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The role of inflammations and EMT in carcinogenesis

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ABSTRACT

Cancer is one of the major health burdens in modern world, and its mechanism is very complex, which is one of the main reasons for difficulties in cancer drug development. The development of cancer is associated with chronic inflammation, although inflammation is an essential biological process. The epithelial-mesenchymal transition (EMT) is a crucial step in development process of human tissue and involve in the regulatory pathways. On the contrary, the uncontrolled EMT is responsible for the initiation of cancer, its metastasis, immunosuppression, and resistance to antitumor treatment. Interestingly, there is an interrelationship between inflammation and EMT process. Usually, proinflammatory cytokines activate EMT inducing transcription factors (EMT-TFs), causing epithelial cells to change into cancerous mesenchymal cell by activating the mesenchymal cells markers, such as N- Cadherin, Fibronectin, Vimentin etc., and inhibiting the epithelial cells markers such as E– Cadherin, Claudin 1, Occludin, and β-catenin. Consequently, epithelial cells are dissociated, invasive, motile, resistant to therapy, resistant to apoptosis, and undergo mesenchymal cells angiogenesis. Some natural products and short RNAs have been identified to interfere with inflammation-EMT axis to inhibit cancer progression and metastasis. We have described these relationships in this review article and also described the therapeutic perspectives for cancer.

1. Background

In every country, cancer is a primary cause of death and a significant impediment to extending life expectancy [1]. The International Agency for Research on Cancer's GLOBOCAN 2020 projections of cancer incidence and mortality were used to calculate the worldwide cancer burden. In 2020, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) would be diagnosed worldwide, with around 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) [2]. It is a multifarious disorder which affects the various organ of human body. The development and the maintenance of a normal cell population are closely related with apoptosis that is a highly regulated process of cell death [3]. Cancer is the process of accumulation of aberrant cells due to uncontrolled proliferation with negligible apoptosis [4]. Acute and transient inflammation is an important part of tissue damage management and repair, tumor-associated inflammation, which is seen in almost all cancers, is a prolonged, unresolved kind of inflammation that promotes tumor proliferation [5]. The tumor microenvironment is important in the progression of cancer [6]. Inflammatory cells such as macrophages, neutrophils, and dendritic cells are found there, and they secrete a variety of cytokines, and growth factors [7].

On the other hand, the epithelial-to-mesenchymal transition (EMT) defines the trans differentiation of stationary epithelial cells to a motile, mesenchymal phenotype, which was first seen in early development [8]. The process of EMT is fundamental for embryonic morphogenesis and when epithelial cells lose their integrity and properties, gain mesenchymal traits, and become motile [9]. This program is hijacked in cancer to confer crucial morphological and motility alterations that fuel invasion [9]. It is suspected that EMT involves in the prime stage of cancer development and metastasis [10,11]. Inflammation is an inducer of EMT where the aggressiveness of cancer cells along with tumor-involved macrophages will be increased in the result of combined effect of inflammation and EMT. In this review article we have discussed an

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interrelationship of the inflammation-EMT axis with cancer progression and metastasis, and how controlling inflammation/EMT could be a beneficial for the cancer therapeutics. This is less explored area, and so tried to review this area comprehensively.

2. EMT and cancer

The development of both normal and neoplastic stem cells has been related to the activation of transition (EMT), a latent cell-biological mechanism involved in development and wound repair [12]. EMT is a complex but well-coordinated process in which epithelial cells shed many biological characteristics involved in epithelial differentiation. EMT is induced by the EMT-convincing transcription factors (EMT-TFs). EMT-TFs are embedded within a microRNA regulatory network involving reciprocal, double-negative feedback loops. The two most prominent feedback loops involve SNAIL–miR-34 and zinc-finger E-box-binding homeobox 1 (ZEB1)–miR-200 [12]. EMT-TFs alter the construction of extracellular matrix (ECM) degrading enzymes, expression of particular cell-surface proteins, restructuring the appearance of cytoskeletal proteins, and cell stemness [13]. Several activating transcription factors like basic helix-loop-helix (bHLH), Twist-related protein 1 (Twist1), zinc finger protein Snai2 (Slug) and zinc finger E-box binding proteins (Zeb1 and Zeb 2) are involved in EMT regulation [11, 14]. EMT causes the damage of epithelial cell schism plus tight cell-cell connection biomarkers (E-cadherin, β-catenin, Claudin 1 and Occludin) leading to the enhancement of the migration and invasion by increasing the mesenchymal biomarkers such as N-cadherin, vimentin and fibronectin [15,16].

2.1. N-cadherin

E-cadherin protein presents in epithelial cells and β-catenin on the cell membrane of non-tumorous tissues and a small transmembrane protein claudin-1 maintain epithelial cell polarity by doing a crucial role in epithelium homeostasis. The classic cadherins family includes several types of proteins such as E (epithelial), N (neural), P (placental), VE (vascular-endothelial), R (retinal), and K (kidney)-cadherins; among these, E-cadherin is most frequently recognized in the formation of adherens junctions in epithelial cells [17]. The cadherin family member N-cadherin is predominantly expressed in mesenchymal tissues such as cartilage [18]. Studies indicated that several signaling cascades including Akt, signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), Wnt, and EMT-TFs (Twist1, Snail, Slug, Zeb1, Zeb 2) are associated with cancer cell metastasis through downregulating E-cadherin and upregulating metastatic proteins [11]. N-cadherin signaling that comes from E-cadherin is the actual hallmark of EMT [19]. Epithelial cells which undergo the EMT show, on the contrary, the dissociation of cell-cell junctions and a reduced E-cadherin expression [20]. Recently published report has showed that tumor antagonism in esophageal carcinoma connected with N-cadherin and others demonstration of the value of N-cadherin as an indicator of invasive and malignant tumors [21]. The appearance of E-cadherin can be prevented by EMT-TFs such as Snail1 with the help of several enzymes like histone deacetylase 1 (HDAC1), histone deacetylase 2 (HDAC2), AJUBA-protein arginine methyl transferase 5 (PR MT5), or polycomb repressive complex 2 [22]. Multiple signal transduction pathways like Akt, STAT3, MAPK, Ras, and Wnt signaling will trigger Twist1 which in turn up regulates N-cadherin and down regulates E-cadherin that are distinctive features of EMT [11].

2.2. Vimentin

Vimentin is a structural protein encoded by the *Vimentin* gene which is derived from Latin word vimentum [23]. More specifically, vimentin is a type III intermediate filament protein, which is mainly expressed in fibroblasts, endothelial cells, and lymphocytes, and is also the most widely distributed intermediate filament [24]. Vimentin is extensively involved in multiple physiological activities and plays a significant role in regulating cell function and morphology. It participates in various cellular activities such as cell migration, differentiation, proliferation, adhesion, and invasion, and exerts anchoring effects in the nucleus and organelles [25,26]. Regarding organ function, vimentin is involved in the development of the mammary gland, nervous system, and in angiogenesis. Numerous studies have confirmed that vimentin can regulate the EMT affecting diverse physiological and pathological processes, such as growth and wound healing. EMT is of great significance in tumor progression; therefore, vimentin acts as an important marker of EMT [26]. Studies have shown that increased expression of vimentin correlates to decreased survival rate in a variety of cancers such as colorectal, cervical, breast, gastric, and non-small cell lung cancers, to name a few [27]. Throughout the EMT process, the receiving of efficient and morphological mesenchymal features in epithelial cells and the cellular building towards a seasonal and intrusive phenotype are guided by vimentin upregulation. It is consistently observed to be overexpressed during cancer metastasis and is therefore generally acknowledged as a canonical biomarker of type-3 EMT [28,29]. Vimentin filaments provide a viscoelastic framework that protects cancer cells from mechanical stresses during migration or squeezing through confined areas, as well as supporting the placement and integrity of organelles, particularly the nucleus, during EMT and cancer growth [30]. During initial stages of cancer development, vimentin concentration is very low, however, it increases when cancer starts to invade the surrounding areas [31]. Vimentin is widely studied as an EMT marker of cancer cells, the novel function of vimentin in regulating cancer proliferation via Rictor/AKT/β-catenin signaling pathway, which suggested that it need more careful consideration before inhibiting metastatic cancers through targeting vimentin [32].

2.3. Fibronectin

Fibronectin is a high-molecular-weight glycoprotein that consists of two subunits, covalently linked by a pair of disulfide bonds at the C-termini. Despite fibronectin protein being produced from a single gene, there are 20 isoforms of human fibronectin as a result of alternative splicing. Fibronectin exists soluble as a dimer in the plasma (pFN) or as an insoluble part of the ECM (cellular FN) where it interacts with many other ECM components. Fibronectins have been shown to interact with integrins, collagen, tenascin-C, fibrillin, glycosaminoglycans as well as with growth factors [33]. Plasma fibronectin is synthesized and secreted without ED-A or ED-B segments by hepatocytes [33]. Cellular fibronectin is synthesized by many cell types, including fibroblasts, endothelial cells, macrophages and tumor cells, and secreted with ED-A and/or ED-B extra-domains [34]. Cancer associated fibroblasts (CAFs) have generally considered a source of fibronectin [35,36]. CAFs secrete and assemble fibronectin as parallel fibers mediating directional cancer cell migration. The expression of fibronectin is elevated in many solid tumors and is supposed to correlate with tumor grade/aggressiveness and can serve as a prognostic marker [37,38]. The role of fibronectin in promoting growth, survival and invasion of cancer cells has been highlighted by in vitro studies. It was shown that detachment of pancreatic cancer cells from ECM stimulated necrosis but fibronectin and laminin markedly increased the cells' survival by inhibiting both mitochondrial dysfunction and caspase activity. In pancreatic cancer cells fibronectin increased intracellular reactive oxygen species (ROS) production and NADPH oxidase activation. The prosurvival effect of fibronectin on pancreatic cancer cells has been further investigated and shown to be mediated through the *trans*-activation of IGF-IR. The mechanism involved fibronectin-mediated complex formation between integrin β3 and protein-tyrosine phosphatase SHP-2 that prevented SHP-2 from dephosphorylation of IGF-IR resulting in its sustained phosphorylation and the downstream activation of AKT kinase, up-regulation of anti-apoptotic Bcl-xL and inhibition of apoptosis [37].

It was also found that exogenous fibronectin stimulates lung carcinoma cell proliferation via integrin α5β1 through activation of the AKT/m-TOR/p70S6K pathway and inhibition of AMPK and LKB1 expression [37]. Exogenous fibronectin significantly enhanced proliferation and invasion in gallbladder cancer cell lines and markedly activated AKT/mTOR/4E-BP1 signaling cascade [39]. The role of fibronectin in promoting growth and migration via Src and TGF-β1 signaling was also demonstrated in renal cell carcinoma [37,40]. Fibronectin can support cancer cell proliferation through Erk and Rho-kinase signaling [37]. A recent study provided evidence that collagen and fibronectin together, but not alone, facilitate proliferation and tumorigenesis of glioma cells through PI3K/AKT/SOX2 and CDC42/F-actin/YAP-1/Nupr1/Nestin signaling pathways via integrin αvβ3 [37,41]. The production of fibronectin by cancer cells also contributes to the tumor development. In suspension cultures, squamous cell carcinoma cell aggregates, but not single cells, had high levels of fibronectin and were more resistant to anoikis through a mechanism involving fibronectin and the integrin αv receptor/FAK signaling [37].

3. Inflammatory process in cancer

Inflammation is a normal physiological response needed for an array of biophysical processes to repair of injured tissue, heal wound and combat against invading foreign pathogens; on the contrary, persistent and indomitable inflammation plays a crucial role in carcinogenesis [42,43]. Basically, inflammation represents three main types of having intrinsic, extrinsic, and chronic inflammation. Both extrinsic and intrinsic stimuli cause inflammation that is a complex part of the biological tissue response in the human body [44]. Different types of reasons such as physical injury, ischemic injury, infection, pathogens, and exposure to toxins, etc. are accountable for inflammation [45]. It was assumed that the initiation and the development of carcinogenesis are promoted by an inflammatory atmosphere [46,47].

3.1. Intrinsic pathway

The intrinsic pathway of inflammation plays a key role in the carcinogenesis. Genetic events including various oncogenes activation by mutation, chromosomal rearrangement or amplification, and the inactivation of tumor-suppressor genes trigger the intrinsic pathway. Then, neoplasia, the uncontrolled growth of cells, is instigated due to this pathway where inflammatory mediators are made by transformed cells. Tumor-intrinsic inflammation is mostly activated by mutations recruitment and activation of different kinds of inflammatory cells that accelerate the progression of malignancy [48]. The activated inflammatory cells such as phagocytes, neutrophils, dendritic cells and non-phagocytic cells release various types of inflammatory cytokines (e.g. IL-1, IL-6, TNF-α, TGF- β) resulting in the production of reactive oxygen species (ROS)/reactive nitrogen species (RNS) in response to inflammatory stimuli. An excess amount of ROS/RNS produced by chronic inflammation causes DNA damage by binding DNA that leads to the mutation of tumor suppressor genes and proto-oncogenes resulting in carcinogenesis [49]. Intrinsic inflammation or cancer-related inflammation, firstly, is stimulated through the production of cytokines and chemokines, leukocyte infiltration, angiogenesis, and tissue remodeling (Due to the activation of oncogenes and inactivation of tumor-suppressive genes, including PTEN, VHL) in the tumor microenvironment (TME). A principal contribution of this TME is in the development of tumors while immunotherapy can target its immune components for better cancer treatment [45,50].

3.2. Extrinsic pathway

In the case of the extrinsic pathway, the risk of developing cancer at certain anatomical sites, for example, the colon, prostate, and pancreas, is increased by inflammatory or infectious conditions. A number of agents that cause tumor-extrinsic inflammation by enhancing cancer vulnerability and progression of malignancy involve microbial agents (e.g. bacteria, virus etc.), autoimmune disorders, smoking, asbestos exposure, obesity and exceeding alcohol consumption. All of these factors trigger the danger of cancer development and metastasis [45]. Infection by *Helicobacter pylori* is more prone to cause gastric cancer which adopts NF- κB activation signaling through toll-like receptor (TLR) inducing COX-2\PGE2 pathway [51]. Both extrinsic and intrinsic pathways activate the transcription factors that are nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor 1α (HIF1α) in tumor cells. NF- κB may regulate more than 500 cancer related genes [52].

3.3. Chronic inflammation

In 1863, Rudolf Virchow first suggested the censorious role of chronic inflammation in cancer for the existence of white blood cells in neoplastic tissues. Inflammation could also be detrimental leading to disease when it is chronic. Then chronic inflammation is clinically related to pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes that result in a variety of diseases, for instance, cardiovascular diseases, cancer (tumorigenesis and metastasis), diabetes, arthritis, Alzheimer's disease, pulmonary diseases, and autoimmune diseases [53–55]. Progression of cancer, especially, is also co-related with chronic inflammation such as liver cancer (resulting from alcohol or hepatitis virus B or C infection), gastric cancer, mucosal lymphoma (due to *Helicobacter pylori*), cervical cancer (papillomavirus and hepatitis) [56,57]. Furthermore, chronic inflammation may induce dysregulation of the innate immune and inflammatory signaling in hematopoietic cells and connected with pre leukemic states, for example, CHIP (Clonal Hematopoiesis of Indeterminate Potential) and MDS (Myelodysplastic Syndromes) [58]. Chronic inflammation also causes different kinds of macromolecular injury in nucleic acids, proteins, and lipids which lead to tissue damage and the generation of cancer stem cells, finally causing cancer metastasis [49,59]. Chronic inflammation can initiate cancer through mechanism which include elevated generation of cytokines, chemokines, ROS\RNS, expression of oncogenes, cyclo-oxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), matrix metallo-proteinases (MMPs) and increased expression of oncogenes, and master transcription factors- NF-κB, STAT3, HIF-1α and activator protein 1 (AP-1), all of them persuade tumor cell multiplication, angiogenesis, invasiveness, transfiguration, metastasis, viability, and resistance to cancer therapy. Moreover, a set of atmospheric and civilization-related agents induces inflammation that ultimately leads to the pathways for cancer development, and is responsible for as much as 90% of all cancers [59].

3.4. Inflammation and epigenome

Inflammation also affects the epigenome. Under an inflammatory milieu, ROS/RNS or IL-6 induces epigenetic silencing via the down regulation of tumor suppressor markers and microRNAs that modulate the transcription of the DNA methyltransferase 1 (DNMT1) protein enhancing tumor suppressor markers methylation and microRNAs methylation, and leading to carcinogenesis [60]. Global DNA hypomethylation can be induced by ROS/RNS resulting in genomic instability. The initiation step of carcinogenesis is stimulated through the suppression of a tumor suppressor marker by DNA methylation of promoter [60]. In case of inflammatory response, NF-κB acts as a crucial factor to govern the expression of iNOS [61] which form mutagenic DNA lesion through the establishment of cytokine network that leads to carcinogenesis in response of inflammatory microenvironment [61].

4. Role of EMT in inflammatory process in cancer

Inflammation is an inducer of EMT where the aggressiveness of

cancer cells along with tumor-involved macrophages will be increased in the result of combined contribution of inflammation and EMT. For example, a key cell-intrinsic role in the development and instigation of various immune cells such as natural killer (NK) cells, cytotoxic T-cells (CTLs) and dendritic cells is being appeared in the stage of cancer immune-surveillance by Zeb family [62]. Different types of inflammatory elements like nuclear factor kappa B (NF-κB), TNF-α, transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), fibroblast growth factors (FGF), insulin-like growth factor (IGF), C-reactive protein (CRP), and Notch ligands of extracellular matrix microenvironment stimulate the EMT dynamic process [63,64]. Tumor and tumor-related cells in tumor microenvironment cause chronic inflammation by producing various inflammatory mediators such as IL1, IL6, IL8 TGF-β, TNF-α, CRP, and several chemokines [65,66]. Inflammatory cytokines initiate different signaling pathways that lead to the induction of NF- κB, STAT3 and Smads. Besides, EMT is performed by promoting EMT-TFs like Snail1, Twist1 and Zeb1 [67]. Inflammation and EMT are collaboratively involved in cancer development through the alteration of tumor microenvironment that is able to head tumor promotion. By the activation of EMT-TFs, some mechanisms of immunosuppression such as inhibitory cytokines, weakened dendritic cell activity and malfunction of cytotoxic T cells may be triggered in response of inflammation resulting in the initiation of cancer metastasis [68]. As EMT increases the circulation of cancer cells, inflammation facilitates invasiveness and dissemination of cancer cells [69]. A simplified figure (Fig. 1) shows the association of inflammation and EMT process in carcinogenesis. STAT3 pathway and EMT have been profoundly interconnected that is studied in variety of cancer. Activated STAT3 by IL6/11 dramatically promotes the expression of Twist1 and Snail1 which leads to the induction of an EMT process in the breast cancer cells. Moreover, a positive feedback loop is completed by Twist1 through the generation of inflammatory cytokines that maintained EMT phenotype and constitutively activated STAT3 signaling pathway [70]. Similarly, in colorectal cancer, EMT would be promoted by STAT3 through the upregulation of Zeb1, and in ovarian cancer, EMT is also induced by EGF receptor/IL6R activation in which STAT3 is overexpressed [71]. Therefore, STAT3 may stimulate the invasiveness of cells and offer resistant to cancer therapy and apoptosis in colorectal cancer progression during EMT. At the molecular level, inflammatory cytokine TNF- α stimulates EMT process by stabilizing activated Snail1 through the up regulation of NF-κB pathway [72]. TNF-α facilitates angiogenesis, tissue remodeling, tumor development and then promoting tumor cell metastasis by activating NF-κB. As Snail1

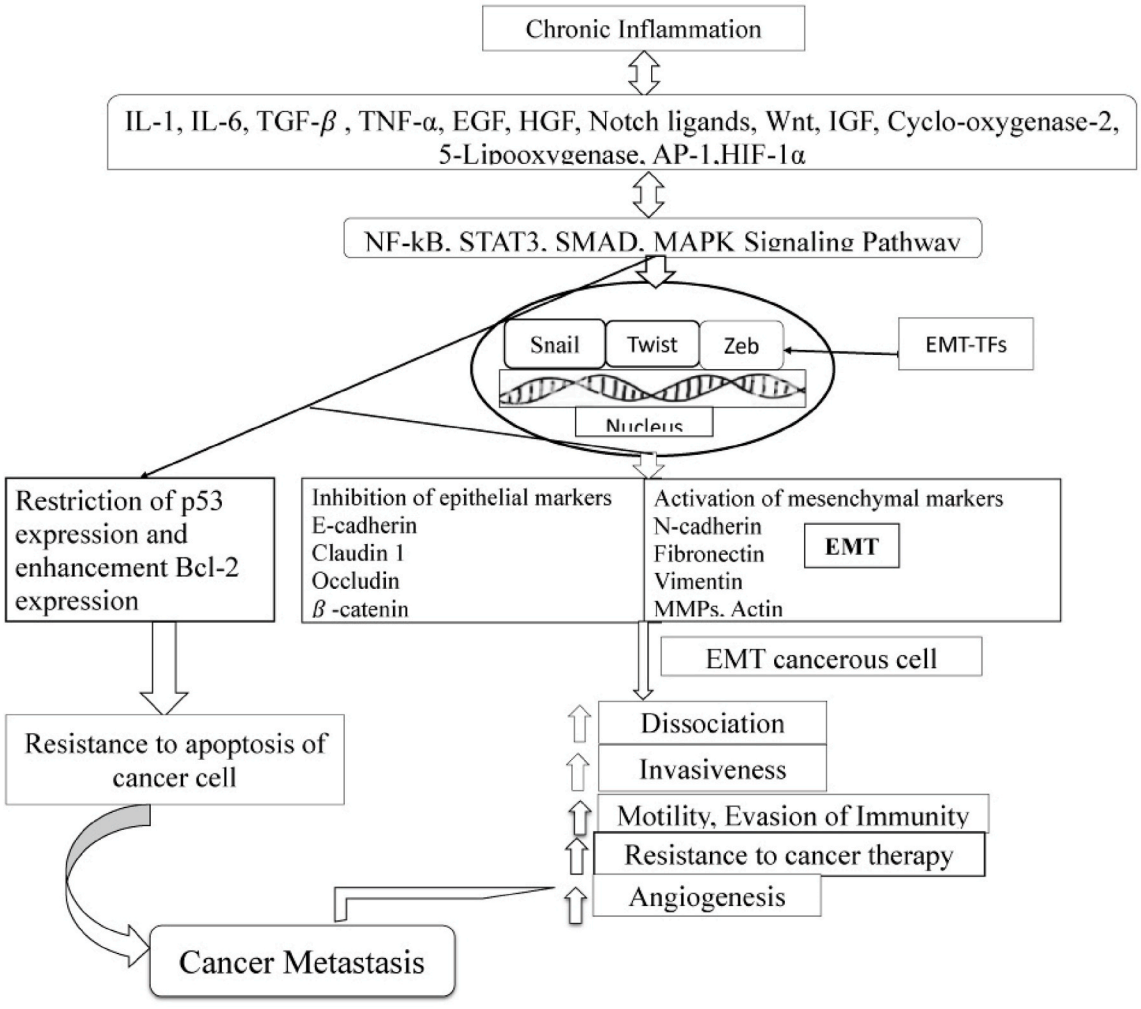

Fig. 1. Interconnection between inflammation and EMT-TFs in carcinogenesis. Chronic inflammation switch to cancer by activating different signaling pathways such as NF-kB, STAT3, SMAD, MAPK that activated various pro inflammatory cytokines (e.g., TGF-β, TNF-α), interleukins (e.g., IL-1, IL-6), growth factors (e.g., EGF, IGF), Cyclooxygenase-2, 5-Liooxygenase, Notch ligands, Wnt ligands, HIF-1-alpha and Ap-1. Then the EMT-TFs (Twist, Snail, Zeb) are activated in response to chronic inflammation along with restricted expression of p53 and enhanced the expression of Bcl-2. As a result, epithelial cells are switched to cancerous mesenchymal cell through activating the mesenchymal cells markers such as N- cadherin, Fibronectin, Vimentin etc. and inhibiting the mesenchymal cells markers such as E– Cadherin, Claudin 1, Occludin, β-catenin, leading to dissociation, increased invasiveness, increased motility, resistant therapy, resistant apoptosis and angiogenesis. All events lead to cancer metastasis.

itself represses the epithelial phenotype and inhibits apoptosis, inflammation promotes EMT via cells migration. Furthermore, TGF-β that is an important regulator of EMT process in association with Wnt, Notch, and MAPK pathway during morphogenesis. EMT is also up regulated by TGF-β/Smad pathway in cooperation with Wnt and Ras signaling of stem cell [73].

Another signaling pathway for carcinogenesis is p38α mediated mitogen-activated protein kinase (MAPK) pathway in the process of inflammation [61]. P38-MAPK pathway is activated by pro-inflammatory cytokines, such as TNF-α and TGF- β, which significantly stimulates the induction of EMT process. But NF-κB acts as a main transducer in response of inflammation activated by TNF-α and also promoter of tumor progression. Snail1 is up regulated by NF-κB in response to TNF-α and TGF-β signaling. It was also noted that in breast cancer, EMT is preceded by NF-κB-mediated up regulation of EMT inducer Twist1 via TNF-α activation pathway [74]. Likewise, in pancreatic cancer, NF-κB signal was demonstrated as a vital downstream factor for both TNF-α and TGF-β induced EMT [75]. NF-κB was also identified as an essential downstream mediator of EMT by cooperative action of TGF-β and Ras. For collagen type I-induced EMT, NF-κB was also shown to play a necessary role in pancreatic and colon cancer by the up regulation of Snail1 and LEF1 [73].

C-reactive protein (CRP) is an acute-phase protein that used as a systematic marker of inflammation and usually released into circulation in response to tissue injury and inflammation. It is produced by IL-6-dependent hepatic biosynthesis [76]. Increased CRP is seen in the case of inflammatory conditions, for example, rheumatoid arthritis, some cardiovascular diseases, and infection. The baseline CRP level can also be changed due to age, gender, smoking status, weight, lipid levels, and blood pressure [76]. However, a positive relationship between augmented CRP levels and an amplified threat of cancer including ovarian, colorectal, lung, and gastric cancer, has been seemed [77]. On the other hand, an emphasis on the activation of the C1q molecule in the complement pathway is the key role of CRP in inflammation which leads to the opsonization of pathogens. Moreover, cell-mediated pathways are started by CRP binding to Fc receptors of IgG leading to the discharge of pro-inflammatory cytokines. C-reactive protein stimulates the up regulation of p53 in monocytes and affects cell cycle kinetics of monocytes through CD32 (FcγRII), then induction of apoptosis is occurred by G2/M arrest in the cell cycle [77]. Thus the role of EMT in inflammatory process is to cooperate in cancer metastasis as it furnishes neoplastic cells with migratory and invasive properties, evasion of immunity and resistance to apoptosis.

5. Targeting EMT/inflammatory axis: possibilities in cancer therapeutics

EMT plays important role to achieve stem cell phenotypes in cancer cells, and targeting EMT process is promising in cancer therapeutics; some options for targeting EMT related proteins are given in Table 1. A study has conspicuously elucidated that Claudin proteins like claudin-3, claudin-6, are observed to exert therapy resistance in cancer cells, a feature of cancer stem cells [78]. Claudins act as a potential target in antibody-based therapies for carcinomas [79]. According to report by Shintani et al. [80] the peptide ADH-1 (antidiuretic hormone) encloses N-cadherin and represses tumor development in a mouse replica of pancreatic cancer. Thereafter, vimentin level is importantly decreased by the antibiotic salinomycin and the growth of E-cadherin appearance in CD133+ colorectal cancer cell lines HT29 and SW480 with a subsequent reduction of malicious character is stimulated [81].

Currently, one of the classic and basic drugs named 5-fluorouracil (5-FU) is widely used in adjuvant chemotherapy and palliative chemotherapy of colorectal cancer patients. Sometimes 5-FU is being resistant to local recurrence and distant metastasis. In contrast, a drug named FLNA (Filamin A, alpha) becomes possibly potential chemotherapeutic marker of drug sensitivity for CRC patients through inducing EMT and

Table 1
Overview of the mechanism of targeting agents on EMT-related proteins in cancer therapy.

Targeting Agents	Targeted Proteins	Mechanism of action
Cisplatin Erlotinib	Snail	siRNA technique in three glioblastoma cell lines (KNS42, U87, and U373) subdues the proliferation, viability, migration, and invasion of cells by deranging the EMT process [81,82]
Curcumin	Twist1	Decrease malignant glioma growth by preventing the JAK1, 2/STAT3 signaling pathway [85].
Doxorubicin and Paclitaxel	E-cadherin	E-cadherin, the epithelial factor, was downregulated in all recovered BCSCs for triple-negative breast cancer (TNBC) patients & the cells became elongated and the dense cell clusters disappeared in BCSC2 and BCSC5 [84].
Filamin A	Snail	Induce epithelial-mesenchymal transition and smad2 signaling pathway in CRC patients [82].
Quercetin	Twsit1, N-Cadherin, Vimentin	Diminish the migration ability of head and neck cancer-derived sphere cells partially by lessening the productions of Twist1, N-cadherin, and vimentin [86].
Thymoquinone	Twist1, Zeb1	Repress the expression of Twist1, Zeb1 expression, and expand E-Cadherin expression at the molecular level [84].
Salinomycin	Vimentin	Vimentin decrease the expression in CD133+ (Cluster of Differentiation) colorectal cancer cell lines HT29 and SW480 resulting in reduced malignant traits [81].
Salinomycin	E-cadherin	E-cadherin increase the expression in CD133+ (Cluster of Differentiation) colorectal cancer cell lines HT29 and SW480 resulting in reduced malignant traits [81].
shRNA	Snail	The inhibition of hedgehog signaling can hinder pancreatic cancer cells from acquiring tumor-initiating property and undergoing EMT [92].
Src kinase inhibitors	Mesenchymal cells to EGFR	Stimulate the inhibition of integrin-linked kinase (ILK) in hepatocellular carcinoma [91].

Smad 2 signaling pathway [82]. Thymoquinone, a natural product with anticancer potential can control cancer cell growth and metastasis potentially through Twist1/E-Cadherin/EMT or Zeb1/E-Cadherin/EMT signaling pathways [83,84]. Down regulation of Twist1 by another natural agent curcumin prevents the JAK1, 2/STAT3 signaling pathway intended to decrease malignant glioma cell growth [85]. The movement aptitude of head and neck cancer-derived sphere cells are partly diminished by another plant product quercetin through lessening the assemblies of Twist1, N-cadherin, and vimentin [86].

Breast cancer suppressor candidate-1 (BCSC1) forms unambiguous epithelial colonies including cobblestone-like morphology in which up regulation of Twist1/Snail/Zeb1 is occurred. For the treatment of triple-negative breast cancer (TNBC) patients, doxorubicin and paclitaxel are the two widely used drugs, and a little expression of Twist1, Snail, Zeb1 are showed in BCSC1 due to the combined treatment of these two drug [87]. A study also provides that activation of EMT with upregulation of the expression of Twist1 and Zeb1/2 are mostly done by Rac 1-MEK/Src signaling pathway [88].

Some small molecule inhibitors like C19 have significantly repressive activity against hippo signaling in mammalian cells which have an opposite reaction to Wnt and TGF-β pathways. For this reason, cancer cell migration and proliferation were being hindered and robust by C19 showing antitumor action in a mouse tumor xenograft model with no toxicity, but doxorubicin displays its resistance in vitro [89]. In another study, androgen receptor (AR) signaling is principally required during

prostate cancer and its therapy. Study has also indicated that the improvement of drug sensitivity to prostate cancer is occurred by the novel mechanisms of antitumor and anti-migratory purpose of miR-299–3p via exerting AR and vascular endothelial growth factor A (VEGFA) signaling pathways. Expression of EMT proteins like Slug, TGF-β3, phospho-Akt and phospho-PRAS40 is also impeded by the excess miR-299–3p, but expanded E-cadherin appearance. Thus, miRNAs are also deployed by the way of possible therapeutic implements targeting and regulating the multiple genes toward re-establishing the equilibrium in the middle of oncogenes plus tumor suppressors in prostate malignancy [90].

Expression of integrin-linked kinase (ILK) escalates the susceptibility of mesenchymal cells to EGFR-targeted treatment in hepatocellular carcinoma. In vitro reports showed that the inhibition of the cells undergoing EMT process are actively done by Src kinase inhibitors [91]. Thereby, obtaining tumor-initiating effects can be hindered by the obstruction of hedgehog signaling as well as go through EMT in pancreatic cancer cells. As an example, MET is being persuaded by shRNA quieting of Snail expression and decreases tumor development in vivo condition [92]. EMT of breast cancer cells is instigated by adipocytes through paracrine IL-6/SRAT3 signaling. In an analysis, encouraged EMT is monitored by an internationally approved medication named niclosamide due to its anti-breast cancer action and its aptitude to constrain adipocytes. Adipocyte-convinced EMT in association of the obstruction of IL-6/STAT3 instigation and down regulation of EMT-TFs Twist1 and Snail is altered by niclosamide [62].

Moreover, chemo sensitivity of cisplatin can be effectively reinstated by reducing Twist1 or Snail expression in the lung carcinoma cell route. According to the report of Myung et al. [93], propagation, feasibility, relocation, and incursion of cells are being subdued by reducing Snail1 expression using siRNA method by deranging the EMT process in the three glioblastoma cell lines (KNS42, U87, and U373). Furthermore, during second and third-line therapies of non-small-cell lung cancers, erlotinib, an EGF receptor tyrosine kinase inhibitor was found to work well [81].

6. Conclusions

EMT is one of the important biological features that contribute to cancer metastasis. Chronic inflammation is also responsible for cancer development in many aspects. Chronic inflammation might have influence on EMT process and vice versa. Their interconnectivity can affect cancer cell immortality and progression of metastasis, and targeting this axis might open a new door in cancer therapeutics. Some molecular agents are already identified which can target EMT proteins through modulating inflammatory pathways, and thus control cancer progression and metastasis. However, further clarification is needed, and this should be established clinically.

Data availability

Not applicable.

Code availability

Not applicable.

Author's contribution

MSI & MRM drafted manuscript; GB collected information and edited manuscript; MAK, designed the work, edited and finalized the manuscript.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

EMT	Epithelial-mesenchymal transition
ECM	Extracellular matrix
bHLH	Basic helix-loop-helix
STAT3	Signal transducer and activator of transcription 3
MAPK	Mitogen-activated protein kinase
HDAC2	Histone deacetylase 2
CAFs	Cancer associated fibroblasts
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
TME	Tumor microenvironment
HIF1α	Hypoxia-inducible factor 1α
VEGFA	Vascular endothelial growth factor A
CHIP	Clonal hematopoiesis of indeterminate potential
MDS	Myelodysplastic syndromes

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