspase inhibitors enhance 5-FU-induced necroptosis, which was mediated by TNF- α autocrine secretion. The pan-caspase inhibitor in combination with 5-FU synergistically blocked tumor growth (97).

On the other hand, many soluble factors derived from stromal cells are related to tumor drug resistance. IL-6 secreted by CAFs enhances the proliferation, migration and invasion of bladder cancer cells, as well as the resistance of NSCLC cells to cisplatin, by inducing EMT in tumor cells (98,99). IL-6 secreted by bone marrow stromal cells derived from patients with multiple myeloma promotes the proliferation and resistance of cancer cells to melphalan or bortezomib by inhibiting the expression of miRNA-15a and miRNA-16 (100). TGF- β 1 and PAI-1 secreted by CAFs play an important role in drug resistance in esophageal squamous cell carcinoma. In fact, TGF- β 1 induces tumor cell resistance to various chemical drugs, including cisplatin, paclitaxel, irinotecan, 5-FU, carboplatin, docetaxel, daunorubicin and vincristine, while the TGF β R1 inhibitor LY2157299 can reverse chemoresistance (101). Cisplatin-activated PAI-1 secretion further promotes resistance to cisplatin and tumor growth by activating the AKT and ERK1/2 pathways and inhibiting caspase-3 activity and ROS accumulation (102). CAF-derived midkine enhances the resistance of oral

squamous cell carcinoma to cisplatin by increasing the expression of lncRNA ANRIL (103). SDF-1 secreted by CAFs binds to CXCR4 to upregulate the expression of SATB-1 in pancreatic cancer cells, leading to the malignant progression of cancer and resistance to gemcitabine (104). In colorectal cancer, HIF-1 α and CAF-secreted TGF- β 2 synergize to upregulate the Hedgehog transcription factor GLI2 in cancer stem cells, enhancing their stemness and inducing resistance to the FOLFOX regimen (combination of 5-Fu and oxaliplatin). The combination of GNT61 (which blocks the DNA binding activity of GLI1/2 transcription factors) and SD208 (a TGF- β inhibitor) effectively reverses chemoresistance via a synergistic effect (105). Snail-positive fibroblasts have CAF characteristics and secrete CCL1 to induce colorectal cancer cell resistance to 5-FU and paclitaxel through the TGF- β /NF- κ B pathway (106).

In addition, TAMs secrete IL-10, 14-3-3 ζ , CCL2 and MMP-9 into the tumor microenvironment. Of those, IL-10 activates STAT3/Bcl-2 signaling in breast cancer cells to induce resistance to paclitaxel (107). Extracellular 14-3-3 ζ can passively diffuse through the plasma membrane and interact with AXL, one of the 14-3-3 ζ binding partners, resulting in the activation of AXL-mediated prosurvival pathways and pancreatic cancer cell resistance to gemcitabine. Consistent with this, patient serum 14-3-3 ζ levels significantly increase following chemotherapy (108,109). CCL2 activates the PI3K/AKT/mTOR pathway in breast cancer cells to induce tamoxifen resistance (110). Resistin secreted by bone marrow adipocytes inhibits chemotherapy-induced apoptosis in myeloma cells by activating NF- κ B and PI3K/AKT signaling. In myeloma, resistin downregulates the expression of the DNA methyltransferases DNMT1 and DNMT3a and thus reduces the degree of methylation of ATP-binding cassette (ABC) gene promoter to increase the mRNA and protein expression of ABCG2 and ABCC5, which promotes drug efflux to induce multidrug resistance (111). Fibronectin (FN) secreted by PSCs could induce pancreatic cancer cell resistance to gemcitabine via activation of ERK1/2 (112). TGM2 derived from pancreatic ductal adenocarcinoma cells stimulates cancer-associated fibroblasts to secrete laminin A1, which protects tumor cells from gemcitabine-induced cytotoxic effects (i.e., confers drug resistance) (113).

Secretory proteins and targeted therapy

Many studies on the implications of secretory proteins in

targeted therapy focus on targeting EGFR and VEGF/VEGFR. It has been reported that the secreted glycoprotein extracellular matrix protein 1 (ECM1) is upregulated in trastuzumab-resistant breast cancer cells and associated with trastuzumab resistance and cellular proliferation due to activation of EGFR signaling (114). IL-6 acts on the tumor cell membrane coreceptor IL-6R (gp130) to activate the mTORC2/NF- κ B pathway, leading to BRD4-dependent expression of BIRC5 and a decrease in sensitivity to EGFR tyrosine kinase inhibitors (TKIs), including gefitinib, erlotinib and lapatinib (115). Paracrine factors secreted by CAFs derived from gefitinib (EGFR-TKI)-resistant lung adenocarcinomas attenuate the inhibitory effect of EGFR-TKIs on pEGFR and pMAPK in tumor cells (116). HGF secreted by CAFs reduces the response of colon cancer-initiating cells to cetuximab (EGFR antibody) through paracrine activation of MET. Inhibition of MET could enhance sensitivity to anti-EGFR therapy (117). Secreted OPN activates integrin α V β 3/FAK and ERK pathways to promote the proliferation of NSCLC cells, contributing to acquire EGFR-TKI resistance. Inhibition of FAK signalling increased sensitivity to EGFR-TKIs in the gefitinib-resistant cells (118).

Tumor-derived VEGF acts on the endothelial cell receptor VEGFR2 to activate AKT signaling and then upregulate multidrug resistance protein 1 (MDR1), resulting in resistance to paclitaxel. Ki8751 (VEGFR inhibitor) and LY294002 (PI3K-Akt inhibitor) block tumor-conditioned medium-induced MDR1 upregulation (119). Under hypoxic conditions, tumor-derived microsemipoprotein (MSMP) secretion triggers MAPK signaling in endothelial cells and promotes the formation of tubules, which results in resistance to ovarian cancer anti-VEGF therapy (B20 antibody) (120).

IGF2 secretion induced by Id1-overexpressing ESCC promotes cancer cell metastasis by activating IGF2/IGF-IR/AKT signaling in an autocrine manner. Targeting IGF2 (via an IGF2-neutralizing antibody) and IGF-IR (with cixutumumab) significantly suppressed tumor growth and metastasis, and cixutumumab enhanced the sensitivity of xenografts to fluorouracil and cisplatin (121). IGF2 secreted by ESCC with high levels of Id1 expression stimulates fibroblasts to secrete VEGF, recruiting VEGFR1+ bone marrow cells to growing tumors. Treatment with Avastin (anti-human VEGF antibody) is sufficient to suppress esophageal tumor growth (122).

Secretory proteins and immunotherapy

Cytokines produced and secreted by immune and nonimmune cells are considered regulatory mediators of multiple processes, such as cell growth, differentiation, and immune responses, etc. Cytokines and their receptors are immune mediators and have been applied in tumor immunotherapy (123). In the process of immunotherapy, cytokines directly stimulate immune effector cells and tumor stromal cells to enhance cytotoxicity (124). Cytokines can be divided into immunostimulatory cytokines and immunosuppressive cytokines (125), and immunostimulatory cytokines are usually used in antitumor therapy. Common immunostimulatory cytokines include IFN- α (126), IFN- γ (126-128), IL-2 family (129), IL-12 (127), IL-15 (130) and GM-CSF (131), etc. Cytokines, such as IFN- α and IL-2, have been proved by the Food and Drug Administration for the antitumor therapy. Several other IL proteins have also been in the clinical trials (125).

Recently, an increasing number of studies have revealed the importance of programmed cell death protein 1 (PD-1) as an immunosuppressive molecule that downregulates the immune response, and anti-PD-1 therapy has been proven to be effective in the treatment of many tumor types. NSCLC cells produce secretory PD-L1 splice variants that lack a transmembrane region at the C-terminus. These stable splice variants are secreted from cells and bind PD-1, resulting in resistance to programmed cell death 1 ligand 1 (PD-L1) blockade via trapping of the PD-L1 antibody (132). SDF-1 secreted by CAFs has immunosuppressive effects in several types of cancer via the recruitment and regulation of the activity of regulatory T cells. CAF-S1 cells (defined as CD29^{Med} FAP^{Hi} FSP1^{Low-Hi} α SMA^{Hi} PDGFR β ^{Med-Hi} CAV1^{Low}) in the tumor microenvironment increase CD4⁺CD25⁺ T lymphocyte numbers by secreting SDF-1, and the ligands OX40L, PD-L2 and JAM2 on CAF-S1 cells directly retain them and promote their differentiation into Tregs, which has immunosuppressive impacts on triple-negative breast cancer (133). SDF-1 from CAF-S1 cells also enhances the activity of regulatory T-cells in high-grade serous ovarian cancers by activating SDF-1/CXCR4 signaling in T-lymphocytes (134). Targeting SDF-1 from CAFs (with FAP⁺) synergizes with anti-PD-L1 immunotherapy in pancreatic cancer (135). The cytokine IL-35 is the main immunosuppressive driver of PDAC and promotes tumor growth by inhibiting endogenous anti-tumor T cell response. Targeting IL-35 combined with anti-PD-1 therapy shows a strong

synergistic reduction in tumor growth (136). A high level of tumor-secreted galectin-1 (Gal1) is correlated with a reduced response to immune checkpoint inhibitor treatment and poor survival in patients with head and neck cancer. Blockade of Gal1 with an anti-Gal antibody improves intratumoral T cell infiltration and enhances sensitivity to anti-PD-1 antibody with or without radiotherapy (137). Overexpression of BMP7, a secretory protein that belongs to the TGF- β superfamily, promotes resistance to anti-PD1 treatment. BMP7 secreted by tumor cells inhibits MAPK14 expression in macrophages and CD4+ T cells and reduces proinflammatory responses. BMP7 inhibition overcomes resistance to anti-PD1, anti-CTLA4 and anti-PDL1 immunotherapies (138).

Secretory proteins in blood and their clinical value as biomarkers

Some secretory proteins have been used clinically as serum markers for tumor diagnosis, prognosis and therapeutic monitoring (139,140). Apart from those, a number of candidate serum markers for various types of cancer are under study.

Elevated PKM2 (17), dickkopf-1 (DKK1) (141), karyopherin subunit α -2 (KPNA2) (142), glycodelin (143), and progesterone receptor membrane component 1 (PGRMC1) (144) levels have been detected in the sera or plasma of patients with lung cancer. Of those, PKM2 and DKK1 are associated with tumor progression, and a high serum DKK1 level likely indicates a poor prognosis (17,141). An increase in serum glycodelin could be used as a biomarker for predicting tumor recurrence and metastasis (143).

In breast cancer, chitinase-3-like protein 1 (CHI3L1) levels are significantly higher in the sera of patients than in healthy donors (145). Serum protein S100-A14 (S100A14), CCL2 and CXCL5 levels in breast cancer patients are also significantly higher than in normal individuals (146). Soluble CRK-like protein (CRKL) is primarily increased in the sera of patients with advanced breast cancer (147). High serum SRGN might predict chemotherapy resistance, and elevated serum prosaposin (PSAP) is significantly associated with poor response to endocrine treatment (81,148). A reduction in LRP6 ectodomain (LRP6N) serum levels can be used as a marker for breast cancer metastasis (149).

In gastrointestinal tumors, a 5-protein signature for detecting colorectal cancer, including ceruloplasmin (CP),

paraoxonase/arylesterase 1 (PON1), serpin peptidase inhibitor, clade A (SERPINA3), leucine-rich alpha-2-glycoprotein (LRG1) and tissue inhibitor of TIMP1, is distinct from the currently used carcinoembryonic antigen (CEA) but shows higher diagnostic accuracy than CEA (150). Colon cancer secreted protein-2 (CCSP-2) combined with CEA has a superior ability to detect colorectal cancer than either alone (151). High serum apelin might indicate lymph node metastasis and distant metastasis of colorectal cancer (152). Serum mindin levels are lower in patients with colorectal cancer, esophageal cancer, gastric cancer and breast cancer than in healthy individuals, and elevated mindin levels can be used as a biomarker for predicting a favorable chemotherapy response in colorectal cancer (153). Serum alpha-fetoprotein (AFP) is most commonly used in liver cancer (154-156). A combination of APF and aldo-keto reductase family 1 member B10 (AKR1B10) likely improves the diagnostic accuracy in this disease, especially for early-stage hepatocellular carcinoma (HCC) (157). High serum LCN2 and stanniocalcin 1 (STC1) levels are potential markers for diagnosis and shorter five-year survival of HCC patients, respectively (158,159). Additionally, serum hippocalcin-like 1 (HPCAL1) is significantly lower in HCC patients than in healthy donors (160).

In PDAC, thrombospondin-2 (THBS2) combined with the commonly used marker carbohydrate antigen (CA) 19-9 could distinguish PDAC from pancreatitis, improving the early detection of PDAC patients (161). The serum HSP70/HSP90-organizing protein (HOP) level of patients with GC is significantly higher than that of healthy controls but is markedly reduced after surgical tumor removal (162). In contrast, a sharp drop in serum secreted protein acidic and rich in cysteine (SPARC) levels in multiple types of gastrointestinal tumors, including esophageal cancer, GC, small intestine cancer and colorectal cancer, might indicate a higher risk of death (163).

Perspectives

The aforementioned tumor-related secretory proteins are summarized in *Table 1*. Future research on these secreted proteins should expand sampling to further examine their clinical relevance and determine which of them are indeed of value for clinical application. Another important direction of research on secreted proteins will be to explore potential clinical targets. Any secreted protein that plays an

Table 1 Secretory proteins in common human cancers

Cancer type	Proteins
Breast cancer	Angiopoietin (66), ANXA1 (8), CCL17 (80), CCL2 (110,146), CHI3L1 (145), CRKL (147), CXCL1 (62), CXCL14 (80), CXCL5 (146), ECM1 (114), Hsp90 α (13), IGFBP-3 (31), IL-10 (107), IL-1 β (42), IL-32 (41), Leptin (61), LGALS3BP (73), LOX (22), LRP6N (149), PAI-1 (67), PGRN (9), PKM2 (4), PSAP (148), S100A14 (146), SRGN (81), TGF- α (39), TGF- β 1 (40), TINAGL1 (32)
Colorectal cancer	Apelin (152), CCL1 (106), CCSP-2 (151), CP (150), EGF (2,72), FGL1 (76), HGF (117), IGF2 (36), LRG1 (150), Meprin α (2), Mindin (153), PON1 (150), Reg IV (1), SCF (11), SERPINA3 (150), SPARC (163), TGF- α (2,3), TGF- β 2 (105), TIMP1 (150)
Esophageal cancer	CXCL1 (38), IGF2 (121,122), PAI-1 (102), SPARC (163), TGF- β 1 (101)
Gastric cancer	CCL2 (85), CXCL1 (64), HGF (77), HOP (162), IL-6 (77), IL-8 (44), MMP-9 (50), SPARC (163), TGF- β 1 (77)
Glioma	CCN2 (86), EGFL7 (19), Galectin-8 (24), GPI (25), IL-6 (115), OPN (65)
Hepatocellular carcinoma	AFP (154-156), AKR1B10 (157), CCL2 (37), CCL5 (37), CCL7 (37), COMP (58), CXCL16 (37), HGF (57), HPCAL1 (160), LCN2 (159), OPN (88), SCF (69), STC1 (158), TGF- β (59), TIMP-1 (59)
Lung cancer	DKK1 (141), FGL1 (76), FSTL1 (33), IGF2 (10), IL-6 (99), KPNA2 (142), OPN (33), PD-L1 splice variants (132), PGRMC1 (144), PKM2 (17), SCUBE3 (18), SRGN (23), SFRP1 (28), Glycodelin (143)
Melanoma	FGL1 (76), GM-CSF (74), IL-6 (74), IL-8 (63), TGF- β (74), VEGF (74)
Myeloma	IL-6 (84,100), MIP-1 α (93), Resistin (111), SHH (96)
Oral cancer	CCN2 (29), MFAP5 (35), Midkine (103)
Osteosarcoma	AR (92), bFGF (91), CCN2 (87), IL-6 (45)
Ovarian cancer	ANGII (21), Autotaxin (12), IL-6 (83), IL-8 (5), LPA (12), MGP (89), MSMP (120), PAI-1 (68), Resistin (60), TGF- α (79), TNF- α (79)
Pancreatic cancer	14-3-3 ζ (108), FN (112), HGF (56), IL-1 β (26), IL-6 (54), OPN (53), SDF-1 (55) CA19-9 (161), GM-CSF (43), LIF (52), TGM2 (70,113), THBS2 (161)
Prostate cancer	CCL2 (16), HMGB1 (78), IL-1 β (71), IL-6 (78), MIC-1 (90), TNF- α (15)

important role in a particular tumor must interact with other related molecules. In the case of secreted proteins associated with cancer promotion, directly blocking their action or blocking their interaction with their related molecules should inhibit tumor growth and could be used for cancer treatment. Targeted therapy against tumor angiogenesis using bevacizumab to block VEGF is a typical example. Therefore, although secreted proteins are mainly used as biomarkers for diagnosis or therapeutic monitoring in current clinical practice, it can be expected that further in-depth study of secreted proteins will provide more therapeutic targets in human cancers.

Acknowledgements

This study was supported by National Key R&D Program of China, National Key Research Project (No. 2017YFE0112100) and CAMS Innovation Fund for Medical Sciences (CIFMS, No. 2019-I2M-1-003).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Zhang N, Hao J, Cai Y, Wang M. Research advances of secretory proteins in malignant tumors. *Chin J Cancer Res* 2021;33(1):115-132. doi:10.21147/j.issn.1000-9604.2021.01.12