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Fibrinogen: A new player and target on the formation of pre-metastatic niche in tumor metastasis

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ABSTRACT

Tumor metastasis involves a series of complex and coordinated processes, which is the main cause of patient death and still a significant challenge in cancer treatment. Pre-metastatic niches (PMN), a specialized microenvironment that develops in distant organs prior to the arrival of metastatic cancer cells, plays a crucial role in driving tumor metastasis. The development of PMN depends on a complex series of cellular and molecular components including tumor-derived factors, bone marrow-derived cells, resident immune cells, and extracellular matrix. Fibrinogen, a key factor in the typical blood clotting process, is related to tumor metastasis and prognosis, according to a growing body of evidence in recent years. Fibrinogen has emerged as an important factor in mediating the formation of tumor microenvironment. Nevertheless, a clear and detailed mechanism by which fibrinogen promotes tumor metastasis remains unknown. In this review, we first explore the roles of fibrinogen in the development of PMN from four perspectives: immunosuppression, inflammation, angiogenesis, and extracellular matrix remodeling. We highlight the significance of fibrinogen in shaping PMN and discuss its potential therapeutic values, opening new avenues for targeting fibrinogen to prevent or treat metastasis.

1. Introduction

Tumor metastasis is the main cause of cancer treatment failure and patient mortality, accounting for approximately 90 % of cancer-related deaths (Mani et al., 2024). To successfully colonize a tumor cell "seed", the vital "soil" of the metastatic target organ plays a crucial role. Pre-metastatic niche (PMN), as the "soil," is the specialized microenvironment within distant organs that are modified by primary tumors to facilitate the establishment and growth of metastatic cells (Peinado et al., 2017; Wang et al., 2024a), including the recruitment of bone marrow-derived cells (BMDCs), angiogenesis, inflammatory response, immunosuppression and extracellular matrix (ECM) remodeling (Liu and Cao, 2016). We previously reviewed that various cellular and molecular components, such as tumor-derived soluble factors (TDSFs), BMDCs, immune cells, and extracellular vesicles (EVs), are involved in PMN formation (Yang et al., 2021). Targeting and inhibiting PMN formation represents a promising strategy in cancer therapy aimed at disrupting the early stages of metastasis (Liu and Cao, 2016).

Fibrinogen is a glycoprotein complex with a molecular weight of 340 kDa, which is synthesized in the liver by hepatocytes, and then circulates in the bloodstream as a coagulation factor (Wolberg, 2023). It is a triplex spherical structure made up of three distinct sets of polypeptide chains: α, β, and γ (Lipitsä et al., 2019). Traditionally recognized as a clotting factor, fibrinogen plays a crucial role in the coagulation cascade and fibrinolysis; however, its functions extend far beyond just clot formation, including acute response to inflammation and immune (Luyendyk et al., 2019), especially linked to cancer progression (Han et al., 2024; Wu et al., 2024). In recent years, an increasing number of studies have highlighted fibrinogen as a promising biomarker for predicting cancer prognosis and classifying tumor stages (Yang et al., 2018;

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Zhang et al., 2019; Ke et al., 2024a). Elevated fibrinogen levels are linked to reduced overall survival and an increased risk of recurrence in various cancers (Perisanidis et al., 2015), such as breast (Hu et al., 2024; Zheng et al., 2020), lung (Ma and Wang, 2024; Sinn et al., 2022), colorectal and gastric cancers (Ying et al., 2022; Lin et al., 2021). Nevertheless, the mechanism by which fibrinogen influences tumor metastasis is still unclear.

In recent years, a growing body of researchers has investigated the function and mechanism of fibrinogen in the development of the tumor microenvironment. For example, in pancreatic ductal adenocarcinoma, fibrinogen forms an ICAM1-fibrinogen-ICAM1 bridging structure through the GP130-STAT1 signaling pathway upon IL-35 stimulation, which enhances the adhesion and transendothelial migration of cancer cells to endothelial cells (Huang et al., 2017). In colorectal cancer, fibrinogen-mediated p53 downregulation through activating FAK leads to cellular proliferation and senescence (Sharma et al., 2021). The interaction between Fibrinogen Alpha Chain (FGA) and integrin α5 also modulates the AKT-mTOR signaling pathway, influencing tumor growth and metastasis (Wang et al., 2020). Additionally, fibrinogen-like protein 2 (FGL2), a member of the fibrinogen family, facilitates the proliferation of MDSCs and augments their immunosuppressive capabilities through the enhancement of cholesterol metabolism and activation of XBP1 signaling in colorectal cancer (Wu et al., 2023). Even though fibrinogen's role in the broader tumor microenvironment has been well studied, its specific involvement in PMN formation in distant organs is often overlooked and less frequently highlighted. Here, we first discuss how fibrinogen plays in PMN formation and provide a comprehensive overview of the role of fibrinogen on PMN evolution, which will open promising avenues for developing new therapies to manage metastatic cancer more effectively.

2. Fibrinogen induces an immunosuppressive PMN

Immunosuppression is a crucial characteristic of PMN in tumor metastasis (Liu and Cao, 2016). Multiple immune cells, including macrophages, myeloid-derived suppressor cells (MDSCs), neutrophils, regulatory T cells (Tregs), B regulatory (Breg) cells, dendritic cells (DCs) and natural killer (NK) cells, and suppressed $CD4^+$/$CD8^+$ T cells, are involved in generating an immunosuppressive PMN (Patras et al., 2023a). Fibrinogen, a protein primarily involved in blood clotting, has several interactions with the immune system, even though it is not an immune cell. A growing body of studies has shown that fibrinogen, as well as members of the fibrinogen family, such as fibrinogen-like protein 1 (FGL1) and FGL2, bind well to the surface of macrophages and T cells that express integrin αMβ2 to exert a crucial role in regulating immunity (Takada et al., 2010; Hu et al., 2020). Fibrinogen is increasingly recognized for its crucial role in immunosuppression by regulating the function and activity of the immune cells, potentially promoting PMN formation.

2.1. Fibrinogen induces macrophage recruitment and polarization

Macrophages are versatile immune cells that play a crucial role in establishing the tumor microenvironment. They secrete growth factors and cytokines (e.g., EGF, IL-10, TGF-β) to support tumor cell proliferation, produce pro-angiogenic factors such as VEGF to enhance vascularization and interact with Tregs to prime an immunosuppressive environment (Vitale et al., 2019; Liu et al., 2021a). During the development of PMN, macrophages are recruited to and accumulate at the metastatic sites by factors released from tumor cells or other chemotactic signals, such as CXCL10 (Shang et al., 2022), CCL15 (Liu et al., 2019), CCL2, and STAT3 (Wang et al., 2017). This recruitment is essential for creating an immunosuppressive microenvironment in distant organs for incoming metastatic cells.

Fibrinogen has several effects on macrophages, influencing their function and behavior via directly binding to receptors on macrophages. As early as the beginning of the 20th century, Colvin *et al.* revealed that fibrinogen bound to the cell surface of macrophages plays an important role in cell-mediated immunity (Colvin and Dvorak, 1975). The binding interactions were subsequently reported in many studies, such as fibrinogen to the integrin $\alpha_M\beta_2$ (Vidal et al., 2012), CD11b/CD18 (Mac-1), and CD11c/CD18(p150/95) in inflammation and allergic diseases (Landers et al., 2019; Lukácsi et al., 2020). This dynamic binding and interplay are vital for the recruitment and polarization of macrophages, as confirmed by Ana *et al.* In her study, macrophages were recruited to the metastatic lung through tissue factor-induced clot formation during the PMN development in melanoma, although the specific receptor on macrophages that binds fibrinogen was not shown (Gil-Bernabé et al., 2012). Furthermore, the interaction with fibrinogen can lead to the release of specific cytokines and chemokines that further enhance macrophage accumulation, even M2 polarization. Jiang *et al.* revealed that fibrinogen attracted macrophage recruitments by inducing chemokines ICAM1 in gallbladder cancer liver metastasis (Jiang et al., 2022). Higher expression of FGL2, a member of the fibrinogen family, recruited the macrophages to glioma tumors through binding on the surface of macrophages with CD16 receptor and releasing chemokine CXCL7 (Yan et al., 2021). Additionally, FGL2 elicited the M2 phenotype of macrophage polarization, promoting the recruitment of various immune cells including $CD8^+$ T cells, B cells, and macrophages in esophageal and colorectal cancer (Yuan et al., 2021; Zhu et al., 2018). The M2-polarized macrophages support tumor progression not only through immune suppression, but also by facilitating inflammation, angiogenesis, and tissue remodeling (Liu et al., 2021a), all of which help to create a favorable PMN for metastatic cell colonization.

In addition to the above influences of fibrinogen on macrophages, macrophages can accordingly affect the production of fibrinogen, degradation of fibrin, and the remodeling of the fibrin matrix, which are critical for PMN establishment (Loscalzo, 1996). The latest study reported that tumor-associated macrophages can enhance the stabilization of FGL1 through NF-κB activation to facilitate the immune escape of T cells in liver PMN of colorectal cancer (CRC) (Li et al., 2023a). Yuan *et al.* revealed that the M2-like macrophages could help create an immunosuppressive tumor microenvironment by secreting FGL2 in esophageal cancer (Yuan et al., 2020). In the future, more evidence is needed to validate this reciprocal interaction between fibrinogen and macrophages in shaping PMN. Further study is needed to explore whether the conversion of fibrinogen to fibrin provides a scaffold that influences macrophage accumulation, as well as the effect of fibrinogen on macrophage polarization in shaping PMN.

2.2. Fibrinogen attenuates NK cell activity

NK cells, one important component of the innate immune system, play a key role in the immune response against tumors (Chiossone et al., 2018). NK cells engage in crosstalk with other immune cells, facilitating their recruitment, maturation, polarization, differentiation, and cytotoxicity (Coënon et al., 2024). For example, they bind to corresponding receptors on target cells to trigger apoptosis through the expression of TNF receptor ligands (e.g., TRAIL, FASL and TNFR) (Joshi and Sharabi, 2022); they release cytotoxic particles like perforin and granzyme B to induce tumor cell lysis and apoptosis (Ambrose et al., 2020); furthermore, they promote immune escape via interactions with coagulation factors and a variety of immune cells to help establish an immunosuppressive microenvironment in tumor progression (Rahimi et al., 2023). NK cells can directly kill tumor cells through the release of cytotoxic granules, and secrete various cytokines (e.g., IFN-γ, TNF-α) that enhance the immune response and help recruit other immune cells to the tumor sites (Wong et al., 2023). Numerous ligands and receptors on the surface of NK cells, such as NKp30 and MHC-I, play a critical role in regulating tumor escape (Ponath et al., 2021). In the tumor microenvironment, NK cell exhaustion impairs their ability to effectively recognize and eliminate tumor cells, allowing tumors to evade immune

surveillance (Jia et al., 2023).

In cancer, fibrinogen is often found in the tumor microenvironment, helping tumors evade immune surveillance by dampening NK cell activity, and promoting tumor growth and metastasis. A well-established theory is that tumor cells have a propensity to adhere to fibrinogen, forming a dense fibrin layer that shields them from NK cell cytotoxicity (Zheng et al., 2009). Tumor cells can provoke platelets to produce thrombin, and in the presence of thrombin, fibrinogen is converted into a protective fibrin matrix encasing the tumor cells (Zheng et al., 2009). In this process, both platelets and the coagulation cascade act as vital mediators. Fibrinogen and platelets are key components in clot formation, which create microthrombin around tumor cell emboli, thereby hindering NK cell-mediated tumor cell clearance and facilitating the development of an immunosuppressive microenvironment (Palumbo et al., 2005). Besides, tumor cells can induce NK cell functional tolerance via fibrinogen-like proteins, FGL1 and FGL2. Ostapchuk *et al.* revealed that the human pancreatic cancer cell (MiaPaCa2-TT) cultures significantly decreased NK cell IFNγ secretion, CD107a, and DNAM-1 expression, while increasing PD-1 expression, resulting in reduced cytotoxic activity and functions (Ostapchuk et al., 2022). In HCC, FGL1 can inhibit the function of $CD8^+$ T cells and NK cells by interacting with LAG-3 receptors (Xi et al., 2024). In this intricate process, NK cells and $CD8^+$ T cells exhibit reciprocal regulation. Deficiencies in CD8 + T cells compromise NK cell function, while NK cell impairments simultaneously disrupt $CD8^+$ T cell activity (Ostapchuk et al., 2022). A recent study shows that inhibiting the transcription factor CEBP-δ can enhance the expression of Vtn and ZC3H12D, reduce NK cell attachment to fibrinogen within blood vessels, boost NK cell cytotoxicity, and consequently, inhibit tumor metastasis (Yin et al., 2023). Nevertheless, the specific role of fibrinogen in NK cell activity and function in PMN formation has not been thoroughly investigated and more research is needed to identify it.

Fibrinogen helps shape an immunosuppressive PMN in tumor metastasis through its interactions with various immune cells, including macrophages, MDSCs, T cells, and NK cells. The schematic diagram of the mechanisms by which fibrinogen plays in PMN formation is **shown in** Fig. 1**.** There are still some problems to be solved: Do fibrinogen-derived factors (e.g., cytokines, chemokines, even fibrin that is produced from fibrinogen) participate in regulating the recruitment and function of immune cells? Are there more ligands and receptors for the binding of fibrinogen to immune cells? It remains unclear and requires further studies to be confirmed.

2.3. *Fibrinogen-like protein (FGL) elicits immunosuppression*

Fibrinogen-like protein (FGL) is a family of proteins that share structural similarities with fibrinogen, a key protein in blood clotting (Sulimai et al., 2022). Among the members of this family, FGL1 and FGL2 have attracted significant interest due to their emerging role in cancer biology, particularly in contributing to immune evasion (Yu et al., 2021). They have been identified as an immunosuppressive protein in shaping tumor microenvironment by interacting with immune checkpoints (like LAG-3 receptor) on T cells (Shi et al., 2021), or promoting immune cells migration to facilitate the metastatic spread of cancer cells to distant organs (Zhang et al., 2023a). Here is how FGL1 and FLG2 may contribute to an immunosuppressive PMN:

2.3.1. *FGL inhibits T cell activation and proliferation*

T cells play a crucial role in the immune response against cancer. Tumor cells and stromal components indeed create a complex microenvironment that can subtly regulate T cell function to evade immune surveillance (Kumagai et al., 2024). In this complex regulatory network, both **fibrinogen and its related proteins**, including FGL1 and FGL2, can have an inhibitory effect on T cell activation and proliferation so as to elicit an immune-suppressive environment in PMN formation.

The first demonstration that T cells can bind to fibrinogen was reported by Takada *et al.,* who showed that the fibrinogen gamma chain (gammaC399tr) bound to the integrin αMβ2 on T cells to attenuate autoimmunity (Takada et al., 2010). Fibrinogen can also bind or stimulate macrophage secretion of chemokines such as MIP-1α, MIP-1β, and MIP-2, to interact with T cell function (Smiley et al., 2001). The $CD8^+$ T cells frequently accumulate in glioblastoma fibrinogen-positive areas, indicating the diffusion of fibrinogen due to leaky vessels (Lohr et al.,

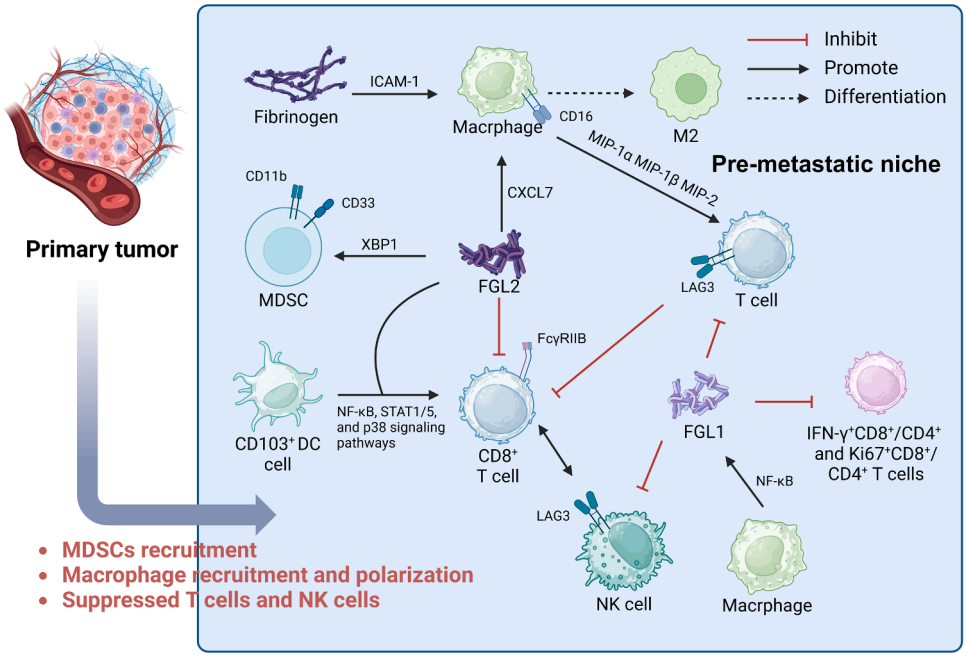

Fig. 1. Fibrinogen induces an immunosuppressive PMN. This diagram illustrates the immunosuppressive mechanisms of fibrinogen in shaping PMN. By promoting the recruitment of MDSCs, inducing the polarization of tumor-associated macrophages, and inhibiting the function of T cells and NK cells, fibrinogen creates an immunosuppressive microenvironment favorable for tumors and metastasis. These effects are mediated through various signaling pathways and molecular mechanisms, including cytokine networks, receptor-ligand interactions, and epigenetic modifications, collectively forming a complex immune regulatory network in the PMN.

2011). Even though there is still a lack of solid evidence regarding whether it can directly bind to T cells, FGL1 and FGL2, proteins of the fibrinogen family, are correlated to the inhibition of T cell activation via binding to the surface receptor of T cells in tumor metastatic environment (Qian et al., 2021). FGL1 is the major ligand for the lymphocyte-activation gene 3 (LAG3) receptor on the surface of T cells, their binding and interaction inhibits T-cell activation and proliferation (Chai et al., 2022). Mechanistically, the FGL1/LAG3 axis exerts tumor epithelial-to-mesenchymal transition, immune escape, and immune checkpoint blockade resistance in tumor progression (Wang et al., 2019a). In hepatocellular carcinoma, FGL1-LAG3 binding led to the exhaustion of $CD8^+$ T_{RM} cells and NK cells causing immune evasion in both in vitro and vivo experiments, which contributed to liver metastasis (Xi et al., 2024; Yang et al., 2023; Sun et al., 2024). In CRC liver metastasis, high FGL1 helped to facilitate an immunosuppression hepatic microenvironment via attenuating the infiltration of IFN-$\gamma^+CD8^+/CD4^+$ and $Ki67^+CD8^+/CD4^+$ T cells by TAM-OTUD1-FGL axis (Li et al., 2023a). Besides FGL1, FGL2 also plays a significant role, as it can bind to FcγRIIB on $CD8^+$ T cells to limit the T cell immune response by inducing apoptosis in these cells (Morris et al., 2020). FGL2 expressed by glioblastoma cancer cells inhibits the differentiation of $CD103^+$ dendritic cells to suppress $CD8^+$ T cells through NF-κB, STAT1/5, and p38 signaling pathways in brain tumors (Yan et al., 2019). Soluble FGL2 attenuated the activity of dendritic cells-mediated $CD8^+$ T cells and Th1 cells, inducing immunosuppression in the liver cancer microenvironment (Yang et al., 2019). These findings reveal FGL1 and FGL2 as novel immune targets for novel immunotherapies, which indirectly affect T-cell function by regulating antigen-presenting cells.

2.3.2. FGL promotes MDSCs recruitment

MDSCs, a heterogeneous population of myeloid cells that are expanded and activated in various pathological conditions, support tumor growth and metastasis by creating an immunosuppressive tumor microenvironment (Lasser et al., 2024). MDSCs directly downregulate L-selectin expression on naive T cells, impairing their ability to home to lymph nodes and tumor sites, which consequently inhibits anti-tumor immune responses (Hanson et al., 2009). In breast cancer, MDSCs not only suppress T cell activation but also enhance the stem-like properties of tumor cells. Through the interplay of the IL-6/STAT3 and NO/NOTCH signaling pathways, MDSCs confer stem-like characteristics on breast cancer cells, thereby promoting tumorigenesis and facilitating immune escape (Peng et al., 2016). Yet, MDSCs play a significant role in promoting the formation and maintenance of the PMN and supporting tumor metastasis due to their immunosuppressive function by inhibition of T cell function, production of reactive oxygen species, and expression of negative immune checkpoint molecules (Ya et al., 2022; Tang et al., 2021).

The fibrinogen protein family, FGL2, has been proven to be positively correlated with tumor size and the expression of MDSCs surface markers CD11b and CD33, and FGL2 maintained the undifferentiated state of bone marrow cells, thereby promoting the accumulation of MDSCs and suppressing the production of immune cells in hepatocellular carcinoma (Liu et al., 2021b). The latest research demonstrated that FGL2 regulated the differentiation and immunosuppressive function of MDSCs through the XBP1 signaling axis for regulating cholesterol biosynthesis in MDSCs in the colorectal cancer environment (Wu et al., 2023). The pharmacological inhibition of FGL2 or XBP1 lowers cholesterol levels in MDSCs, attenuates their immunosuppressive activity, and facilitates their differentiation into macrophages and dendritic cells. Nevertheless, the specific mechanism of fibrinogen's effect on MDSC remains unclear, and the authors only speculated that FGL2 may bind to FcγRIIB on the MDSC surface, as previous studies reported (Morris et al., 2020; Liu et al., 2008; Selzner et al., 2012). Could fibrinogen interact directly with cell surface receptors on MDSCs to influence their behavior in PMN? Are there fibrinogen-binding proteins on MDSCs that may mediate their adhesion to the ECM and to tumor cells in cancer PMN? Further investigations are needed to test this hypothesis.

2.4. Fibrinogen conversion to Fibrin promoting immune cells recruitment

As it is known to all, fibrinogen can convert to fibrin during clot formation, creating a fibrin matrix. This matrix not only helps to prevent further bleeding but also provides structural support for incoming cell adhesion and migration (Mosesson, 2005). Therefore, we speculated whether fibrinogen could be converted into fibrin to elicit immune cells recruiting to the tumor microenvironment. In the late 20th century, Harold et al. revealed that fibrin deposition in tumor stroma might serve as a barrier that interferes with tumor-associated antigens, to influence the host's immune response (Dvorak et al., 1983). Fibrin increasingly serves as a vital component of hydrogels, playing an important role in cancer therapy research (Zhou et al., 2024; Ke et al., 2024b). Han *et al.* reported that the fibrin deposition induced by tumor-derived tissue factor was associated with an increased percentage of $CD11b^+Gr\text{-}1^+$ MDSC recruitment within the lung cancer microenvironment; nevertheless, the specific mechanism of fibrin on MDSC accumulation is still unclear (Han et al., 2017). Recent studies have demonstrated that fibrin hydrogels can decrease the secretion of pro-inflammatory cytokines, such as TNF-α while enhancing the release of anti-inflammatory cytokines, such as IL-10, and promoting the infiltration of anti-inflammatory macrophages (Tanaka et al., 2019). Even though the studies about fibrinogen converting to fibrin to influence tumor immunity are still limited, it prompts us to explore and speculate about it. Future investigations should be conducted to explore the effect of fibrinogen converting to fibrin on MDSCs recruitment in cancer PMN formation.

Fibrinogen and its derivative fibrin can form a provisional matrix to provide a scaffold for cell migration and tissue repair (Li et al., 2024). Could it create a fibrous environment in metastatic organs, limiting T-cell access to antigen-presenting cells? Can a physical barrier formed by fibrinogen-related matrix structure limit the migration of effector T cells, thereby dampening immune responses to shape a suitable PMN for cancer cell colonization? Are there other receptors, except for integrin and LAG3 on T cells, that can bind to fibrinogen? Due to Treg cells expressing chemokine receptors (e.g., CCR4, CCR8, CCR5) (Li et al., 2020), are there corresponding ligands on fibrinogen that can bind to Treg cells, thereby secreting chemokines to recruit Treg cells to PMN? All of the above are unclear and need more research to confirm.

3. Fibrinogen promotes an inflammatory PMN

Fibrinogen is a crucial acute-phase reaction protein in chronic inflammatory diseases (Luyendyk et al., 2019). Elevated fibrinogen levels can indeed exacerbate the inflammatory state in cancer patients, creating a feedback loop that supports tumor growth. High levels of fibrinogen are often associated with systemic inflammation and can indicate a poor tumor prognosis (Randerson-Moor et al., 2024; Deng et al., 2023). Several studies have shown that circulating fibrinogen is the main inflammatory biomarker, and the fibrinogen/albumin ratio is significantly associated with TNM stage, metastasis, and tumor size in colorectal cancer (Ying et al., 2021; Wang et al., 2019b; Xu et al., 2023), gastric cancer (Lin et al., 2021; Ren et al., 2024; Zhang et al., 2023b; Jagadesham et al., 2017), and intrahepatic cholangiocarcinoma (Liu et al., 2021c; Xu et al., 2022).

Fibrinogen is a key inflammatory and prognostic indicator for tumor metastasis; the specific mechanisms of fibrinogen's effects on the tumor inflammatory microenvironment are as follows: Fibrinogen interacts with immune cells to mediate inflammation. There were several receptors present on immune cells that bind with fibrinogen, the interacting effect of which can promote inflammatory signaling pathways or secrete various pro-inflammatory cytokines (like IL-6 and TNF-α) to amplify the inflammatory response (Hsieh et al., 2017), For instance, through its interaction with macrophage TLR4, fibrinogen significantly upregulates the expression of chemokines such as MIP-1α, MIP-1β,

MCP-1, and MIP-2, thereby exacerbating the inflammatory environment (Smiley et al., 2001); through binding to macrophage integrin $\alpha_M\beta_2$, fibrinogen can activate FAK and inhibit p53/14-3-3σ to induce cell proliferation and growth of colorectal cancer (Sharma et al., 2021), which is also closely linked to various inflammatory responses via NF-κB activation (Murphy et al., 2021). In pancreatic cancer, fibrinogen interacts with pancreatic stellate cells to promote IL-8 production (Masamune et al., 2009), and the IL-8-CXCR2 signaling pathway is critical for enhancing PMN inflammation, increasing vascular permeability, and promoting tumor spread (Lee et al., 2012). Fibrinogen also exacerbates inflammation in lung cancer by stimulating the extracellular regulated kinase (ERK) pathway, which results in the phosphorylation of tyrosine 1185 on methyltransferase SET1A (Jiang et al., 2024). Additionally, the fibrinogen family (e.g., FGL1, FGL2) plays important roles in promoting inflammation within the tumor microenvironment. Studies have demonstrated that FGL1 and IL-6 protein levels in NSCLC are favorably linked with the TNM stage, and there is a substantial positive association between FGL1 expression and IL-6 abundance (Tian et al., 2023). In liver cancer, IFN-γ and IL-2 elevate FGL2 expression and activate prothrombin, further promoting tumor metastasis (Su et al., 2008).

Overall, the relationship between fibrinogen, inflammation, and cancer is intricate and underscores the need for further research to explore potential therapeutic interventions targeting these pathways. How does fibrinogen modulate the function of immune cell types beyond macrophages to amplify inflammation? What other pro-inflammatory mediators and signaling pathways are implicated in this process? These are questions that warrant further investigation.

4. Fibrinogen stimulates angiogenesis and vascular leakage in PMN

Angiogenesis, the formation of new blood vessels from existing ones, plays a crucial role in tumor development and progression (Liu et al., 2023a). During PMN formation, angiogenesis supplies adequate oxygen and nutrients for the PMN while also offering excretion channels. Enhanced vascular permeability facilitates cellular entry and exit, fostering interactions with the surrounding environment and promoting the growth of PMN (Wang et al., 2024a; Liu and Cao, 2016). Various cells (e.g., fibroblasts, endothelial cells) and molecules (e.g., VEGF, FGF, PDGF) regulate this complex process. The cancer-associated fibroblasts facilitate an angiogenic PMN through IncRNA SNHG5-mediated vascular permeability in breast cancer lung metastasis (Zeng et al., 2022). Colorectal cancer cells transfer miR-25-3p to endothelial cells via exosomes, subsequently regulating the expression of VEGFR2, ZO-1, occludin, and Claudin-5, which significantly enhances vascular permeability and promotes neovascularization in liver PMN (Zeng et al., 2018). Tumor exosomes contain pro-angiogenic factors like VEGF and IL-8 that stimulate endothelial cells to promote angiogenesis while also upregulating VE-cadherin, EGFR, and uPA, leading to disrupted cell connections and increased vascular permeability (Liu et al., 2023b).

When fibrinogen is converted to fibrin, it forms a fibrin matrix that provides a structural scaffold to support the migration and proliferation of endothelial cells (ECs), which are crucial for forming new blood vessels (Mosesson, 2005). Fibrin degradation product E stimulates the proliferation, migration, and differentiation of human skin microvascular endothelial cells, enhancing the angiogenic effects of VEGF and basic fibroblast growth factor (bFGF) (Bootle-Wilbraham et al., 2001). These factors are essential for stimulating endothelial cell proliferation and new blood vessel formation (Heinolainen et al., 2017). Furthermore, fibrinogen and its family (e.g. FGL1, FGL2) play a multifaceted role in angiogenesis in the establishment of the tumor microenvironment (Staton et al., 2003). In the late 20th century, Dvorak *et al.* revealed that fibrinogen and its fragments can significantly impact angiogenesis via the selective accumulation of fibrinogen and anti-fibrinogen antibodies in tumor stroma formation (Dvorak et al., 1992). High FGL2 expression was related to VEGF and IL-8 expression, promoting neovascular reaction in hepatocellular carcinoma HCCLM6 cells (Liu et al., 2012). Knockdown of FGL2 inhibits PAR2 activation and reduces downstream JNK phosphorylation, resulting in tumor cell cycle arrest, decreased expression of VEGF and IL-8, and suppression of tumor proliferation and angiogenesis (Chen et al., 2024). However, higher FGL1 induced the expression of VEGFA, VEGFB, and EGFR to inhibit vascularization in LKB1 mutant lung adenocarcinoma (Bie et al., 2019). Additionally, fibrinogen can attract immune cells, such as macrophages and MDSCs to PMN, as has been shown by us. These immune cells regulate tumor angiogenesis also by interacting with ECs which secrete additional pro-angiogenic factors (e.g., VEGF, EGF, FGF-2, and PDGF) (Yang et al., 2024; Hsu et al., 2019; Jetten et al., 2014; Barbera-Guillem et al., 2002), which play a crucial role in enhancing the PMN vascularization for tumor progression. As described above, fibrinogen, its fragments, and family members contribute to a vascularized PMN by promoting the release of pro-angiogenic factors. Further exploration should focus on the role of FGL2 and FGL1, which may exert opposite effects in the process of angiogenesis.

The hypercoagulable state of the tumor further provides a favorable environment for distant metastasis and can also promote the formation of tumor blood vessels (Unruh and Horbinski, 2020; Akita et al., 2015). During coagulation, thrombin cleaves fibrinogen, inducing an increase in D-dimer levels and the production of fibrin monomers, which covalently bond to form stable fibrin networks that participate in thrombosis (Tran et al., 2024; Zhao et al., 2020). Platelet activation leads to the production of thromboxane A2, the release of adenosine diphosphate, increased clotting activity, and eventual exposure of the αIIbβ3 integrin (Kuo et al., 2019). Fibrinogen activates the platelet-carried αIIbβ3 integrin conformation by recruiting cytoskeleton, adaptor proteins, and phosphorylated proteins, including Src-family kinases and Syk kinases, and transmitting signals to cell attachment sites (Durrant et al., 2017; Wu et al., 2015). Thrombin binds to PAR1 and PAR4 receptors, directly activating the PLC/PKCα/c-Src pathway and downstream transcription factor (p65), and activating NF-κB on the MMP-2 and MMP-13 promoters, which leads to tumor metastasis (Chen et al., 2010).

Nevertheless, recent reviews have discussed the role of fibrinogen as a “friend or foe” and have shown that fibrinogen can also weaken angiogenesis to impede tissue regeneration in some conditions (Melly and Banfi, 2022; Vilar et al., 2020). Whether it will also play a “friend” or “foe” role in tumor angiogenesis, just like FGL2 and FGL1, requires more attention in future studies. Regardless, understanding the role of fibrinogen in angiogenic PMN is crucial for developing effective therapies against cancer metastasis (Fig. 2). Continued research in this area may reveal novel targets for intervention and improve outcomes for patients with tumor metastasis.

5. Fibrinogen modulates ECM remodeling

ECM is a complex network of proteins and carbohydrates that provides structural and biochemical support to surrounding cells (Naba, 2024). It’s a critical component of tissue architecture consisting of various proteoglycans, fibrous proteins, and proteins linked with matricellular structures, which play several essential roles in structural support, cell adhesion, and tumor microenvironment remodeling (Popova and Jücker, 2022). When metastasizing to a new location, cancer cells must adhere to and survive in the new environment, simultaneously interacting with the ECM to facilitate tumor growth and dissemination (Sleeboom et al., 2024). The ECM’s dynamic role in shaping the tumor microenvironment, including recruiting immune cells (Patras et al., 2023a), increasing stiffness, and interacting with tumor-stromal cells, is pivotal for the PMN establishment, which can create a more hospitable environment for tumor cell colonization.

Here’s how fibrinogen contributes to the process of ECM remodeling in PMN. The deposition of fibrinogen and other adhesive glycoproteins in the ECM serves as a scaffold, facilitating the binding of growth factors

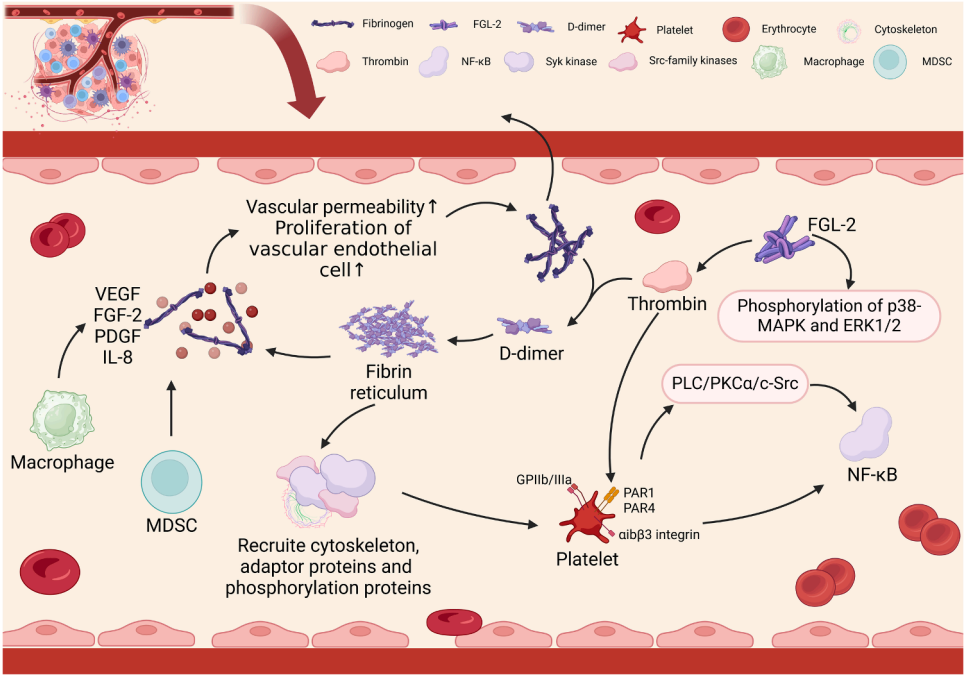

Fig. 2. Fibrinogen stimulates angiogenesis in PMN. This diagram illustrates the amplifying cycle and pathway through which fibrinogen facilitates PMN angiogenesis. Fibrinogen alters vascular permeability and promotes angiogenesis by engaging with various angiogenic factors (e.g. VEGF, FGF-2, PDGF). Immune cells further influence PMN angiogenesis by enhancing the production of inflammatory and pro-angiogenic factors, such as IL-8 and VEGF, through their interactions. A series of interactions between fibrinogen and platelets contribute to a hypercoagulable state, subsequently promoting PMN angiogenesis.

and stimulating cellular responses such as adhesion, proliferation, and metastasis during angiogenesis and tumor growth (Kwaan and Lindholm, 2019). Intercellular adhesion is crucial for ECM remodeling and tumor metastasis, influencing the survival, migration, and ultimate metastatic potential of tumor cells (Liu et al., 2023c). Research has demonstrated that fibrinogen plays a crucial role in sustaining the adherence and survival of melanoma cells in the metastasis of the lungs (Palumbo et al., 2000). In melanoma, fibrinogen mediates cell adhesion by interacting with ICAM-1 on melanoma cells and β2 integrin on polymorphonuclear leukocytes, thus promoting tumor metastasis (Zhang et al., 2011). Fibrinogen stimulates αvβ3 integrins in areas of intercellular contact, enhancing the stability of cell aggregation (Cluzel et al., 2005). Furthermore, fibrinogen promotes the recruitment of various cell types, including immune cells and fibroblasts, which are vital for ECM remodeling in PMN. For instance, MDSCs can activate the CXCR2 receptor on tumor cells by secreting the cytokine CXCL2, establishing a CXCL2-CXCR2 signaling axis that significantly influences ECM restructuring (Zhang et al., 2017; Yao et al., 2024a). Additionally, cancer-associated fibroblasts expressing sulfatase-1 enhance ECM deposition and angiogenesis through increased VEGFA release (Wang et al., 2024b). Fibrinogen can also modulate the activity of matrix metalloproteinases (MMPs)-2 and MMPs-9 to degrade ECM components such as collagen, elastin, and stromal glycoproteins (Zong et al., 2024), which helps create migration pathways for tumor cells, thereby enhancing tumor invasiveness in glioblastoma metastasis (Dzikowski et al., 2021). The latest study revealed that fibrinogen in the ascites promoted ECM protein organization of mesothelium to facilitate the implantation of ovarian cancer cells in peritoneal PMN via αV and α5β1 integrins (Laurent-Issartel et al., 2024).

Overall, fibrinogen is pivotal in shaping the ECM, influencing the PMN formation, and ultimately impacting cancer metastasis. It can form a provisional matrix scaffold; promote the recruitment of various types including immune cells and fibroblasts, which are essential for remodeling the ECM; enhance intercellular adhesion and influence the activity of MMPs, enzymes that degrade ECM components, thus playing a role in cancer progression. The tumor immunosuppressive microenvironment, inflammation, and angiogenesis are all closely interconnected with ECM remodeling (Patras et al., 2023b), nevertheless, the details of their interactions require further investigation. Investigating the role of fibrinogen in facilitating ECM remodeling in PMN enhances our understanding of the molecular mechanisms driving tumor metastasis and provides a crucial experimental foundation for developing novel anti-metastatic therapeutic strategies.

6. Fibrinogen post-translational modifications promote tumor progression

Fibrinogen undergoes various post-translational modifications (PTMs) such as glycosylation, citrullination, phosphorylation, and proteolytic cleavage, which not only enhance its role in coagulation but also contribute to tumor progression, particularly citrullination (De Vries et al., 2020). Citrullination is a PTM where the amino acid arginine is converted to citrulline, and this modification can alter the structure and function of fibrinogen, influencing cancer progression (Yao et al., 2024b). Fibrinogen, especially when citrullinated, can enhance the inflammatory responses, making it more conducive to tumor growth and metastasis. Rappu *et al.* found that fibrinogen was the most frequently citrullinated protein in cancer metastatic datasets, and its citrullination was associated with elevated levels of inflammation proteins (e.g., MMPs and PAD enzymes) (Rappu et al., 2022). Recently, Hiratsuaka et al. revealed that citrullinated fibrinogen, in complex with serum amyloid A, induced breast cancer extravasation and accumulation in the pre-metastatic lung in the humanized mice model (Han et al., 2023). This study highlights fibrinogen citrullination's role in promoting tumor metastasis by establishing PMN and suggests potential therapeutic strategies targeting fibrinogen PTMs to inhibit cancer spread. Additionally, studies have shown that the concentration of hydroxylated fibrinogen is significantly higher in the plasma of pancreatic cancer patients (Ono et al., 2009; Yoneyama et al., 2013), while phosphorylated fibrinogen level is elevated in ovarian cancer patients (Ogata et al., 2006). Prolyl 4-hydroxylated α-fibrinogen has been shown to be correlated with the production of αFG-565HyP, which is closely related to

cancer and inflammation (Ono et al., 2009). Totally, PTMs of fibrinogen are involved in tumor metastasis by influencing tumor cell adhesion, migration, and PMN formation. However, the specific mechanisms underlying this process remain to be further explored. More evidence is needed to fully understand how fibrinogen PTMs contribute to shaping PMN, particularly in processes like angiogenesis, immunosuppression and inflammation.

7. Fibrinogen as a therapeutic target and prognostic biomarker

Fibrinogen has emerged as a topic of interest in the tumor microenvironment. Although the role of fibrinogen in PMN is still being elucidated, its involvement in tumor biology suggests it could be a promising target for future therapeutic strategies. The effect that fibrinogen has on PMN development, e.g., immunosuppression, inflammation, angiogenesis, and ECM remodeling **(shown in Fig. 3)**, underscores its potential as a therapeutic target and prognostic biomarker in cancer treatment and management. Understanding these mechanisms further can help develop strategies to disrupt the supportive role of fibrinogen in tumors.

Researchers are exploring strategies to target fibrinogen or signaling pathways to disrupt PMN establishment in various cancer types (Table 1). Ana *et al.* have demonstrated that the coagulation cascade served to recruit monocytes and macrophages to lung PMN. That is, the inhibition of clot formation including platelet activation and fibrin deposition, might result in a decreased recruitment of monocytes/macrophages to inhibit the establishment of PMN in melanoma lung metastasis (Gil-Bernabé et al., 2012). Recently, several studies revealed the therapeutic effect of the fibrinogen family (e.g., FGL1 and FGL2) on tumor metastasis. For instance, disrupting the signaling axis of FGL2/XBP1 is an effective therapeutic intervention for diminishing MDSC recruitment to liver PMN (Wu et al., 2023), while targeting the TAM-OTUD1-FGL1 axis inhibits macrophage recruitment to the liver in colorectal cancer (Li et al., 2023a). In hepatocellular carcinoma, targeted therapy for the FGL2-CD11b/CD33 axis significantly decreased the number of MDSCs accumulation (Liu et al., 2021b), while targeting the FGL1-LAG-3 axis promoted the functions of $CD8^{+}$T and NK cell to enhance the antitumor effect in liver metastatic environment (Xi et al., 2024). Also, blocking the FGL2-CXCL7 paracrine loop effectively decreases macrophage recruiting to the tumor microenvironment in glioma (Yan et al., 2021), All the above fibrinogen-related targeting therapies would help to prevent PMN formation, thereby inhibiting tumor metastasis via attenuating recruitment of immune cells.

Additionally, developing strategies that target fibrinogen offers promising avenues for inhibiting inflammatory, angiogenic, and ECM remodeled-PMN formation. For example, targeting fibrinogen-induced FAK/NF-κB pathways in colorectal cancer might modulate inflammatory processes (Sharma et al., 2021), as FAK activation of NF-κB is closely related to inflammation effects (Murphy et al., 2021; Capece et al., 2022). Jiang *et al.* indicated that fibrinogen induces ICAM1 expression in gallbladder cancer to promote vascularization and endothelial permeability hence, blocking the fibrinogen/ICAM1 signaling axis might help to inhibit angiogenesis to decrease tumor migration (Jiang et al., 2022). Additionally, altering fibrinogen-induced

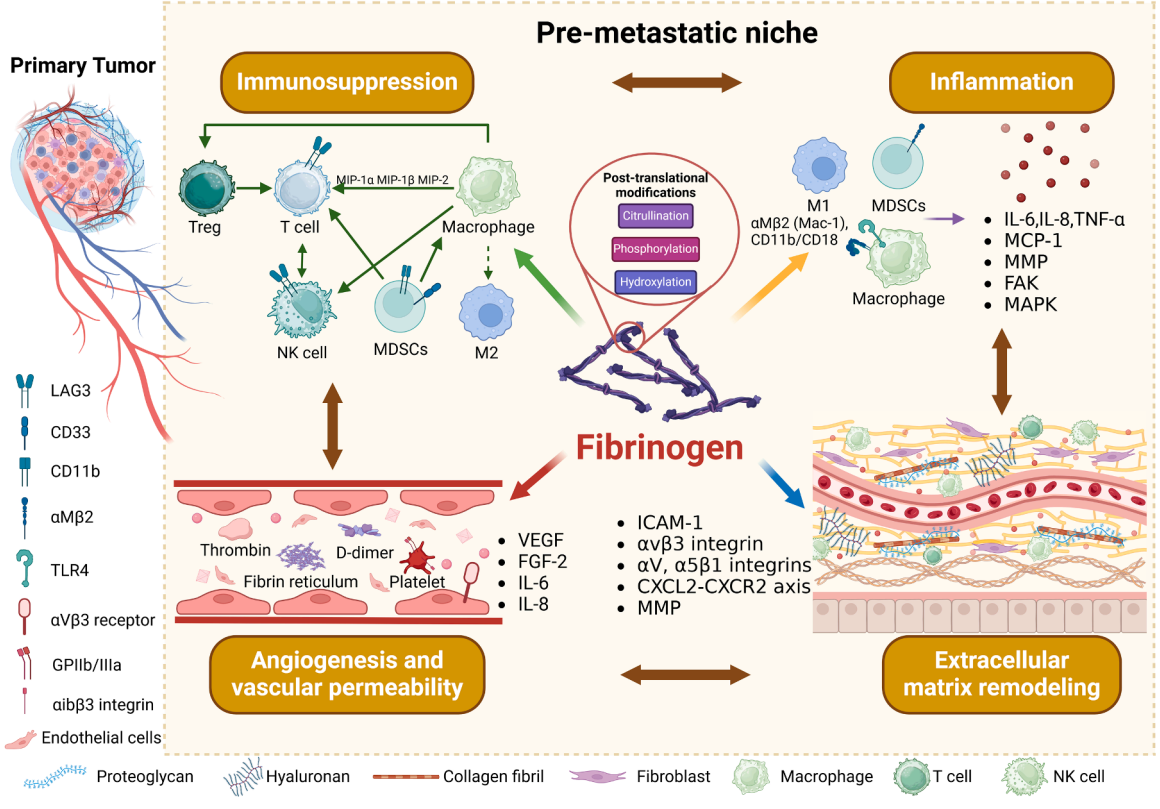

Fig. 3. Roles of fibrinogen in the formation and development of PMN. This diagram outlines the mechanisms by which fibrinogen facilitates tumor PMN formation. Fibrinogen primarily enhances PMN formation by fostering immune suppression, driving inflammation, promoting angiogenesis, and remodeling the ECM. Fibrinogen interacts with the immune cells including macrophages, MDSCs, T cells, and NK cells to induce immunosuppression. The immune cells, such as macrophages can be activated to secrete inflammatory factors (e.g., IL-6, IL-8, TNF-α, FAK, and MAPK), thereby amplifying inflammatory responses in metastatic organs. Additionally, fibrinogen and its fibrin degradation product stimulate the proliferation and migration of endothelial cells, secreting various pro-angiogenic factors like VEGF, EGF, and FGF-2 to induce angiogenesis. Fibrinogen also helps form scaffolds and modulate the ECM to increase tissue stiffness, enhancing cell aggregation stability and recruiting immune cells to shape a favorable PMN for tumor metastasis. Throughout this process, these four factors interact and influence one another, collectively contributing to PMN formation.

Table 1
Potential therapeutic strategies of tumor metastasis concerning fibrinogen and related signaling pathways in various cancer types.

Authors and published year	Research	Treatment/Molecular	Targets/pathways	Mechanisms
Hepatocellular carcinoma (HCC)				
Han, X. et al. 2024 (Han et al., 2024)	Animal models	FGA	PI3K/AKT pathway	FGA suppressed EMT via the PI3K/AKT pathway.
Xi, F. et al. 2024 (Xi et al., 2024)	Animal models	Anti-FGL1 treatment	FGL1	FGL1 reduces $CD8^+$ T and NK cell activity through its receptor LAG-3.
Yin, C. et al. 2023 (Yin et al., 2023)	Animal models	CEBPδ-siRNA treated anti-metastatic NK cells	Transcription factor CEBPδ	CEBPδ inhibited the NK cells' adherence to the fibrinogen-rich bed in the pulmonary arteries as well as their sensitivity to the ambient mRNA activator. ZC3H12D was restored as a result of CEBPδ suppression, which enhanced tumoricidal activity by ensnaring extracellular mRNA.
Hiratsuka, S. et al. 2018 (Hiratsuka et al., 2018)	Animal models	Liver-primed B220 CD11c NK1.1 cells	FX, IFN-γ	B220 CD11c NK1.1 cells expressed FX to remove fibrinogen deposits from pre-metastatic lungs, and simultaneously induced IFN-γ to combat metastatic tumors.
Liu, Y. et al. 2007 (Liu et al., 2007)	Animal models	CH50	αvβ3 signaling	CH50 exhibited inhibitory effects on MMP-9 and αvβ3 integrin, reducing αvβ3 integrin's ability to bind to fibrinogen and downregulating cdc2 expression.
Colon cancer				
Li J. et al. 2023 (Li et al., 2023a)	Animal models	Benzethonium chloride	TAM-OTUD1-FGL1 axis	FGL1 promotes metastatic tumor growth by reducing tumor-infiltrating T cells in the liver microenvironment.
Breast cancer				
Porshneva, K. et al. 2019 (Porshneva et al., 2019)	Animal models	Concurrent use of CORM-A1 and DETA/NO	CO, NO	By reducing the levels of endothelin-1, sICAM, and sE-selectin plasma, concurrent usage of CORM-A1 and DETA/NO was able to suppress the EMT process, downregulate platelets activation, and lower the binding of fibrinogen and vWf to platelets.
Porshneva, K. et al. 2018 (Porshneva et al., 2018)	Animal models	Combination Therapy with DETA/NO and Clopidogrel	TGF-β, TXB2, NO	Combination therapy reduced fibrinogen binding to resting platelets in the early phase of tumor progression.
Non-small cell lung cancer (NSCLC)				
Liu, T.Y. et al. 2024 (Liu et al., 2024)	Animal models	Anti-FGL1 treatment	FGL1, KDM4A/STAT3 pathway	STAT3 demethylated H3K9me3, KDM4A boosted the transcriptional activity of STAT3 and upregulated FGL1 expression.
Zhao B. et al., 2020 (Zhao et al., 2020)	Animal models	r-hirudin, DTIP	NF-κB signaling pathway	Thrombin induces VM formation through a PAR-1 mediated NF-κB signaling cascade.
Glioma tumor				
Yan J. et al. 2021 (Yan et al., 2021)	Animal models	-	CD16/SyK/PI3K/HIF1α	Inducing macrophages to secrete CXCL7 enhances the stem-like function of glioma cells.
Dzikowski et al. 2021 (Dzikowski et al., 2021)	Clinical sample study	Inhibition of MMP	MMP	Fibrinogen interacts with MMP-2 and MMP-9 to enhance tumor invasiveness.
Gallbladder cancer				
Jiang, C. et al. 2022 (Jiang et al., 2022)	Clinical sample study	Inhibit ICAM1	ICAM1	Fibrinogen promotes migration, and cell adhesion of gallbladder carcinoma cells by inducing ICAM1 expression.
Melanoma				
Hayashi, Y. et al. 2019 (Hayashi et al., 2019)	Animal models	Gal−3	Integrin β3	A higher expression of Gal-3 in cancer cells inhibits the ability of fibrinogen-mediated platelet adhesion, which in turn prevents tumor metastasis.
Akita, N. et al. 2015 (Akita et al., 2015)	Animal models	PCI	anticoagulant serine protease	PCI enhances tumor metastasis with its procoagulant characteristics.
Pancreatic ductal adenocarcinoma				
Huang, C. et al. 2017 (Huang et al., 2017)	Animal models	IL-35	GP130-STAT1 signaling pathway	IL-35 stimulates ICAM1 overexpression via a GP130-STAT1 signaling pathway, which increases endothelial adhesion and transendothelial migration via an ICAM1-fibrinogen-ICAM1 bridge.
Renal cell cancer				
Chai, D. et al. 2022 (Chai et al., 2022)	Animal models	PLGA/PEI-pFGL1/pCAIX co-immunization vaccine	CAIX, FGL1/LAG-3 pathway	The PLGA/PEI-pFGL1/pCAIX vaccination may effectively prevent kidney cancer metastasis by enhancing the immunological responses of DC-mediated multifunctional $CD8^+$ T cells.
Verheul, H.M. et al. 2007 (Verheul et al., 2007)	Animal models	VEGF Trap	VEGF signaling pathway	VEGF Trap-induced suppression of RENCA tumor growth was related to decreased MVD, decreasing fibrinogen leaking into the tumor microenvironment and reducing vascular leakage.

Abbreviation: HCC, hepatocellular carcinoma; FGA, fibrinogen alpha; EMT, epithelial-mesenchymal transition; FGL1, Fibrinogen-like protein 1; FX, coagulation factor X; BCMPs, breast cancer cell-derived microparticles; NO, nitric oxide; CO, carbon monoxide; CORM, carbon monoxide releasing molecules; vWf, von Willebrand Factor; TXB2, Thromboxane B2; ICAM-1, intercellular adhesion molecule; KDM4A, Lysine-specific demethylase 4A; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; Gal-3, Galectin-3; PCI, Protein C inhibitor; MMPs, matrix metalloproteinases; RENCA, renal cell carcinoma cells.

intercellular adhesion and inhibiting ECM degradation are promising therapeutic avenues for preventing PMN formation and tumor metastasis. Fibrinogen could be considered an effective therapy to reduce invasiveness by inhibiting MMP-2 and −9 production, which is critical for delaying ECM degradation and remodeling (Zong et al., 2024) in the glioblastoma microenvironment (Dzikowski et al., 2021). The latest study revealed that fibrin clot shields in tumor microenvironment act as a protective barrier against chemotherapeutic agents in pancreatic adenocarcinoma, hence, blocking the fibrin network formation could inhibit cancer cell mobility in tumor microenvironment to improve resistance to the anticancer agents (Tran et al., 2024). Overall, targeting fibrinogen to prevent PMN formation can provide a new potential therapeutic strategy to inhibit tumor metastases. Ongoing research is essential to better understand its mechanisms and optimize its use in cancer treatment.

It has been demonstrated that elevated levels of fibrinogen in the blood have been associated with poorer prognosis in several types of cancers, including lung (Ma and Wang, 2024), breast (Hu et al., 2024), colorectal (Yan et al., 2024), and pancreatic (Li et al., 2023b) cancers. This suggests that fibrinogen can serve as a valuable biomarker for cancer progression and patient outcomes. For instance, high fibrinogen expression in brain tumor cells in the glioblastoma microenvironment predicts tumor invasiveness and prognosis (Dzikowski et al., 2021). Fibrinogen in ascites is linked to peritoneal PMN formation in ovarian

cancer, suggesting its potential as a prognostic indicator for ovarian cancer peritoneal metastasis (Laurent-Issartel et al., 2024). Also, fibrinogen provided a matrix scaffold for pancreatic and breast adenocarcinoma cells to predict tumor progression and resistance to anticancer therapy (Tran et al., 2024). The Fibrinogen family, FGL2, served as biomarkers for liver metastasis in hepatocellular carcinoma by inducing MDSCs accumulated-microenvironment formation (Liu et al., 2021b). High plasma FGL1 levels predict poor outcomes and reduced checkpoint blockade therapy benefits by promoting immunosuppression of liver PMN in colorectal cancer (Li et al., 2023a), and might also be a novel biomarker to indicate angiogenesis in lung adenocarcinoma (Bie et al., 2019). While fibrinogen can indicate the tumor prognosis, it has some limitations as a prognostic biomarker: (1) Its levels can fluctuate in response to acute inflammation, infection or injury, or anticoagulant treatment (Luyendyk et al., 2019), potentially reducing its reliability in early assessment for tumor metastasis and survival. (2) Fibrinogen's prognostic value often relies on combining it with the immune-inflammation index (e.g., fibrinogen-to-albumin or -pre--albumin ratio (Ma and Wang, 2024; Ying et al., 2022), platelet-lymphocyte or neutrophil-lymphocyte ratio (Liu et al., 2020), limiting its independent effectiveness in early assessment. Despite these limitations, fibrinogen shows promise as a predictor of cancer prognosis, and its role in PMN formation remains a promising area for further research.

8. Perspective

Fibrinogen's involvement in immune modulation, migration, inflammation, angiogenesis, adhesion, and ECM remodeling underscores its significance in the development of PMN, making it a potential target for therapeutic strategies aimed at disrupting these processes. Nevertheless, our knowledge about the effect of fibrinogen on PMN formation is still limited. Many questions remain unclear and need to be further explored: (1) the focus has mainly been on the characteristics of PMN, including immunosuppression, inflammation, angiogenesis, and ECM remodeling; however, few reports about the role of fibrinogen on the PMN of lymph angiogenesis, organotropism, or metabolic reprogramming. (2) What other receptors on immune cells can bind to fibrinogen and exert their effects? (3) Elevated fibrinogen levels are closely linked to a state of chronic inflammation and tumor progression, whereas, the specific mechanism of fibrinogen on tumor inflammation is still unclear. (4) Can fibrinogen be packaged and transported by exosomes or EVs to exert their effect on distant metastatic organs? For instance, a recent study showed that fibrinogen is carried by plasma EVs and contributes to $CD8^+$ T cell immunity in mouse multiple sclerosis (Willis et al., 2019). (5) Although fibrinogen serves as a critical biomarker to evaluate tumor tumorigenesis and metastasis, it is unclear what the exact sensitivity and specificity of fibrinogen are for diagnosing and predicting tumor prognosis, Further evidence support from large samples and multiple centers is needed. (6) Fibrinogen levels can vary due to a range of factors, including infection and other inflammatory conditions. This variability might complicate its use as a reliable biomarker for targeted therapies. (7) The role of fibrinogen in tumor microenvironment, particularly in PMN formation, is multifaceted, influencing not just cancer cells but also immune cells, endothelial cells, and the ECM. This complex relationship needs more exploration. Addressing these challenges requires a nuanced understanding of fibrinogen's biology and its role in PMN of various cancer types, paving the way for more targeted and safer therapeutic strategies in clinics.

9. Conclusion

In this review, we first examine the roles of fibrinogen in PMN development from four perspectives: immunosuppression, inflammation, angiogenesis, and extracellular matrix remodeling. We emphasize its significance in shaping PMN and explore its therapeutic potential, offering new opportunities for targeting fibrinogen to prevent or treat metastasis. While many issues remain unresolved, the significance of fibrinogen in PMN formation is undeniable.

Abbreviations

PMN, pre-metastatic niche; ECM, extracellular matrix; EVs, extracellular vesicles; ICAM-1, intercellular adhesion molecule; IL, Interleukin; STAT, signal transducer and activator of transcription; FGA, fibrinogen alpha chain; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; NK, natural killer; FGL1, fibrinogen-like protein 1; FGL2, fibrinogen-like protein2; EGF, epidermal growth factor; LAG3, lymphocyte-activation gene 3; MIP, macrophage inflammatory protein; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated kinase; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; MMP, matrix metalloproteinase; PTMs, post-translational modifications.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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