haematologica
Journal of the Ferrata Storti Foundation

# When fibrinogen stops clotting and starts plotting: discovery of a new miRNA–GPCR axis in acute myeloid leukemia progression

*by Byeong Yeop Lee and Leonardo Salmena*

*Received: May 27, 2026.*
*Accepted: June 1, 2026.*

*Citation: Byeong Yeop Lee and Leonardo Salmena. When fibrinogen stops clotting and starts plotting: discovery of a new miRNA–GPCR axis in acute myeloid leukemia progression.*
*Haematologica. 2026 June 11. doi: 10.3324/haematol.2026.301296 [Epub ahead of print]*

*Publisher's Disclaimer.*
*E-publishing ahead of print is increasingly important for the rapid dissemination of science.*
*Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.*
*E-publishing of this PDF file has been approved by the authors.*
*After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval, the final version of the manuscript will then appear in a regular issue of the journal.*
*All legal disclaimers that apply to the journal also pertain to this production process.*

# When fibrinogen stops clotting and starts plotting: discovery of a new miRNA–GPCR axis in acute myeloid leukemia progression

Byeong Yeop Lee[1] and Leonardo Salmena[1]

[1] Department of Pharmacology and Toxicology, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada

**Correspondence**

leonardo.salmena@utoronto.ca

**Disclosures**

BYL and LS have no conflicts of interest to disclose.

**Contributions**

BYL designed the figure, BYL and LS wrote the manuscript

Elevated plasma fibrinogen (Fg) is commonly observed in patients with a wide range of malignancies and has been proposed as a prognostic biomarker across multiple tumor types (1). In this issue of *Haematologica*, Yang and colleagues describe a novel mechanism by which Fg promotes acute myeloid leukemia (AML) progression through microRNA-mediated suppression of the orphan G protein–coupled receptor (GPCR) GPR153 (Figure 1). This work begins to address whether elevated Fg acts as a *bona-fide* AML driver, in addition to its previously described roles in contributing to a pro-inflammatory and pro-coagulant tumor microenvironment (2). By delineating a functional role for plasma Fg in AML progression, the authors expand the current understanding, and provide a rationale for considering Fg-directed pathways in AML risk stratification and therapy.

Fg is a large soluble plasma glycoprotein that is cleaved by thrombin to generate insoluble fibrin, which polymerizes into a meshwork forming the structural scaffold of blood clots and stabilizing platelet aggregation during hemostasis and inflammatory responses (3). Due to its high blood concentrations (roughly 2–4 mg/mL), relative stability with a long plasma half-life, and the ease of measurement via standard clinical coagulation tests, Fg serves as a compelling candidate biomarker (3). Fg has been reported to support tumor growth and metastasis through multiple mechanisms. It promotes tumor expansion by accumulating within the tumor microenvironment and stimulating angiogenesis, thereby enhancing nutrient supply (1). Fg further enhances metastatic spread by establishing a matrix framework that allows malignant cells to migrate, infiltrate adjacent tissues, and penetrate the circulation (1). Furthermore, Fg contributes to immune evasion by forming protective coatings around tumor cells that limit recognition by natural killer cells and other immune effectors, while also amplifying inflammation and promoting a chronic pro-tumorigenic inflammatory milieu (4).

A recent meta-analysis of 2,947 AML patients found that patients with high plasma Fg levels had a 21% higher risk of death compared to those with lower levels (5). Notably, in acute promyelocytic leukemia (APL), a rare and distinct AML subtype, low Fg is a negative prognostic factor (6). This is attributed to APL-associated disseminated intravascular coagulation (DIC) and hyperfibrinolysis, which depletes Fg early in the disease course and increases severe bleeding risk (6). When APL cases are excluded, the prognostic association between Fg and AML becomes more consistent, with elevated Fg levels clearly correlating with worse outcomes. This was supported by a study of 215 patients with non-APL AML, in which higher Fg levels at diagnosis were associated with reduced overall survival, and both DIC and Fg levels emerged as independent prognostic factors (6). Despite these clinical associations, the direct functional role of Fg in promoting AML cell growth remains poorly defined.

In this study, Yang *et al.* provide the first evidence that plasma Fg could be a direct driver in AML progression (2). Using a combination of AML cell line experiments, Fg-deficient mouse models, and primary patient samples, the authors demonstrate that Fg enhances leukemic cell proliferation and migration. Mechanistically, Fg exposure increased phosphorylation of AKT and downstreamAKT/mTORC2 effectors, implicating activation of this signaling axis in Fg-mediated oncogenic effects.

To further define the underlying regulatory network, Yang *et al.* performed integrated RNA-seq and microRNA-seq analyses in Fg-treated AML models. This approach identified a coordinated signature in AML cells characterized by significant upregulation of miR-486-5p and downregulation of GPR153, suggesting a functional miRNA–mRNA interaction driving the oncogenic functions of Fg. miR-486-5p has been characterized as an oncogenic miRNA in AML, with elevated expression observed in cytogenetically normal AML and prior links to JAK/STAT

pathway activation (7,8). By contrast GPR153, an orphan G protein–coupled receptor, has not been functionally characterized in AML; however, transcriptomic analyses have shown that GPR153 expression is enriched in AML cases harboring the t(8;21) translocation, a subtype associated with favorable prognosis (9). In validating experiments, GPR153 knockdown enhanced AML cell growth and activated the AKT/mTOR pathway, phenocopying the effects of Fg treatment. Moreover, direct targeting of the GPR153 3′ UTR by miR-486-5p was confirmed, and inhibition of miR-486-5p increased GPR153 expression, altogether establishing an Fg–miR-486-5p–GPR153–AKT signaling axis in AML.

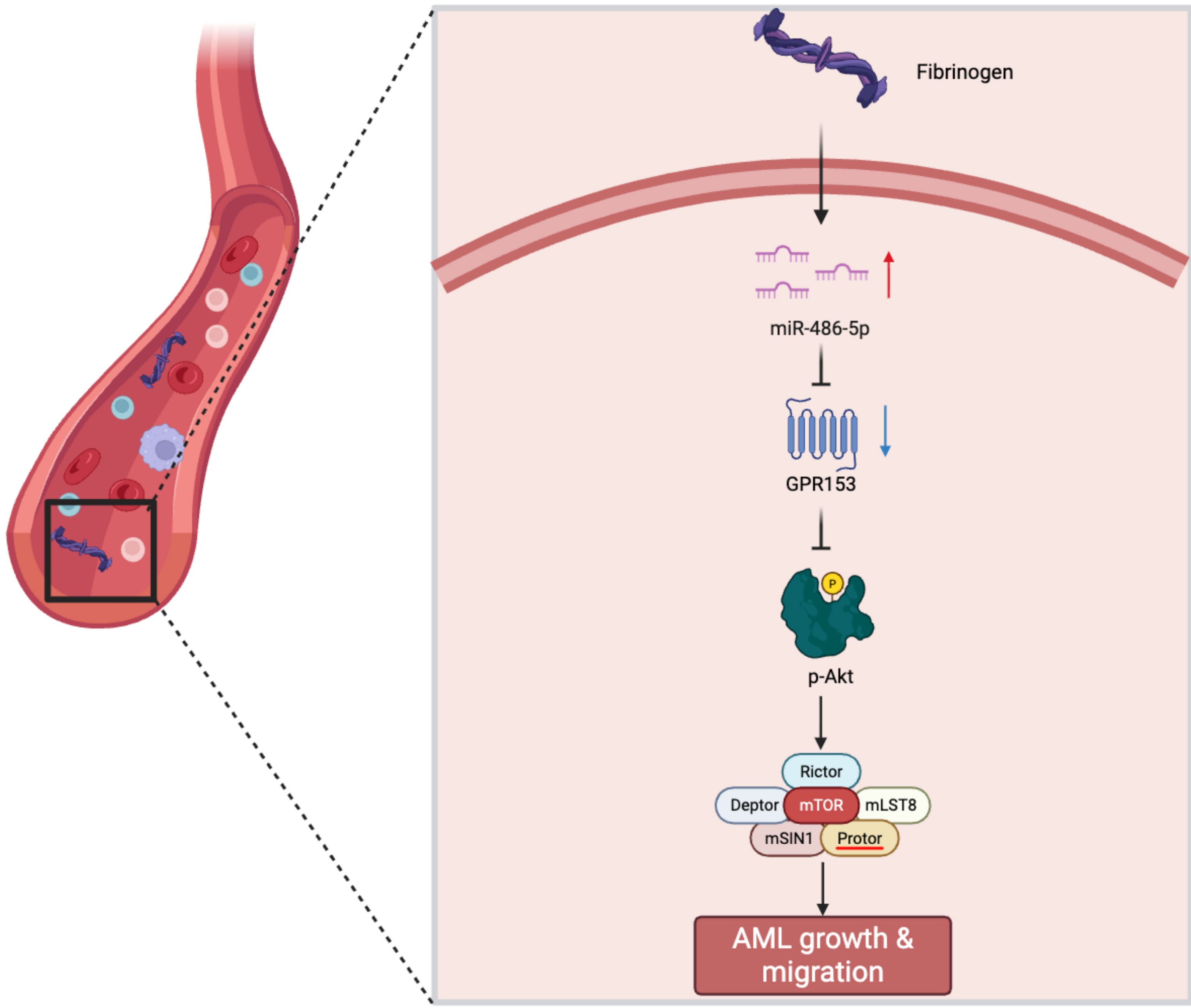
Yang *et al.* offer an important first look at the molecular circuitry through which plasma Fg may directly contribute to adverse prognosis in AML. While these findings are compelling, several key questions remain unresolved, including how Fg upregulates miR-486-5p and the precise mechanisms by which GPR153 constrains AKT/mTOR signaling. Nevertheless, this work reinforces plasma Fg as a promising prognostic biomarker in AML and highlights miR-486-5p as a potentially actionable oncogenic miRNA, particularly in patients with elevated plasma Fg or heightened AKT/mTOR pathway activity, which is observed in an estimated 60–80% of AML cases (10). Finally, the identification of GPR153 as a putative tumor suppressor that restrains AKT/mTOR signaling adds a novel component to the emerging Fg–miRNA–GPCR axis in AML biology.

## References


1. Wu X, Yu X, Chen C, et al. Fibrinogen and tumors. Front Oncol. 2024;14:1393599.
2. Yang M, You X, Zhao F, et al. Fibrinogen promotes acute myelogenous leukemia progression via miR-486/GPR153 axis. Haematologica. xxx
3. Wolberg AS. Fibrinogen and fibrin: synthesis, structure, and function in health and disease. J Thromb Haemost. 2023;21(11):3005-3015.
4. Zheng S, Shen J, Jiao Y, et al. Platelets and fibrinogen facilitate each other in protecting tumor cells from natural killer cytotoxicity. Cancer Sci. 2009;100(5):859-865.
5. Zhang Z, Zhang R, Qi J, et al. The prognostic value of plasma fibrinogen level in patients with acute myeloid leukemia: a systematic review and meta-analysis. Leuk Lymphoma. 2020;61(11):2682-2691.
6. Dai K, Zhang Q, Li Y, Wu L, Zhang S, Yu K. Plasma fibrinogen levels correlate with prognosis and treatment outcome in patients with non-M3 acute myeloid leukemia. Leuk Lymphoma. 2019;60(6):1503-1511.
7. Seyyedi SS, Soleimani M, Yaghmaie M, et al. Deregulation of miR-1, miR486, and let-7a in cytogenetically normal acute myeloid leukemia: association with NPM1 and FLT3 mutation and clinical characteristics. Tumour Biol. 2016;37(4):4841-4847.
8. Sha C, Jia G, Jingjing Z, Yapeng H, Zhi L, Guanghui X. miR-486 is involved in the pathogenesis of acute myeloid leukemia by regulating JAK-STAT signaling. Naunyn Schmiedebergs Arch Pharmacol. 2021;394(1):177-187.
9. Maiga A, Lemieux S, Pabst C, et al. Transcriptome analysis of G protein-coupled receptors in distinct genetic subgroups of acute myeloid leukemia: identification of potential disease-specific targets. Blood Cancer J. 2016;6(6):e431.
10. Zhang J, Gu Y, Chen B. Mechanisms of drug resistance in acute myeloid leukemia. Onco Targets Ther. 2019;12:1937-1945.

**Figure legends**

Figure 1. Schematic of the fibrinogen-induced AML signaling pathway. Extracellular fibrinogen within the leukemia microenvironment triggers the upregulation of miR-486-5p which subsequently inhibits GPR153 expression, relieving baseline repression on Akt and promoting its phosphorylation (p-Akt). Activated p-Akt drives downstream assembly of the mTORC2 complex (comprising mTOR, Rictor, mLST8, mSIN1, Protor, and Deptor), ultimately promoting AML cell growth and migration.


Fibrinogen
miR-486-5p
GPR153
P
p-Akt
Rictor
Deptor
mTOR
mLST8
mSIN1
Protor
AML growth & migration