https://www.scientificarchives.com/journal/journal-of-cellular-signaling

Journal of Cellular Signaling Mini Review

# Plasminogen Activator Inhibitor-1 and Oncogenesis in the Liver Disease

**Da-eun Nam[1], Hae Chang Seong[1], Young S. Hahn[1,2*]**

[1]Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, USA

[2]Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, USA

[*]Correspondence should be addressed to Young S. Hahn; ysh5e@virginia.edu

**Received date:** August 13, 2021, **Accepted date:** September 20, 2021



## Abstract

Hepatocellular carcinoma (HCC) is a significant cause of cancer mortality worldwide. Chronic hepatic inflammation and fibrosis play a critical role in the development of HCC. Liver fibrosis develops as a result of response to injury such that a persistent and excessive wound healing response induces extracellular matrix (ECM) deposition leading to HCC. PAI-1 is a fibrinolysis inhibitor involved in regulating protein degradation and homeostasis while assisting wound healing. PAI-1 presents increased levels in various diseases such as fibrosis, cancer, obesity and metabolic syndrome. Moreover, PAI-1 has been extensively studied for developing potential therapies against fibrosis. In the present review, we summarize how PAI-1 affects oncogenesis during liver disease progression based on the recently published literatures. Although there are controversies regarding the role of PAI-1 and approaches to treatment, this review suggests that proper manipulation of PAI-1 activity could provide a novel therapeutic option on the development of chronic liver disease via modulation of cancer stem-like cells (CSCs) differentiation.

**Keywords:** PAI-1, CSCs, HCV, Hepatocytes, HCC

## Plasminogen Activator Inhibitor-1 (PAI-1) Plays a Major Role in Regulating Protein Synthesis and Wound Healing Process

The plasminogen pathway regulates the homeostasis of ECM structures through fibrinolysis. Plasminogen is converted to plasmin by plasminogen activators (PAs): tissue-type PA (tPA) and urokinase-type PA (uPA) in various tissues, leading to proteolysis. Plasminogen activator inhibitor-1 (PAI-1) is a major regulator of the plasminogen pathway and is involved in regulating the tPA/uPA activity (Figure 1A). PAI-1 is a member of the serine protease inhibitor gene family, and is mainly produced by the endothelium and is expressed on various cell types such as adipocytes, macrophages, cardiomyocytes, and fibroblasts. PAI-1 gene expression is affected by numerous transcription factors and cell types, and is closely regulated by cytokines and growth factors including transforming growth factor-β (TGF-β), interleukin-1β (IL-1β), epidermal growth factor (EGF), and insulin. Specifically, injured cells undergo oxidative stress in response to various damage and induce TGF-β to activate fibroblast. Thereby TGF-β promotes the expression of PAI-1 and collagen genes contributing to develop fibrogenesis. Under normal condition, PAI-1 plays a role in the wound repair process by ECM protein deposition via inhibiting the activity of uPA/tPA/plasmin-dependent MMPs. This activity can be regulated by the formation of the trimeric PAI-1/uPA/uPAR complex or by binding to vitronectin (Figure 1A). However, sustained PAI-1 activity induces excessive accumulation of proteins which leads to an epithelial-mesenchymal transition (EMT) state as well as an increase in cell invasiveness that contributes to fibrosis (Figure 1B). It suggests that excessive PAI-1 activity promotes fibrosis development and thereby may facilitate progression of HCC. However, underlying mechanisms for the pathogenic role of PAI-1 in fibrosis are still unclear. Our recent report demonstrates a correlation between the increase of PAI-1 and CSC differentiation under pathological conditions caused by HCV. These results suggest a potential role for PAI-1 in liver disease progression [1].

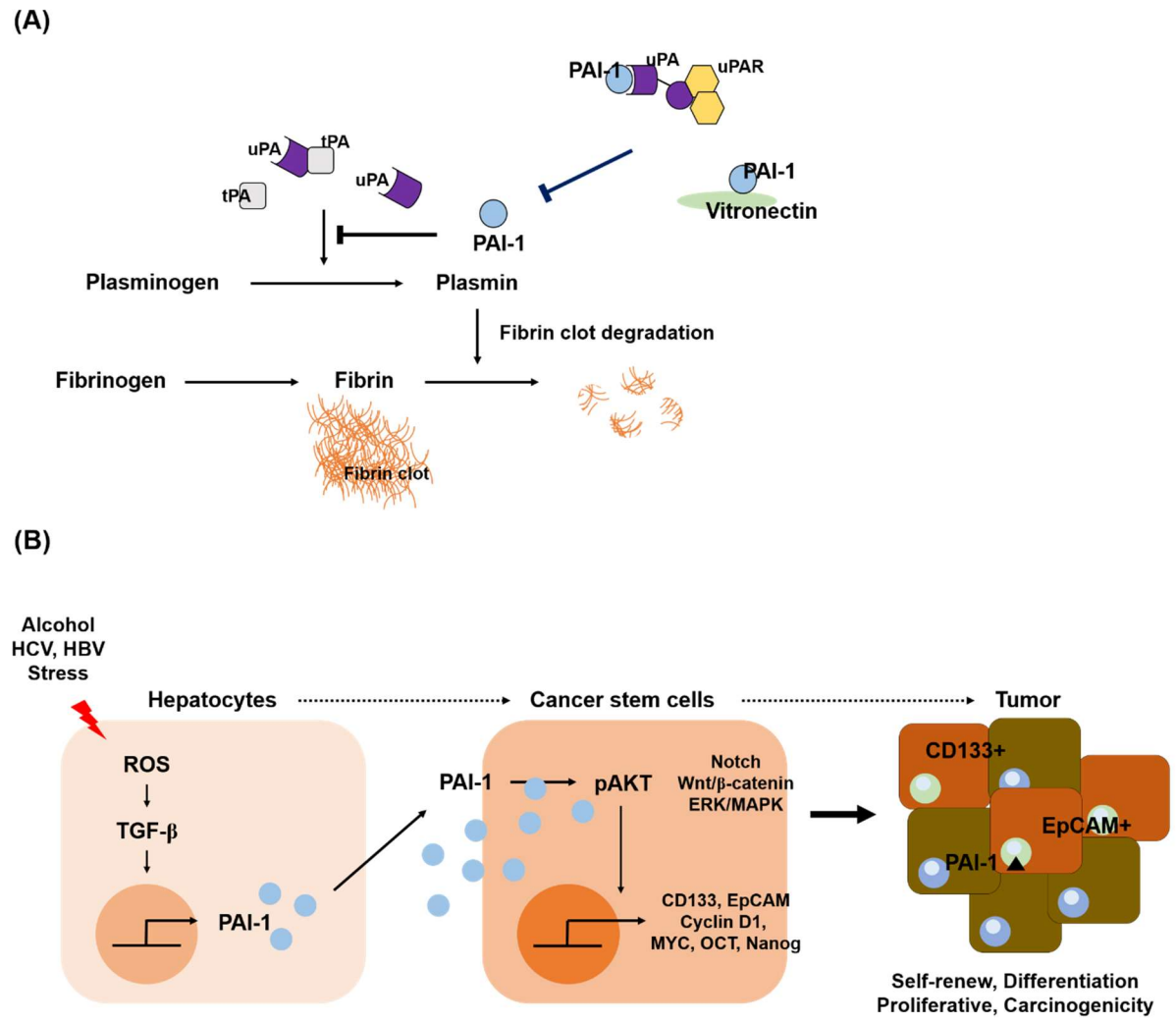


**Figure 1: Schematic showing regulation of PAI-1 activation and its role in hepatocytes. (A)** Plasminogen pathway and PAI-1 regulation in normal condition. **(B)** Hepatic injury caused by alcohol, HCV, stress, and a high-fat diet, stimulates TGF-β synthesis leading to PAI-1 expression in hepatocytes. The increase in PAI-1 level induces AKT activation and promotes differentiation into cancer stem-like cells (CSC) with characteristics such as self-renewal, cell proliferation and cell survival. Differentiation into CSC is accompanied by increased expression of numerous oncogenes such as Cyclin D1, MYC, OCT, and Nanog, and ultimately plays a key role in the progression of HCC.

## Pathogenic Role of PAI-1 in Chronic Liver Diseases

Abnormal wound healing response under the pathological condition leads to excessive accumulation of ECM proteins in the wound area, and is characterized by aggressive cell growth, hardening and scarring. Fibrosis is defined as a persistent and abnormal wound healing response that occurs while damaged cells are replaced. Therefore, a mechanism of liver tumorigenesis has been proposed based on its ability to induce tissue damage and proliferative repair. PAI-1, involved in collagen synthesis and ECM protein homeostasis, has been suggested as biomarker and a potential therapeutic target in the progression of fibrotic diseases, including cirrhosis and HCC. PAI-1 not only contributes to the fibrinolysis process, but also triggers signal transduction for cell transition, and cell migration in liver tissue [2,3]. The major profibrotic cytokine TGF-β induces PAI-1 expression, and increases collagen and ECM protein synthesis through activation of hepatic stellate cells (HSC). Reports on TGF-β synthesis stimulated by exogenously delivered PAI-1 could support the presence of PAI-1/TGF-β-positive feedback mechanism [4]. Recent study reported that increased PAI-1 level plays a crucial role in angiogenesis and tumor growth induced by TGF-β stimulation in the endothelium

[5], and showed that increased PAI-1 along with TGF-β exacerbated fibrosis in mouse models [6]. Genetic deletion of PAI-1 attenuates high-fat diet induced hepatic steatosis [7]. Oral administration of the PAI-1 inhibitor TM5275 attenuates liver fibrosis under the metabolic syndrome in mice [8]. Moreover, there was a significant increase in PAI- expression in chronic HCV patients with HCC/cirrhosis [9]. Direct-acting antiviral (DAA) therapy resulted in a significant decrease in serum PAI-1 from patients with HCV related chronic liver disease compared to chronic HCV patients without treatment [10]. Notably, a recent study identified that an increase in PAI-1 by HCV infection induces AKT activation, which can promote differentiation into cancer stem-like cells (CSC) from hepatocytes [1]. These results provide strong evidence that increased PAI-1 in liver disease may further exacerbate the progression to HCC by engaging in differentiation of the CSC phenotype.

## Liver Cancer Stem-like Cells

CSC are known to be cancer-propagating cells involved in tumor metastasis as they are characterized by self-renewal, cell proliferation and cell survival. CSC have been identified in several tumors such as liver, lung, breast, and pancreatic cancers [11,12]. Several recent studies strongly supported the role of CSC as specialized cells in initiating, maintaining, and giving anticancer drug resistance in liver tumors. Recent studies have identified the role of the CSC as well as their specific markers in the liver disease progression [11], and further on it has been confirmed that increased CSC properties increased EMT from HCV-infected hepatocytes [13-15]. Studies are still ongoing on investigating CSC differentiation and characteristics in liver disease to elucidate clear mechanisms involved in the progression into CSC state. Human Differentiated Protein 133 (CD133), EpCAM, CD44, and CD90 are known as representative markers of a CSC state in various tumor tissues, including HCC [16-18]. CD133+ liver cancer cells showed more powerful capacity in proliferation than CD133- liver cancer cells, and higher levels of pAKT were identified in CD133+ cancer cells than in CD133- cancer cell [19-21]. The PI3K/AKT pathway may be involved in activation through the interaction between Src (Proto-oncogene tyrosine-protein kinase) of CD133 and P85 [22,23]. Epithelial cell adhesion molecule (EpCAM) is a single transmembrane glycoprotein overexpressed in various tumor types, and is also known as a representative marker of CSC status in liver cancer [24,25]. EpCAM induces cell plasticity within epithelial tissues by weakening cadherin-mediated cell adhesion, which can promote cell proliferation and motility during tumor progression [26]. Moreover, excessive EpCAM expression induces cell proliferation with c-MYC known as a carcinogenic transcription factor. Cell cycle protein Cyclin D1 and pluripotency markers such as Octamer 4 (Oct4) and Nanog, are also reported to be positively correlated with EpCAM [27,28]. Notably, EpCAM-positive cells isolated from HCC patients showed strong CSC features like differentiation and self-renewal properties [16,29]. We observed that HCV-associated elevation of PAI-1 levels induces AKT activation, leading to upregulation of CSC markers including CD133, EpCAM, and oncogenes (eg, MYC, Nanog, OCT, and Cyclin D1) in hepatocytes (Figure 1B). Importantly, inhibition of PAI-1 expression interfered with the progression of the CSC state and AKT activation in HCV-infected hepatocytes [13]. These results suggest that HCV infection in hepatocytes increases cell invasiveness and mobility by stimulating AKT activation through PAI-1 upregulation. It implicates that the manipulation of PAI-1 activity could provide potential therapeutics to prevent the development of HCV-associated chronic liver diseases.

## Therapeutic Strategy

Regulation of protein synthesis is a key system for maintaining cellular homeostasis, therefore abnormal protein synthesis/degradation is inevitably linked to diseases such as thrombosis, fibrosis, and cancer. Numerous studies demonstrate that PAI-1 is significantly elevated in most human cancer. The increased PAI-1 level is positively correlated with poor clinical outcome in patients with breast, ovarian, non-small cell lung cancers, and HCC [30-34]. Particularly, PAI-1 level is significantly elevated in plasma from patients with cirrhosis and hepatocellular carcinoma following HCV infection compared to that of uninfected healthy donors [10,35]. Given this clinical importance of PAI-1 levels related to severity of human diseases, inhibitors have been synthesized and some inhibitors are under clinical trials in various diseases including ovarian cancer, alzheimer's disease, cardiovascular disease, pulmonary fibrosis renal diseases and liver diseases [36-39].

The most notable drugs are tiplaxtinin (PAI-039) and TM series. Tiplaxtinin has not been successful in human clinical trials because of its unfavorable risk-benefit ratio, potential for bleeding disorders, and the need for stringent dose control. However, both drugs are still widely used in preclinical research and there have been efforts to develop new drugs that share the same mechanism of action. PAI-1 levels are elevated in various diseases and is associated with a poor prognosis [40-44], whereas in some models of plasminogen system deficiency it has reported the opposite effect [45-47)]. For instance, human SERPINE1 mutations caused bleeding disorders due to poor blood coagulation [48]. In contrast, complete inactivation of SERPINE1 mutations reduced the prevalence of metabolic diseases and contributed to increased survival rate [49]. Additionally, while an increase in serum PAI-1 levels has a positive correlation between mortality rates in HCV-

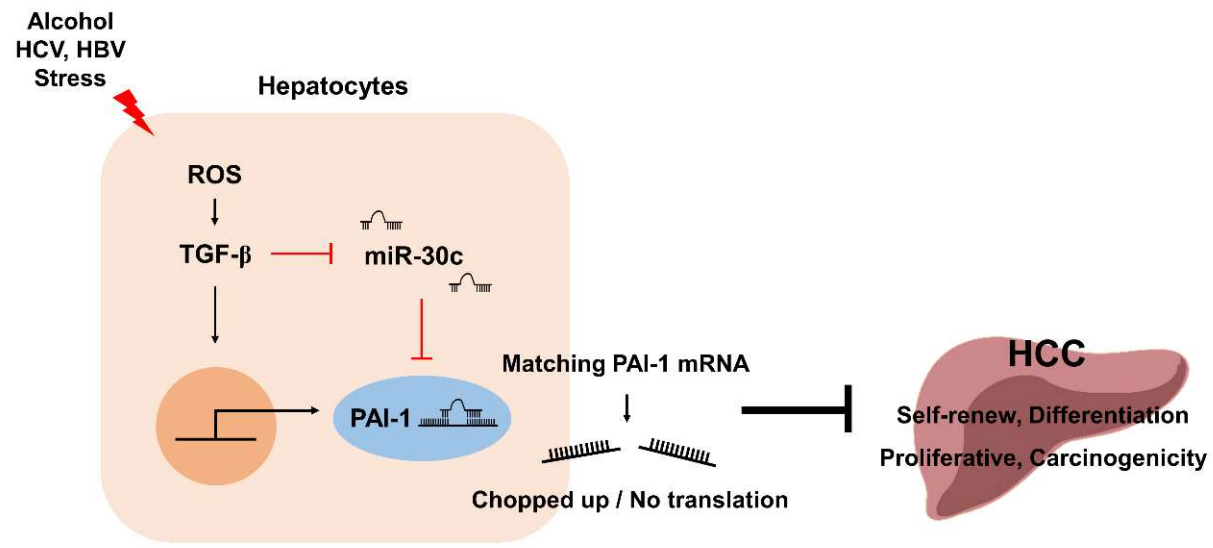


**Figure 2:** Schematic diagram showing the potential for therapeutic drug development using the pathway to inhibit PAI-1 expression by miR-30c.

infected liver cirrhosis/HCC patients [10,50], other study suggested that HCV viruses may downregulate PAI-1 expression to promote replication [45]. Although the ultimate clinical goal is to treat or prevent disease by modulating PAI-1 activity, these opposing results raise concern that excessive control of PAI-1 may lead to negative consequences on disease progression.

Targeting PAI-1 can be subtle since PAI-1 is involved in extensive biological processes. Most of PAI-1 inhibitors act in a reversible manner, either by directly blocking the PAI-1 active domain or the docking site of PAI-1 thereby eliminating or converting tPA/uPA activity to inactive PAI-1 [51,52]. Thus, it would be worthwhile to develop potential drugs targeting PAI-1-associated signaling pathways and/or human-derived PAI-1 regulators like microRNAs. Hepatocyte differentiation into CSC and its related signaling pathway including PI3K/AKT, Wnt/β-catenin, MAPK/ERK, ROS, Notch, and TGF-β, may provide insight on the development of therapeutic agents targeting PAI-1. Furthermore, microRNAs can be considered as another approach to manipulate the expression of PAI-1. Previous studies have reported that microRNA-30c (miR-30c) is involved in the differentiation and activation of hepatocytes and HSC. miR-30c can downregulates PAI-1 expression by binding directly to the 3'-UTR. In particular, it has been reported that miR-30c plays a role in inhibiting collagen synthesis in fibroblasts [53, 54], and TGF-β downregulates miR-30c expression in endothelial cells and HSC [5,55]. Interestingly we observed that inhibition of PAI-1 expression by miR-30c interfered the differentiation into CSC and AKT activation in HCV-infected hepatocytes [13]. This suggests that controls other factors related to PAI-1 regulation may be a more promising strategy, given the limitations on the use of PAI-1 targeted drugs in clinical trials (Figure 2).

## Conclusions

PAI-1 has been studied to understand its pathogenic role in fibrosis and to use it as a therapeutic strategy. However, some conflicting results raise major risks and challenges for developing PAI-1-based new drugs. In particular, the instability and short half-life of PAI-I active form is problematic for exerting therapeutic effects in chronic diseases. Moreover, potential effects of PAI-1 inhibitors on hemostasis make therapeutic approaches difficult. These are important considerations for overcoming the limitations of clinical trials to develop effective PAI-1-based therapeutics. Extensive further research will be needed for the successful development of PAI-1 therapeutics to treat severe human diseases.

Our recent studies reenforce the clinical significance of PAI-1 and its role in oncogenesis of hepatocytes. In particular, the inhibitory effect of PAI-1 in liver fibrosis/HCC appears to be evident. Given the high level of PAI-1 expression and its pathogenic role in fibrosis, the development of therapeutic agents to modulate PAI-1 signaling pathways and specific molecules targeting for regulating PAI-1 expression would provide promising anti-fibrotic strategies.

## Abbreviations

PAI-1: Plasminogen Activator Inhibitor-1; CSC: Cancer Stem-like Cells; HCV: Hepatitis C Virus; HSC: Hepatic Stellate Cells; EMT: Epithelial-mesenchymal Transition; ECM: Extracellular Matrix, DAA: Direct-acting Antiviral

## Competing and Declaration of Interests

All listed authors have approved the manuscript and agreed with the submission. In addition, we declare no financial interest related to this work.

## Funding

We thank the members of the Hahn lab, especially Hae Chang Seong for providing critical advice on this work. This work was supported by NIH Grant (DK122737 to YSH).

## References

1. Nam DE, Angelucci A, Choi D, Leigh A, Seong HC, Hahn YS. Elevation of Plasminogen Activator Inhibitor-1 Promotes Differentiation of Cancer Stem-Like Cell State by Hepatitis C Virus Infection. J Virol. 2021;95(10).

2. Wing LR, Hawksworth GM, Bennett B, Booth NA. Clearance of T-Pa, Pai-1, and T-Pa-Pai-1 Complex in an Isolated Perfused-Rat-Liver System. J Lab Clin Med. 1991;117(2):109-14.

3. Zheng Q, Tang ZY, Xue QW, Shi DR, Song HY, Tang HB. Invasion and metastasis of hepatocellular carcinoma in relation to urokinase-type plasminogen activator, its receptor and inhibitor. J Cancer Res Clin. 2000;126(11):641-6.

4. Seo JY, Park J, Yu MR, Kim YS, Ha H, Lee HB. Positive Feedback Loop between Plasminogen Activator Inhibitor-1 and Transforming Growth Factor-Beta1 during Renal Fibrosis in Diabetes. Am J Nephrol. 2009;30(6):481-90.

5. McCann JV, Xiao L, Kim DJ, Khan OF, Kowalski PS, Anderson DG, et al. Endothelial miR-30c suppresses tumor growth via inhibition of TGF-beta-induced Serpine 1. J Clin Invest. 2019;129(4):1654-70.

6. Wang H, Zhang Y, Heuckeroth RO. PAI-1 deficiency reduces liver fibrosis after bile duct ligation in mice through activation of tPA. Febs Lett. 2007;581(16):3098-104.

7. Henkel AS, Khan SS, Olivares S, Miyata T, Vaughan DE. Inhibition of Plasminogen Activator Inhibitor 1 Attenuates Hepatic Steatosis but Does Not Prevent Progressive Nonalcoholic Steatohepatitis in Mice. Hepatol Commun. 2018;2(12):1479-92.

8. Noguchi R, Kaji K, Namisaki T, Moriya K, Kawaratani H, Kitade M, et al. Novel oral plasminogen activator inhibitor-1 inhibitor TM5275 attenuates hepatic fibrosis under metabolic syndrome via suppression of activated hepatic stellate cells in rats. Mol Med Rep. 2020;22(4):2948-56.

9. Benkheil M, Paeshuyse J, Neyts J, Van Haele M, Roskams T, Liekens S. HCV-induced EGFR-ERK signaling promotes a pro-inflammatory and pro-angiogenic signature contributing to liver cancer pathogenesis. Biochem Pharmacol. 2018;155:305-15.

10. Saraiva GN, do Rosario NF, Medeiros T, Leite PEC, Lacerda GD, de Andrade TG, et al. Restoring Inflammatory Mediator Balance after Sofosbuvir-Induced Viral Clearance in Patients with Chronic Hepatitis C. Mediat Inflamm. 2018;2018.

11. Xiao YH, Lin M, Jiang XM, Ye J, Guo T, Shi YJ, et al. The Recent Advances on Liver Cancer Stem Cells: Biomarkers, Separation, and Therapy. Anal Cell Pathol. 2017;2017.

12. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414(6859):105-11.

13. Kwon YC, Bose SK, Steele R, Meyer K, Di Bisceglie AM, Ray RB, et al. Promotion of Cancer Stem-Like Cell Properties in Hepatitis C Virus-Infected Hepatocytes. J Virol. 2015;89(22):11549-56.

14. Kwon YC, Sasaki R, Meyer K, Ray R. Hepatitis C Virus Core Protein Modulates Endoglin (CD105) Signaling Pathway for Liver Pathogenesis. J Virol. 2017;91(21).

15. Machida K, Tsukamoto H, Mkrtchyan H, Duan L, Dynnyk A, Liu HM, et al. Toll-like receptor 4 mediates synergism between alcohol and HCV in hepatic oncogenesis involving stem cell marker Nanog. P Natl Acad Sci USA. 2009;106(5):1548-53.

16. Yamashita T, Budhu A, Forgues M, Wang XW. Activation of hepatic stem cell marker EpCAM by Wnt-beta-catenin signaling in hepatocellular carcinoma. Cancer Res. 2007;67(22):10831-9.

17. Zhu Z, Hao XF, Yan MX, Yao M, Ge C, Gu JR, et al. Cancer stem/progenitor cells are highly enriched in CD133(+)CD44(+) population in hepatocellular carcinoma. Int J Cancer. 2010;126(9):2067-78.

18. Song W, Li H, Tao K, Li R, Song Z, Zhao Q, et al. Expression and clinical significance of the stem cell marker CD133 in hepatocellular carcinoma. Int J Clin Pract. 2008;62(8):1212-8.

19. Jang JW, Song Y, Kim SH, Kim JS, Kim KM, Choi EK, et al. CD133 confers cancer stem-like cell properties by stabilizing EGFR-AKT signaling in hepatocellular carcinoma. Cancer Lett. 2017;389:1-10.

20. Sartelet H, Imbriglio T, Nyalendo C, Haddad E, Annabi B, Duval M, et al. CD133 expression is associated with poor outcome in neuroblastoma via chemoresistance mediated by the AKT pathway. Histopathology. 2012;60(7):1144-55.

21. Wang YK, Zhu YL, Qiu FM, Zhang T, Chen ZG, Zheng S, et al. Activation of Akt and MAPK pathways enhances the tumorigenicity of CD133+primary colon cancer cells. Carcinogenesis. 2010;31(8):1376-80.

22. Jang JW, Song Y, Kim SH, Kim J, Seo HR. Potential mechanisms of CD133 in cancer stem cells. Life Sci. 2017;184:25-9.

23. Wei YY, Jiang YZ, Zou F, Liu YC, Wang SS, Xu N, et al. Activation of PI3K/Akt pathway by CD133-p85 interaction promotes tumorigenic capacity of glioma stem cells. P Natl Acad Sci USA. 2013;110(17):6829-34.

24. Baeuerle PA, Gires O. EpCAM (CD326) finding its role in cancer (vol 96, pg 417, 2007). Brit J Cancer. 2007;96(9):1491-.

25. Munz M, Murr A, Kvesic M, Rau D, Mangold S, Pflanz S, et al. Side-by-side analysis of five clinically tested anti-EpCAM monoclonal antibodies. Cancer Cell Int. 2010;10.

26. Wu CJ, Mannan P, Lu M, Udey MC. Epithelial Cell Adhesion Molecule (EpCAM) Regulates Claudin Dynamics and Tight Junctions. J Biol Chem. 2013;288(17):12253-68.

27. Chaves-Perez A, Mack B, Maetzel D, Kremling H, Eggert C, Harreus U, et al. EpCAM regulates cell cycle progression via control of cyclin D1 expression. Oncogene. 2013;32(5):641-50.

28. Ng VY, Ang SN, Chan JX, Choo ABH. Characterization of Epithelial Cell Adhesion Molecule as a Surface Marker on Undifferentiated Human Embryonic Stem Cells. Stem Cells. 2010;28(1):29-35.

29. Terris B, Cavard C, Perret C. EpCAM, a new marker for cancer stem cells in hepatocellular carcinoma. J Hepatol. 2010;52(2):280-1.

30. Look MP, van Putten WL, Duffy MJ, Harbeck N, Christensen IJ, Thomssen C, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. J Natl Cancer Inst. 2002;94(2):116-28.

31. Niki M, Yokoi T, Kurata T, Nomura S. New prognostic biomarkers and therapeutic effect of bevacizumab for patients with non-small-cell lung cancer. Lung Cancer (Auckl). 2017;8:91-9.

32. Harbeck N, Schmitt M, Meisner C, Friedel C, Untch M, Schmidt M, et al. Ten-year analysis of the prospective multicentre Chemo-No trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. Eur J Cancer. 2013;49(8):1825-35.

33. Mazzoccoli G, Pazienza V, Panza A, Valvano MR, Benegiamo G, Vinciguerra M, et al. ARNTL2 and SERPINE1: potential biomarkers for tumor aggressiveness in colorectal cancer. J Cancer Res Clin. 2012;138(3):501-11.

34. D'Amico M, Pasta F, Pasta L. Thrombophilic genetic factors PAI-1 4G-4G and MTHFR 677TT as risk factors of alcohol, cryptogenic liver cirrhosis and portal vein thrombosis, in a Caucasian population. Gene. 2015;568(1):85-8.

35. Hayashi T, Kamogawa A, Ro S, Yamaguchi K, Kobayashi Y, Takahashi Y, et al. Plasma from patients with cirrhosis increases tissue plasminogen activator release from vascular endothelial cells in vitro. Liver. 1998;18(3):186-90.

36. Flevaris P, Vaughan D. The Role of Plasminogen Activator Inhibitor Type-1 in Fibrosis. Semin Thromb Hemost. 2017;43(2):169-77.

37. Samarakoon R, Higgins SP, Higgins CE, Higgins PJ. The TGF-beta1/p53/PAI-1 Signaling Axis in Vascular Senescence: Role of Caveolin-1. Biomolecules. 2019;9(8):341.

38. Samad F, Ruf W. Inflammation, obesity, and thrombosis. Blood. 2013;122(20):3415-22.

39. Li S, Wei X, He J, Tian X, Yuan S, Sun L. Plasminogen activator inhibitor-1 in cancer research. Biomed Pharmacother. 2018;105:83-94.

40. Krause MP, Moradi J, Nissar AA, Riddell MC, Hawke TJ. Inhibition of Plasminogen Activator Inhibitor-1 Restores Skeletal Muscle Regeneration in Untreated Type 1 Diabetic Mice. Diabetes. 2011;60(7):1964-72.

41. Tamura Y, Kawao N, Shimoide T, Okada K, Matsuo O, Kaji H. Role of plasminogen activator inhibitor-1 in glucocorticoid-induced muscle change in mice. J Bone Miner Metab. 2018;36(2):148-56.

42. Ma LJ, Fogo AB. PAI-1 and kidney fibrosis. Front Biosci-Landmrk. 2009;14:2028-41.

43. Khoukaz HB, Ji Y, Braet DJ, Vadali M, Abdelhamid

AA, Emal CD, et al. Drug Targeting of Plasminogen Activator Inhibitor-1 Inhibits Metabolic Dysfunction and Atherosclerosis in a Murine Model of Metabolic Syndrome. Arterioscl Throm Vas. 2020;40(6):1479-90.

44. Arteel GE. New role of plasminogen activator inhibitor-1 in alcohol-induced liver injury. J Gastroen Hepatol. 2008;23:S54-S9.

45. Yang CH, Li HC, Ku TS, Wu PC, Yeh YJ, Cheng JC, et al. Hepatitis C virus down-regulates SERPINE1/PAI-1 expression to facilitate its replication. J Gen Virol. 2017;98(9):2274-86.

46. Suelves M, Vidal B, Serrano AL, Tjwa M, Roma J, Lopez-Alemany R, et al. uPA deficiency exacerbates muscular dystrophy in MDX mice. J Cell Biol. 2007;179(1):165.

47. Koh TJ, Bryer SC, Pucci AM, Sisson TH. Mice deficient in plasminogen activator inhibitor-1 have improved skeletal muscle regeneration. Am J Physiol-Cell Ph. 2005;289(1):C217-C23.

48. Fay WP, Parker AC, Condrey LR, Shapiro AD. Human plasminogen activator inhibitor-1 (PAI-1) deficiency: Characterization of a large kindred with a null mutation in the PAI-1 gene. Blood. 1997;90(1):204-8.

49. Khan SS, Shah SJ, Klyachko E, Baldridge AS, Eren M, Place AT, et al. A null mutation in SERPINE1 protects against biological aging in humans. Sci Adv. 2017;3(11):eaao1617.

50. El Edel RH, Essa ES, Essa AS, Hegazy SA, El Rowedy DI. Serum PAI-1 and PAI-1 4G/5G Polymorphism in Hepatitis C Virus-Induced Cirrhosis and Hepatitis C Virus-Induced Hepatocellular Carcinoma Patients. Viral Immunol. 2016;29(9):510-5.

51. Leik CE, Su EJ, Nambi P, Crandall DL, Lawrence DA. Effect of pharmacologic plasminogen activator inhibitor-1 inhibition on cell motility and tumor angiogenesis. J Thromb Haemost. 2006;4(12):2710-5.

52. Gorlatova NV, Tale JM, Elokdah H, Li DH, Fan's K, Warnock M, et al. Mechanism of inactivation of plasminogen activator inhibitor-1 by a small molecule inhibitory. J Biol Chem. 2007;282(12):9288-96.

53. Abonnenc M, Nabeebaccus AA, Mayr U, Barallobre-Barreiro J, Dong XB, Cuello F, et al. Extracellular Matrix Secretion by Cardiac Fibroblasts Role of MicroRNA-29b and MicroRNA-30c. Circ Res. 2013;113(10):1138.

54. Duisters RF, Tijsen AJ, Schroen B, Leenders JJ, Lentink V, van der Made I, et al. miR-133 and miR-30 Regulate Connective Tissue Growth Factor Implications for a Role of MicroRNAs in Myocardial Matrix Remodeling. Circ Res. 2009;104(2):170-U61.

55. Patel N, Tahara SM, Malik P, Kalra VK. Involvement of miR-30c and miR-301a in immediate induction of plasminogen activator inhibitor-1 by placental growth factor in human pulmonary endothelial cells. Biochem J. 2011;434:473-82.