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Short review

Tumor microenvironment mediated by suppression of autophagic flux drives liver cancer malignancy

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ABSTRACT

The physiological role of autophagy in the catabolic process of the body involves protein synthesis and degradation in homeostasis under normal and stressed conditions. In hepatocellular carcinoma (HCC), the role of tumor microenvironment (TME) has been concerned as the main issue in fighting against this deadly malignancy. During the last decade, the crosstalk between tumor cells and their TME in HCC extensively accumulated. However, a deeper knowledge for the actual function of autophagy in this interconnection which involved in supporting tumor development, progression and chemoresistance in HCC is needed but still largely unknown. Recent studies have shown that coagulants tissue factor (TF) and factor VII (FVII) has a pathological role in promoting tumor growth by activating protease-activated receptor 2 (PAR2). Autophagy-associated LC3A/B-II formation was selectively suppressed by FVII/PAR2 signaling which mediated by mTOR activation through Atg7 but not Atg5/Atg12 axis. The coagulant-derived autophagic suppression seemed potentiate a vicious circle of malignancy in producing more FVII and PAR2 which facilitate *in vivo* and *in vitro* tumor progression of HCC and the investigations are consistent with the clinical observations. In this review, we briefly summarize the current understanding of autophagy and discuss recent evidence for its role in HCC malignancy.

Autophagy constitutes some of the most basic reactions in which cells sequesters part of their own cytosolic components and organelles into membrane-bound vesicles for degradation and, upon energy deprivation, convert the protein and lipid contents into life-preserving fuel while delivering to lysosomes. In addition, autophagy also participates in removal of malfolded protein aggregates and dysfunctional organelles under stressed conditions, whereas its cargo contents are

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ultimately broken down and recycled back for supporting metabolic processes [1,2]. Autophagy process is evolutionally conserved which have been categorized into distinct steps with more than 30 autophagy-related proteins (ATG) involved [3–5]. This "self-eating" process is induced by a variety of intracellular and extracellular stimuli, such as oxidative stress, assorted pathogens cytokine stimulation, damaged organelles and accumulated protein aggregates especially in low-nutrient environments [6,7].

The mammalian target of rapamycin (mTOR), a key molecule lies at the heart of nutrient-sensing cascades which has been identified as a main regulator of autophagy activity and plays a pivotal role in coordination of cell growth and progression in various cancers [8,9]. Solid tumors generally experience both nutrient deprivation and hypoxia while lacking vascularization, and induce a proliferation response in cancer cells [10–12] in which mTOR acts as a restriction point regulator between proliferation and differentiation in response to their environmental change [13]. Thus, cancer cells are optimized for growth and survival through the ability to surpass metabolic hurdle, thereby alter cell metabolism toward anabolic conditions, anaerobic glycolysis and acidosis to meet their advantageous demands [14,15].

However, hepatocellular carcinoma (HCC), the third leading cause of death from cancer worldwide is a highly vascularized solid tumor with a rapid annual growth rate to be diagnosed and poor prognosis. Although the incidence of HCC decreased to the third from the second leading cancer causes since 2012, HCC patients are still facing the high risk of recurrence and mortality in Taiwan [16]. In one center experience of Kaohsiung Chang Gung Memorial Hospital, most cases of HCC are due to liver disorders with chronic viral infection (hepatitis B, C and B + C, more than 90%). Furthermore, hospital-based analysis for identifying prognostic factors of HCC was earlier conducted. In a large retrospective cohort of 6381 HCC cases diagnosed from 1986 to 2002 were enrolled and the independent factors influencing survival were revealed by multivariate analysis. Besides those well-known prognostic factors, such as alpha-fetoprotein, HBV surface antigen positivity, degree of liver function impairment and tumor status, relative high platelet counts were identified as a poor prognostic factor [17]. Hence, the special etiologies identified in our clinical observations imply critical tumor microenvironments may be involved in the malignant progression of HCC in this HBV endemic area.

Autophagy and HBV

Chronic HBV infection has been epidemiologically associated to the development of HCC for almost half a century and HBV X protein (HBx) has been found to play critical roles in this hepatocellular carcinogenesis [18,19], however the underlying mechanisms by which infection to drive HCC malignancy are still largely unclear. HBx subverts a variety of cellular activities such as transcription, autophagy and proliferation by interacting with transcription factors without direct DNA binding [20,21]. Autophagy can be triggered by HBx directly through up-regulation of autophagic protein expression, or indirectly through activating class III phosphatidylinositol 3-kinase (PtdIns3K) and ER stress response [22–24]. The relevance of HBx-promoted autophagy has been suggested to promote viral replication, however the mechanisms to affect the cytoplasmic modulation of signal transduction pathways by autophagy are still controversial [22,23,25]. Interestingly, a different group has shown that autophagy-deficient mice with systemic mosaic deletion of Atg5 or liver-specific loss of Atg7 develop multiple tumors [26]. A recent study also demonstrated HBx inhibits autophagy degradation by interfering lysosomal maturation, although the number of autophagosomes was increased in tumor cells. These findings indicates an important suppressive role of autophagy in tumorigenesis of HCC, and that HBx restrained autophagic flux leading to the accumulation of autophagosomes which might contribute to further malignancy.

Coagulant microenvironment in HCC

Tumor-associated inflammation especially procoagulant-driven inflammation is now widely recognized as one of key determinants of various type of cancer [27–30], including HCC [31–33]. The transmembrane tissue factor (TF) triggers downstream signaling upon binding with blood coagulation factor VII (FVII) and transmitting signals through protease-activated receptors (PARs) activation, especially PAR2 [34–36]. In general, a hypoxic microenvironment involves in tumor progression which includes local invasion, distant metastasis and therapeutic resistance [37]. Both TF and FVII are found to be induced in response to hypoxia, and known to initiate key pathogenesis in cancer [38], however their regulatory mechanisms are distinct in ovarian cancer cells [30,39–42]. In addition to ovarian cancer, it has also been demonstrated by immunohistochemical analyses that TF is high expressed in breast cancer and pancreatic cancer tissues [43–45]. Although numerous studies have suggested that TF-fVIIa complex formation on the cell surface contributes to the malignant phenotypes of cancer, TF expression varies among different types of malignancies; some may be more pro-thrombotic than others. 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]. The detailed regulatory mechanisms are not clear; however transcriptional activation appears to be a major mechanism of TF over-expression [30]. Therefore, therapeutic strategies targeting TF has been considered to be advantageous to cancer progression, although the possible impairment of the homeostasis of coagulant physiology should be considered.

Mechanisms of coagulant initiation in HCC are not completed revealed. Interestingly, extremely low level of TF mRNA is expressed in liver compared to other tissues, however the physiological reason is also not clear [46,47]. Angiogenesis has well known to be an important factor in the development, progression and recurrence of HCC and its targeting has been vigorously studied for potential therapeutic strategies [48–50]. Poon et al. have evaluated the correlation between TF expression with tumor angiogenesis and invasiveness in HCC which was the first suggesting a significant association of TF levels with microvascular density, venous

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