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## Autophagy and Coagulation in Liver Cancer and Disorders

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### Abstract

The physiological role of autophagy in metabolism of the body involves both protein synthesis and degradation. The autophagy-lysosome and the ubiquitin-proteasome systems are the two major intracellular proteolytic mechanisms. Autophagy in hepatocytes is known to be quite active and contribute to its normal functions and the pathogenesis of liver diseases. The role of autophagy in liver diseases has been widely studied, and growing evidence has now shown that autophagy is involved in the pathogenesis of cirrhosis and hepatocellular carcinoma (HCC). However, the role of autophagy in the progression of liver fibrosis and prognosis of human HCC is not well known. Recent studies have demonstrated that tissue factor (TF) combined with coagulation factor VII (FVII) has a pathological role by activating a protease-activated receptor 2 (PAR2) for tumor growth. Autophagy-related LC3A/B-II formation induced by the inhibition of TF/FVII/PAR2 coagulation axis, particularly by FVII knockdown, was selectively mediated by the Atg7 induction. These results are consistent with clinical observations that indicate the important role of FVII activation in regulating autophagy in HCC. In this chapter, we discuss our findings in which FVII promotes growth and progression in HCC through ERK-TSC/mTOR signaling to repress autophagy and may play a pivotal role in conferring cirrhosis and other liver diseases.

**Keywords:** autophagy, coagulation, hepatocellular carcinoma, cirrhosis, tissue factor, factor VII, protease-activated receptor 2, mammalian target of rapamycin

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## 1. Introduction

Autophagy comprises some of the most fundamental reactions in which the cell sequesters part of its own material for degradation and converts proteins and lipids into life-preserving fuel through times of energy deprivation. In addition, the cell also uses autophagy to remove misfolded protein aggregates and dysfunctional organelles under certain stress conditions [1, 2]. During autophagy, multiple signaling pathways converge on the autophagy-related (Atg) proteins, mediating the formation of a double-membraned structure known as the autophagosome. Recruitment of the Atg12-Atg5 complex and microtubule-associated protein 1 light chain 3 (LC3) is essential for this process and correlates with the level of autophagy. These autophagosomes then fuse with lysosomes to form autolysosomes that lead to the degradation and recycling of their content [3]. Despite the general acceptance that autophagy is a protective mechanism toward cell survival, recent studies have shown an active role of autophagy in cell death [1]. Autophagic cell death is known as the type II programmed cell death in response to several anti-tumor therapies in various types of cancer [3]. Recent studies have revealed the involvement of autophagy in major fields of liver physiology and pathology, including acute/chronic liver injury, lipid accumulation, viral infection, and hepatocellular carcinoma (HCC) [4]. The autophagy pathway may be used by liver cells to generate energy during periods of starvation or exploited as a tumor suppressor mechanism depending on different biological contexts [5]. Studies assessing autophagy in HCC have demonstrated an anti-tumor role in various cellular, animal and clinical models. However, the mechanisms underlying low incidence of autophagy in HCC are not fully elucidated.

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that controls cell growth and survival and is regulated by various stimuli [6]. The mTOR pathway is abnormally activated in a proportion of HCC patients. As the name implies, mTOR is the intracellular target of rapamycin, a naturally occurring small molecule inhibitor that is currently used clinically as an immunosuppressant and in some cases, to inhibit tumor growth and metastasis [7, 8]. In HCC animal models, inhibition of the mTOR/ribosomal protein p70 S6 kinase (p70S6K) pathway demonstrates anti-proliferative and anti-angiogenic effects [9, 10]. Studies using histone deacetylase (HDAC) inhibitors OSU-HDAC42 and SAHA to induce autophagy in HCC cells further reveal that their anti-cancer properties are mainly through blockade of Akt/mTOR signaling [11].

Our recent publications tied together autophagy and the coagulation cascade in HCC and highlighted the important role of factor VII (FVII)/protease-activated receptor 2 (PAR2) signaling in regulation of autophagy, which is dependent upon mTOR activity. More importantly, an inverse correlation between FVII/PAR2 and LC3 expression in HCC tissues and their contiguous normal regions suggests that components of this particular pathway may serve as potential therapeutic targets in HCC and other cancers which exhibit aberrant FVII/ PAR2/LC3 signaling.

## 2. mTOR interconnects coagulation cascade and autophagy in HCC and related disorders

An established relation between cancer and thrombosis can be dated back to more than a century ago, and the association was further refined and supported among patients who showed venous thromboembolism (VTE) and were subsequently diagnosed with clinically overt cancer [12, 13]. Thrombosis is considered as one of the common complications related to the cancer itself as well as interventions for treating the disease. Approximately 15–20% of VTE events are associated with malignancy [14, 15]. In addition, patients with cancer have a fourfold higher risk for VTE compared with non-cancer patients. This risk is even higher in patients who undergo chemotherapy [16]. Recurrent VTE is also twice as likely to occur in cancer patients, even in those who experience oral anti-coagulant therapy [17, 18]. Notably, patients with cancer who have a thrombotic event have reduced survival compared with those who do not [19].

The transmembrane tissue factor (TF) initiates blood coagulation cascade that complexes with activated FVII and transmits signals through direct activation of protease-activated receptors (PARs) [20–22]. In fact, dysregulated cancer cells may have an important contribution to the elevated levels of circulating TF, which in turn activates the coagulation system [23]. Cancer cells release plasma membrane vesicles with pro-coagulant activity. Such activity has been shown to behave as TF, requiring FVII for activation [24]. The role of direct TF signaling in cancer is not fully understood. The best known pathway of TF-dependent signaling is through the activation of PAR2 [25, 26] and in part through the thrombin-PAR1 pathway [27, 28]. It has also been reported a constitutive association of TF with  $\beta 1$  integrins in cancer [25]. Inhibition using specific antibodies or peptide inhibitors concludes that blockade of the FVII/TF/PAR2 signaling independent of the coagulation response can suppress cancer progression [25, 29]. TF expression varies among different types of malignancies; some may be more pro-thrombotic than others. TF levels can also be influenced by tumor staging as well as associated therapeutic interventions [30, 31].

Plasma TF levels are closely related to occurrence of chronic liver diseases [32, 33]. The diagnostic/prognostic value of TF in tumor pathology has also been demonstrated [34]. Angiogenesis is recognized as an important factor in the development, progression, and recurrence of HCC, and targeting vascularization has been vigorously studied for potential therapeutic strategies [35–37]. A recent study to evaluate the correlation between TF expression with tumor angiogenesis and invasiveness in HCC suggests that tissue TF levels have a significant association with microvascular density, venous invasion, microsatellite nodules, tumor staging, and survival [38]. Zhou et al. also demonstrates that TF is overexpressed in both plasma and liver tissue of HCC patients, and it is closely related to many invasive and metastasis indexes [39]. Furthermore, hepatocytes occupy more than half of the total liver volume and carry out critical functions in coagulation factor synthesis (TF, FVII, etc.) in the liver. It has also been discussed that extremely low levels of hepatocyte TF compared with other organs/tissues [40, 41], however, may be the potential source for the activation of coagulation in liver diseases [42].

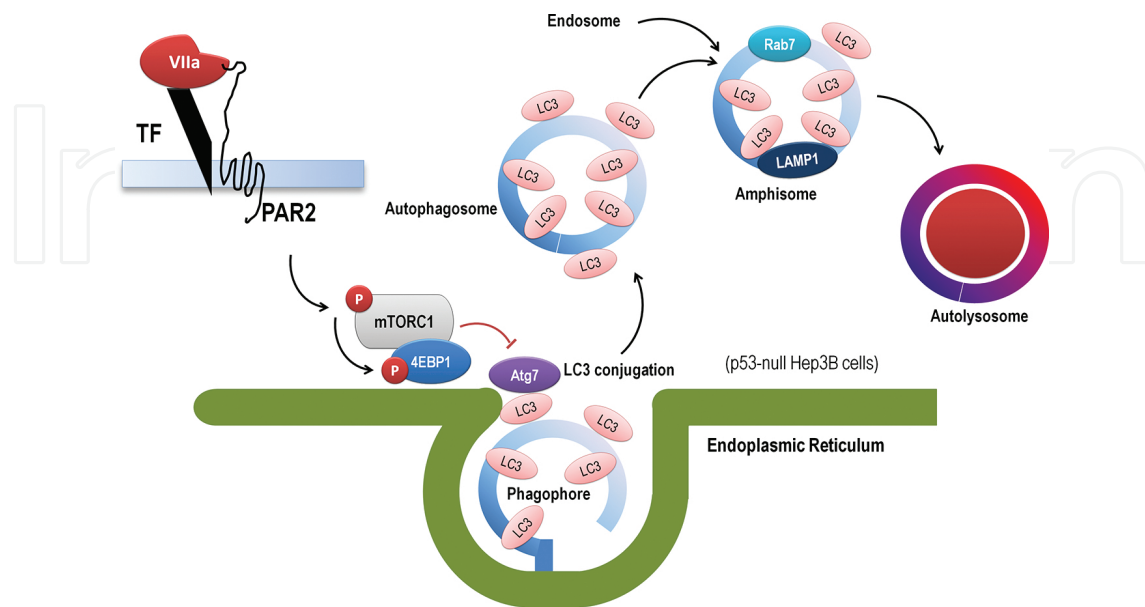
TF is an essential cofactor of FVII, which accelerates the conversion of an inactive FVII into an active FVIIa, propagating a series of serine protease activation events. In addition to pathogenic mechanisms in which TF triggers a pro-coagulant state and aberrant signaling, when TF-expressing tumor cells are in contact with the blood or when TF-positive membrane particles are shed into the circulation, constitutive expression of FVII also participates in the process of tumor invasion and metastasis [43]. Studies that target the TF/FVIIa signaling pathway with specific inhibitor or RNA interference provide a logical path for the development of potential therapeutics [44, 45]. In our clinical observations in HCC, we were the first to demonstrate that the expressions of FVII and PAR2 were inversely correlated with the amount of autophagic effector proteins LC3A/B-II [46]. We have also demonstrated that the treatment with recombinant TF (rTF), rFVII, or PAR2 agonist decreased expression of LC3A/B-II protein in cultured Hep3B cells suggesting a crucial impact of the TF/FVII/PAR2 coagulation pathway on tumor malignancy under certain circumstances. The dependence of mTOR activation on pathological thrombosis has been seen in various studies, in which the risk of thrombotic events while patients were receiving organ transplants [47–52] and coronary stents [53] was associated with TF expression. In this study, treatment with rTF, rFVII, and the PAR2 peptide agonist, rather than thrombin and PAR1 agonist, induced activation and expression of mTOR whereas silencing of TF, FVII, or PAR2 by siRNAs repressed its phosphorylation and expression. Additionally, rTF, rFVII, or PAR2 activation drastically inhibited the LC3A/B-II expression levels which were fully rescued by mTOR knockdown or treatment of mTOR inhibitors *in vitro*. The results illustrated that repression of autophagy by TF/FVII/PAR2 relies upon mTOR activity.

Our study indicated that recombinant FVII, TF, and a PAR2 agonist increased expression of mTOR whereas thrombin or PAR1 agonists did not. Gene silencing of FVII, TF, or PAR2 decreased mTOR. The decrease of LC3A/B-II initiated by recombinant FVII/TF/PAR2 agonist was rescued by mTOR knockdown *in vitro*. These results indicated an mTOR-dependent repression of autophagy by the FVII/TF/PAR2 signaling.

Although our observations suggest that the inhibition of autophagy by the FVII/TF/PAR2 signaling involves mTOR activity, targeting mTOR itself may result in differential outcomes. The relationship between autophagy and mTOR signaling has been comprehensively studied in terms of tumor suppression. However, administration of metformin, which negatively regulates mTOR by activating adenosine monophosphate kinase (AMPK), shows a contradictory effect, suggesting that blockade of mTOR activity does not always lead to autophagy [54]. Other signaling companions may be responsible. Another example is sirolimus (rapamycin). Our results showed that an increase of LC3A/B-II by sirolimus was partially inhibited by recombinant TF and completely blocked in the presence of recombinant FVII or a PAR2 agonist.

Taken together, our results highlight an essential role of the FVII/TF/PAR2 signaling in regulation of autophagy in HCC, which nicely correlates with our observations in clinical and animal research (**Figure 1**). In addition, a recent study demonstrated differential effects of valproic acid-induced autophagy among various human prostate cancer cell lines. The differences were likely due to the existence of alternatively spliced, inactive forms of Atg5 that dampens the formation of Atg12-Atg5 conjugates [55]. Therefore, careful interpretation is

necessary especially in cancer research when aberrant signaling in the autophagic pathway may result from gene variants that do not normally exist in cells.



**Figure 1.** Schematic representation shows that PAR2 transduces the TF/FVII coagulation signaling through mTOR-dependent inhibition in autophagy flux, which may facilitate development and progression of HCC.

Our recent study has demonstrated that the activation of the FVII/TF/PAR2 axis correlates with increased migratory and invasive properties in HCC cells [56]. This finding can be consistently recapitulated in tumor tissues of HCC patients, in which we found that increased levels of FVII and PAR2 were significantly correlated with clinical staging, increased invasion and worse disease-free survival. Notably, the signals that drive FVII/PAR2 stimulation toward cell migration are mainly through ERK-TSC, independent of other coagulation effectors such as thrombin/PAR1. Interestingly, in our cellular model, only FVII, but not soluble TF, activates ERK1/2 through PAR2 signaling. Gene knockdown of FVII abrogates migration and invasion of HCC cells more effectively than knocking down TF. Our speculation is that TF is constitutively expressed in HCC tissue, and therefore, the cells are less sensitive to changes in TF levels. Therefore, the amount of FVIIa determines the ratio that is engaged to regulate PAR2 signaling. Although TF upregulation is well linked to aggressiveness in several cancers, our results are more consistent with the findings from Rullier et al., in which no association between TF levels and clinicopathological characteristics of HCC was found [57]. Several studies also show limited contribution of TF to tumor growth [58–60]. Therefore, the role of TF in cancer progression may be essential in some but not all cancers, and TF may not be a reliable prognostic marker at least for HCC progression. In addition, the animal model using mouse xenografts can well reflect our clinical findings in which we found that FVIIa administration only positively affected vascular density but not size and number of the inoculated tumor. These results were consistent with the expression of FVII in liver tissues of HCC patients which was associated with vascular invasion and capsulations but not the number and size of tumor.



It has been generally accepted that tumor cell motility is necessary for cancer metastasis [61]. The molecular basis to acquire ability to colonize other organs by invading tumor cells has been long studied, but it remains an unmet challenge in therapeutic control on disseminated tumors [62, 63]. Especially in China and other East Asian countries, survival of HCC patients has improved due to advanced surgical skills and technologies such as orthotopic liver transplantation and perioperative medication, prognosis and long-term survival after surgical resection remains low owing to risk of invasive recurrence [64, 65]. Thus, there is an urgent need to identify new targets responsible for impaired metastatic mechanisms and develop of novel therapeutic strategies as well as preoperative biomarkers that supplement current treatment protocols. Although potential risk of bleeding using specific FVII antagonists exists, a recent clinical study has claimed that PCI-27483, a selective inhibitor of FVIIa, is well tolerated in advanced pancreatic cancer patients [44]. Our previous studies also found that two metastatic suppressors, NME/NM23 nucleoside diphosphate kinase 1 (NME1) and the basic helix-loop-helix family member e41 (BHLHE41), were highly induced in FVII/PAR2 knocked down HCC cells. These findings support the idea of targeting the FVII/PAR2 pathway and provide mechanistic insights that specific members involved in autophagic flux could be potential targets for treatment of metastatic HCC.

Emerging cohort studies indicate that HCC is currently the major cause of death in patients with compensated hepatic cirrhosis. The mortality rate of HCC associated with cirrhosis is increasing, whereas mortality rate from non-HCC complications with cirrhosis is reducing and stable. Viral-related cirrhosis especially with hepatitis C virus infection is associated with the highest HCC incidence in cirrhotic cases, occurring with almost two times in East Asia than in the West [66]. Liver cirrhosis is a slowly progressive disease that enhances extracellular matrix (ECM) accumulation after chronic injury, in which healthy liver tissue is replaced with scar tissue and poor function is seen at the terminal stages.

It is generally accepted that the vast majority of chronic liver disease patients with cirrhosis have a dysregulated coagulation system [67, 68]. A growing number of studies represented a thrombotic risk in patients with chronic liver disease [69–72]. Thus, the reevaluation of homeostasis in patients with thrombotic tendency in cirrhosis challenges the dogma that considered this coagulopathy an acquired bleeding disorder and featured in most hematology textbooks [67]. However, the mechanistic basis for this hypercoagulable state in cirrhotic patients of chronic liver disease is not yet understood. A recent study have suggested that hepatocytes are the source of increased TF microparticles, and hepatocyte TF may contribute to the activation of coagulation in patients with chronic liver disease [42]. We recently demonstrated that hepatic steatosis and liver injury by alcohol (AFLD) were exacerbated by chloroquine (an autophagy inhibitor), but alleviated by carbamazepine (an autophagy promoter) or rapamycin (an mTOR inhibitor) [73]. The protective effects of carbamazepine and rapamycin in reducing steatosis were also represented in high fat diet-induced non-alcoholic fatty liver conditions (NAFLD). Furthermore, we also found that a second autophagy promoter amiodarone significantly reduced liver injury and improved liver regeneration and survival after 90% partial hepatectomy in a mouse model [74]. Our data suggests that pharmacological

modulation of autophagy in the liver can be an effective strategy for alleviating liver injury, improve proliferative recovery, and may also ameliorate progression of liver cirrhosis.

Taken together, TF/FVII signaling is the main initiator of the extrinsic coagulation cascade, which is also the major contributor in modulating the systemic balance of homeostasis in healthy persons as well as in response to the pathogenesis in patients with chronic liver disease. Amiodarone is now a potential drug to treat HCC through the modulation of autophagy to decrease oncogenic miR-224 expression [75]. Thus, increasing evidences including our studies support a close relationship between TF/FVII coagulation and liver disease in association with reduced autophagy, suggesting pharmacological modulation of autophagy for AFLD, NAFLD, and/or HCC could be a potential strategy for clinical uses.

## Conflicts

I confirm there are no conflicts of interest.

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