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REVIEW ARTICLE

EMT and Inflammation: Crossroads in HCC

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Abstract
Hepatocellular carcinoma is one of the major causes of cancer-related deaths worldwide and is associated with several inflammatory mediators, since 90% of HCCs occur based on chronic hepatitis B or C, alcoholism or increasingly metabolic syndrome-associated inflammation. EMT is a physiological process, with coordinated changes in epithelial gene signatures and is regulated by multiple factors, including cytokines and growth factors such as TGFβ, EGF, and FGF. Recent reports propose a strong association between EMT and inflammation, which is also correlated with tumor aggressiveness and poor outcomes. Cellular heterogeneity results collectively as an outcome of EMT, inflammation, and the tumor microenvironment, and it plays a fundamental role in the progression, complexity of cancer, and chemoresistance. In this review, we highlight recent developments concerning the association of EMT and inflammation in the context of HCC progression. Identifying potential EMT-related biomarkers and understanding EMT regulatory molecules will likely contribute to promising developments in clinical practice and will be a valuable tool for predicting metastasis in general and specifically in HCC.

Keywords EMT · Inflammation · HCC · Liver cancer

Introduction

Epithelial to mesenchymal transition or EMT is the switch from an epithelial, polarized state to the mesenchymal and unpolarized phenotype. It is a fundamental physiological process for healthy embryonic development; however, it is hijacked in certain pathological conditions such as cancer and inflammation [1–3]. There are 3 classes of EMT. Developmental (type I) EMT is required for mesoderm formation, neural crest delamination, the establishment of the heart valve, palatogenesis, and myogenesis [4–6]. Following tissue damage, EMT becomes activated during fibrosis and wound healing (type II) [7, 8]. However, it is also aberrantly activated during tumorigenesis when cancer cells start to disseminate, invade, and form metastasis (type III) [1, 2]. Mesenchymal cells can also acquire the epithelial state by undergoing a mesenchymal to epithelial transition (MET).

EMT-MET transitions cause cellular plasticity that is a feature of tumor initiation, progression, and metastatic colonization [9, 10]. The roles of EMT and MET in metastasis vary depending on the context. Tumor cells, which are phenotypically very heterogeneous, can benefit from EMT to gain some properties such as increased invasiveness and metastatic capacity, acquisition of stem-like features allowing them to adapt to the rapid shifts of tumor microenvironment resulting in more malignant tumors [11–13].

Plasticity and heterogeneity during EMT play pivotal roles in hepatocellular carcinoma (HCC) [14, 15]. HCC, the predominant form of primary liver cancer, is one of the major causes of cancer-related mortality worldwide and is associated with inflammatory mediators as more than 90% of HCCs occur due to inflammation [16–18].

Inflammation of the liver can result from chronic viral infections (Hepatitis B or C-HBV/HCV), which are among the major causes of HCC, as well as chronic alcohol consumption, aflatoxins, and drug derivatives [19, 20]. Due to

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the poor understanding of the inflammatory mechanisms underlying heterogeneous HCC development, the treatment options are very limited. Growing data show that inflammatory cytokines produced predominantly by macrophages and T lymphocytes lead to the activation of HCC carcinogenesis [21, 22]. For example, recent studies suggest that osteopontin (OPN), a matricellular cytokine that mediates various biological functions such as cell adhesion, migration, and survival is linked to HCC tumor progression and metastasis [23]. It can induce EMT via regulating vimentin expression in HCC cells [24]. In addition, in HCV-infected cells, cellular kinases such as p38 MAPK and JNK, which are involved in EMT regulation, are activated during OPN induction [25, 26].

EMT is an epigenetic reprogramming event accompanied by changes in the epithelial gene signature. This involves alterations in the expression of E-cadherin, which is the hallmark of EMT and is significantly associated with poor prognosis of most cancers, including HCC [1, 27, 28]. EMT is mediated by a group of transcription factors known as the EMT inducers, such as SNAI1/Slug, TWIST1/2, and ZEB1/2 [29, 30]. For instance, it has been shown that EMT inducers such as SNAI1 can regulate the expression and activation of several interleukins in different cancer types such as HCC, thus triggering an inflammatory response, which in some cases may result in the development of EMT-like features [12, 13, 31].

Inflammation is known as an adaptive response to infection, and some infections result in non-resolving inflammation due to host defense mechanisms, which are thought to contribute to the progression of various cancer types by promoting proliferative and survival signaling pathways, becoming a key component of the tumor microenvironment [18, 32]. EMT and inflammation are complex and highly controlled processes, and the functional connection between malignancy and inflammation has long been accepted. However, available data about the molecular mechanisms of these complex processes remain limited. Several recent studies addressed the relationship between EMT and inflammation in cancer progression. High levels of ZEB1 expression were recently shown to promote the malignant transformation of HCC due to activation of EMT, accompanied by reduced patient survival [33]. The ZEB1-attributed induction of EMT is usually associated with increased chemoresistance and eventually poor patient survival [34]. This is intriguing not only for the potential usage of ZEB1 inhibitors as potential treatment strategies, but also as a way for scoring HCC stages based on the predictive power of ZEB1 expression. ZEB1 has been shown to influence the inflammatory pathways in other cancer types [35–37], and together with its ability to induce pronounced EMT, leading to metastasis, puts it in a unique position as a prognostic factor and as a scoring criterion for HCC.

The long-established link between the metastatic capability of tumor cells, stemness, and inflammatory responses strengthens the connection between EMT and inflammatory mediators [10, 38]. Cancer cells that have undergone EMT have been shown to produce proinflammatory factors such as cytokines that contribute to tumor cell phenotypic changes and aggressiveness. Over the past decade, it became evident that a wide variety of inflammatory factors such as transforming growth factor beta (TGFβ), Wnt, several cytokines, and some long non-coding RNAs (lncRNAs) can stimulate EMT activation in cancer cells [12, 39, 40]. Moreover, metastatic progression and poor tumor prognosis are tightly correlated with EMT [12, 15, 41].

Signaling Pathways Involved in EMT and Carcinogenesis.

TGFβ, Wnt, Notch, NF-kβ, hedgehog, and receptor tyrosine kinases are essential signaling pathways inducing EMT during carcinogenesis and metastasis. These pathways are guided by critical mediators including Snai1/Slug, Smads, and Twist activated by signals from the tumor microenvironment [42–44].

TGFβ

The cytokine TGFβ is a potent inducer of EMT and associates with several critical signaling pathways, such as Wnt. The role of TGFβ in the stimulation of EMT and metastasis is intensively studied. Additionally, it is one of the crucial factors of cancer-related inflammation [13, 45]. TGFβ works as a tumor suppressor via regulating cell proliferation as well as a tumor promoter [46, 47]. However, there is limited knowledge available on which mechanisms are involved in mediating the process. TGFβ is well established as a potent inducer of EMT in HCC [48, 49].

TGFβ and hypoxia are dual factors that may induce EMT by increasing the stability of the EMT inducers in the inflammatory environment [20, 40, 50]. Moreover, it has been demonstrated that hypoxia affects the aggressiveness of cancer cells, illustrated by the enrichment of several gene sets correlated with poor prognosis and low survival [20, 51, 52]. For instance, it has been recently shown that HCC metastasis is promoted by the overexpression of HIF-1α, which triggers EMT-like features [12, 50, 53, 54]. Moreover, some ubiquitin ligases responsible for HIF-1α protein stabilization also have key functions in the progression of HCC. One of them is USP14, which is highly expressed in HCC, has a major function in the prognosis of the disease, and emerges as a potential therapeutic target [55]. Although hypoxia is known to be involved in the progression of HCC, because limited oxygenation microenvironment is associated with cancer progression, more research is needed to establish the link between the prognostic role of hypoxia and EMT in cancers.

In response to TGFβ, primary mouse hepatocytes lose their epithelial features due to a rapid decrease in *Cdh1* expression [15]. The expression of *Smad7*, which is known to antagonize the TGFβ/Smad signaling pathway, confirms the reduction of the epithelial traits. Additionally, cirrhotic hepatocytes exposed to TGFβ differ from healthy mouse livers in morphology and gene signature pattern. The underlying mechanisms of hepatocarcinogenesis seem to be related to inflammation due to in part to increased TGFβ levels [15]. Furthermore, a recent study showed that hepatic TGFβ expression was increased after chronic alcohol consumption resulting in the activation of fibrosis and EMT [56].

The stabilization of the SMAD3/SMAD4 complex, which plays an integral role in TGFβ signaling, was recently reported to be mediated by the dynamic scaffolding protein β2-spectrin (β2SP). Overall, nuclear translocation of β2SP, which regulates the nuclear localization of β-catenin and induction of stemness genes, together with the inflammatory cytokine IL6, are related to HCC progression [57–59]. Additionally, sorafenib was shown to upregulate IL6 via the upregulation of STAT3 phosphorylation in hepatocytes [60, 61].

Notch

Notch is a highly conserved developmental signaling pathway required in many fundamental physiological processes, including proliferation, differentiation, apoptosis, homeostasis, and the regulation of the cell fate in several tissues [62–64]. The Notch pathway mediates harmonious equilibrium between cell proliferation and cell death; thus, it is fundamental for tumor progression. Notch can act as a tumor suppressor and oncogene, a dual feature defined by cellular context and signal dose or strength [65–67]. A dysfunctional Notch pathway is implicated in many cancers, including HCC [63]. Activation of the pathway leads to liver fibrosis and is mostly associated with poor prognosis in HCC [68]. The Notch coactivator MAML1 was recently found to contribute to the aggressiveness of most cancers, including HCC [69–71]. Besides, GPR50 endorses HCC progression through Notch pathway by regulating ADAM17 [72]. Notch target genes, such as Myc, cooperate with many signaling pathways to induce EMT during carcinogenesis [73, 74]. TGFβ also induces Notch activity via Smad pathway and suppresses E-cadherin indirectly through Slug [75]. Notch is also known to induce EMT and metastasis through Snai1 expression [76].

NF-kβ

The nuclear factor kappa β (NF-kβ) is a major signaling pathway connected to EMT and inflammation. NF-kβ is a prototypical proinflammatory signaling pathway activated by various inflammatory stimuli such as TNF-α and interleukin-1 (IL-1) and has been associated with the metastatic capacity of tumor cells [40, 77]. The activation of EMT inducers such as Snail1/Slug, Twist, and Zeb1/2 is highly demanded to promote tumors' metastatic potential in several types of cancer [40, 77]. It was revealed that stabilization of Snai1 through the NF-kβ signaling pathway is needed for inflammation-induced metastasis [78]. It is also known that some target genes of NF-kβ and STAT3 pathways are linked and result in more aggressive tumors, which could be explained by the stabilization of cancer stem cells in connection to the activation of STAT3 [18, 79]. CRIF1 plays a paramount role in HCC progression via induction of ROS/NF-kβ signaling cascade resulting in tumor aggressiveness [80].

Cytokines

Cytokines are soluble mediators which are highly associated with cancer-related inflammation, and are mainly divided into 4 types: chemokines, interferons, interleukins, and tumor necrosis factors [12, 81].

Chemokines

Chemokines are small, secreted proteins that bind to G protein-coupled receptors [82, 83]. There are two types of chemokines; inflammatory chemokines, which are activated by inflammation, and homeostatic chemokines, which are constitutively active. Chemokines play critical roles in several biological processes such as embryonic development, angiogenesis, wound healing, migration, inflammation, and immune system homeostasis [83, 84]. They are also tightly associated with carcinogenesis; hence, they can induce proliferation, tumorigenesis, metastasis, stemness, and EMT [85, 86]. CXCL8, CCL5, and CXCL1 are critical chemokines related to EMT. CXCL8 is a well-studied chemokine involved in the TGFβ stimulated EMT through binding to the chemokine receptor CXCR1 during EMT [87, 88]. Beyond EMT, TGFβ itself is a widely accepted immunosuppressive cytokine associated with critical functions, including angiogenesis, metastasis, and cell motility [89–91]. A recent study indicated that TGFβ has an immunosuppression effect on $CD8^+$ T cells via CXCR3 blockage [90]. In liver cancer, chemokines are present in the HCC microenvironment, and some HCC cells express chemokine receptors such as CCR5 to regulate migration, invasion, and growth of the tumor [84, 92, 93].

Interferons

Interferons (IFNs) are a family of anti-inflammatory cytokines involved in many cellular and physiological functions, such as inducing intrinsic pathways in response

to viral infection. There are 3 types of IFNs described so far: types I, II, and III, classified based on functional and structural differences [94, 95]. IFN-α has been recently described to be involved in inflammation via induction of IFN-stimulated genes. IFN-α signaling pathways are known to crosstalk with many cancer-associated pathways such as JAK-STAT [96, 97], Wnt/GSK-3 [98], and Ras/Raf/MEK/ERK [99]. IFN-α also contributes to metastasis through the upregulation of HIF genes. IFN-α induces the expression of HIF-1α, which then activates JAK/PI3K/PTEN/mTOR/AKT and Ras/p38/ MEK/ERK signaling pathways. It has been documented that HIF-1α then stimulates the expression of EMT genes which also contribute to the tumorigenic progression in various cancer cell lines [100]. IFN-α has recently been recognized as a promising therapeutic target in HCC [101]. Besides conflicting results of IFN treatment in HCC, IFN-α and sorafenib seem to have a dual effect on HCC progression and metastasis through tumor-associated macrophage (TAM) polarization [102].

Interleukins

Interleukin family members IL-1α, IL-1β, IL-6, and IL-8, are cytokines known to be involved in cancer-associated inflammation [102, 103]. IL-6 and TNF-α secreted by adipocytes are the keystone proinflammatory cytokines in the tumor microenvironment due to their contribution to many biological processes, including inflammation, EMT, and cancer [104–106]. IL-6 typically induces EMT via STAT3-induced SNAIL expression [107, 108]. IL-6 production in cancer patients elevates platelet counts (para-neoplastic thrombocytosis), which is an indicator of poor prognosis in several types of cancer, such as HCC and ovarian cancer [109, 110]. IL-1α plays a critical role in activating vascular endothelium, which causes infiltration of inflammatory cells in a tumor-promoting environment [111].

TNF-α

TNF-α is crucial both for hepatocyte apoptosis and liver proliferation and is a well-known factor promoting tumor cell proliferation and angiogenesis [112, 113]. Recent reports highlight its essential role as an inflammatory mediator that can induce EMT in synergetic collaboration with TGFβ [12, 103]. TNF-α induces Snai1 promoter activity in some cancer cells, such as colorectal cancer, and has a role in stabilizing Snai1 protein [40, 114]. During inflammation, TNF-α also induces apoptosis by stimulating inflammatory signaling pathways [115, 116].

The Inflammatory Microenvironment in HCC

The tumor microenvironment plays a significant role in cancer progression [20, 117]. It contains inflammatory cells such as macrophages, neutrophils, and dendritic cells, which secrete numerous types of cytokines, ECM remodeling factors, and growth factors [12, 118]. HCC is one of the leading inflammation-related cancer types. Tumor-associated macrophages, which have a central role in tumor progression show EMT-like features in several cancer types such as HCC. TAMs produce multiple factors such as HGF, EGF, IL-1β, IL-6, and TNF-α, which are capable of inducing EMT in a tumorigenic environment [119, 120]. TAMs are also crucial for various biological processes such as angiogenesis, extracellular matrix (ECM) remodeling, and metastasis [40, 121]. There is increasing evidence that the tumor microenvironment has both pro- or anti-inflammatory responses in a context-dependent manner and is highly affected by cell heterogeneity and plasticity [122, 123]. Cell plasticity allows cancer cells to escape from the tumor microenvironment, which also leads to tumor heterogeneity. Tumor heterogeneity is acknowledged as a primary cause behind the failure of current cancer therapies. However, reducing inflammation seems to be a promising solution for better therapeutic strategies.

Other Factors

Despite the recent developments regarding the inflammatory factors associated with EMT, several unknown factors link inflammation to EMT in cancer. miRNAs and long non-coding RNAs (lncRNAs) are among them [124]. miRNAs are single-stranded non-coding RNAs, which play crucial functions in the epigenetic regulation of gene expression at the post-transcriptional level. miRNAs have been indicated to have essential roles during inflammation and carcinogenesis via their tight association with transcription factors. For instance, miR-122 is a tissue-specific miRNA that has an anti-inflammatory role in the liver. It is well described that transcription factors such as hepatocyte nuclear factor (HNF)-1α, HNF-4α, and CCAAT/enhancer binding protein α (C/EBPα) can induce the expression of miR-122 [125–127].

LncRNAs are essential for the advancement and progress in various cancer models such as HCC. One example is lncRNA HULC, which is aberrantly upregulated in liver cancer [128]. It is significant since it promotes EMT via miR-200a-3p/ZEB1 signaling pathway, which is also correlated with the clinical stage in HCC [129].

Cellular heterogeneity of HCC is partially explained by the EMT program [15, 31, 130]. A recent study reported an inflammatory mediator called polymeric immunoglobulin receptor (pIgR) as a prognostic marker of HCC. It induces EMT via Smad2/3 and is critical for the stem cell properties

and the TGFβ linked EMT, closely related to HCC progression and tumor heterogeneity [130–132]. Aberrant expression of pIgR was also correlated with poor survival from HCC [133]. More supporting evidence would eventually corroborate the involvement of inflammatory pathways in HCC heterogeneity.

Activation of hepatic stellate cells (HSCs) is an essential event for the progression of hepatocarcinogenesis. The proteoglycan Agrin utilizes (PDGF)-induced HSCs by providing a tumorigenic microenvironment. Agrin secreted by platelet-derived growth factor (PDGF)-induced HSCs contributes to proliferation, invasion, and the metastatic ability of HCC and HSCs can be inhibited by the multi-kinase inhibitor sorafenib; a drug that has been approved for HCC therapy [134]. Overall, Agrin seems to be a key target for the treatment of HCC because of its contribution to HCC development in liver cirrhosis patients [135, 136].

Recent advances in tumor metastasis research revealed that the absent in melanoma 2 (AIM2) protein is found in the center of the inflammation-carcinogenesis axis [137]. AIM2 promotes HCC metastasis since its silencing activates EMT via targeting FN1 (fibronectin 1), which, in turn, contributes to the regulation of Snai1, N-cadherin, and vimentin [138]. It is demonstrated that HBx (hepatitis B virus X protein) induced loss of AIM2 is correlated with EMT. Recently, several studies have revealed a strong association between EMT and inflammation, which is also correlated with the aggressiveness of the tumor and poor overall duration of survival [103].

Conclusions

Despite significant efforts in the past decade, there remains a gap to be filled to understand the underlying mechanisms controlling EMT in HCC. HCC progression is influenced by complex pathways of EMT and inflammation. Thus, the inflammatory tumor microenvironment and EMT are tightly linked in relation to several aspects of tumor development and tumor metastasis. Since multiple mechanisms underlying both EMT and inflammation have been identified, as listed in this review, these processes provide suitable targets for future tumor intervention strategies. Furthermore, several immune checkpoint inhibitors such as atezolizumab have also been approved, that target the balance between inflammation and immunity. Therefore, it is highly likely that identifying potential EMT-related biomarkers and understanding EMT regulatory molecules will contribute to clinical practice and be a valuable tool for predicting HCC aggression and metastasis. It is now becoming clear that inflammation can both affect cancer progression and treatment responses. However, further efforts are still needed to understand the connection between EMT and cancer stemness in HCC progression.

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Declarations

Ethics Approval Not applicable.

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