Fitoterapia 106 (2015) 247–255

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Review

Modulation of epithelial-to-mesenchymal cancerous transition by natural products

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ARTICLE INFO

Article history:
Received 14 July 2015
Received in revised form 13 September 2015
Accepted 15 September 2015
Available online 18 September 2015

Keywords:
Epithelial-to-mesenchymal transition
Carcinoma
Natural products
Chemotherapy
Metastasis
Pathway signaling

ABSTRACT

Metastasis is mainly responsible for poor prognosis of cancer, and epithelial-to-mesenchymal transition (EMT) is a significant process often activated during cancer invasion and metastasis. Therefore EMT could be an effective target of chemotherapy to inhibit cancer metastasis and improve prognosis. Considering that many chemotherapeutics are plant-based, we reviewed recent reports about natural products extracted from plants and cancer EMT prevention.

Contents

1. Introduction

Normally, epithelial cell junctions, the protagonists of epithelial-to-mesenchymal transition (EMT), sustain an organized and stratified epithelial layer [1]. Cell junction forces, including tight junctions, adherens junctions, gap junctions and desmosomes, are required to maintain epithelial cell apical–basal polarity, stable cell layers and other epithelial phenotypes. When cell–cell junctions are gradually lost, the cytoskeleton and apical–basal polarity degrade and epithelial phenotypes are replaced by mesenchymal phenotypes, including high motility and invasiveness [2].

According to the function and niche, EMT is classified into three subtypes, Type I, Type II, and Type III [3,4]. Type I EMT is critical for embryonic development and organ formation. During embryonic genesis,

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http://dx.doi.org/10.1016/j.fitote.2015.09.013
0367-326X/

epithelial and mesenchymal cells transform mutually through EMT and mesenchymal-to-epithelial transition (MET), a reverse of the EMT process [5]. For wound healing and fibrosis, Type II EMT transfers epithelial cells to myfibroblasts [3], and Type III EMT contributes to the progression and metastasis of tumors derived from epithelial cells [6]. EMT confers epithelial-derived tumor cell higher motility and invasiveness and promotes effective metastasis. Additionally, EMT generates drug-resistance and tumor heterogeneity via induction of a stem-cell like phenotype [7,8]. Once tumor cells acquire mesenchymal and stem-cell like phenotypes, they disseminate from primary tumor, into blood and/or lymphatic circulation and undergo MET at the appropriate niche and time to establish metastasis [9].

Therefore preventing EMT is a novel strategy for metastasis suppression, and chemotherapeutics that can target this event may be promising. Several EMT-suppressing molecules have advanced to clinical trials, the most widely known clinic treatment, is a preferred candidate. Plenty of compounds targeting epithelial–mesenchymal plasticity have proceeded clinic trails [10]. The chemical structure of the anticancer drug is often synthesized from the basic chemical structures of botanic natural products and the clinic trails have demonstrated the anti-cancer effects of natural products [11–17]. Research confirms that botanic natural products can block various pathways involved in EMT (Table 1) such as MAPK/ERK1/2, PI3K/AKT, FAK/Src, WNT/β-catenin, and TGF-β1 or can inactivate key protein such as NF-κB, STAT3 and HIF-1α and lastly inhibit EMT at transcriptional level (Fig. 1).

The inhibition of cellular signal transduction by the botanic natural products mostly finally influences E-cadherin related transcription factors (Fig. 2). As a fundamental component of junction and adherens junction between the epithelial cells, E-cadherin maintains cell–cell junction, apical–basal polarity and cytoskeleton of epithelial cells. Downregulation of E-cadherin is a critical marker of EMT, and reversing the decreased E-cadherin is important strategy of chemotherapeutant. Several zinc-finger transcription factors, especially Snail (Snail1, Snail2 (Slug)) and Zeb (Zeb1, Zeb2) directly combine with the promoter of the E-cadherin encoding gene CDH1, silence E-cadherin expression [18,19]. Besides the zinc-finger factors, helix-loop-helix family (bHLH: E47 and Twist) inhibits expression of E-cadherin on transcriptional level [20,21]. Besides regulation at transcription level, post-transcriptional regulation of EMT is also important. MicroRNA regulates cancer progression through affecting the EMT-related transcription factors and signals [22]. RNA-binding proteins (RBPs) also modulate EMT via alternative splicing at posttranscriptional level [23]. Additionally post-translation of E-cadherin, like endocytosis and lysosomal degradation regulate the process of EMT [24,25].

According to the EMT related pathways and regulators, here we focus on botanical natural products that may prevent metastasis by targeting EMT via NF-κB, HIF-1α, JAK/STAT3, WNT/β-catenin, MAPK/ERK1/2, PI3K/Akt, FAK/Src, TGF-β1, and Hakai pathways. Additionally we briefly analyze the current research and potential phytochemical prevention strategies targeting EMT in tumors.

2. Pathway blocked by the botanic natural products

2.1. NF-κB signaling

Rel/NF-κB, transcription factor, is important to cellular responses, including proliferation, apoptosis, invasion and immuno-meditated inflammatory responses. Multiple molecules activate NF-κB, such as inflammatory factors [69–71], growth factors [72] and hypoxia [73]. Normally, when IκB, the inhibitor of NF-κB, is phosphorylated by activators, NF-κB dimer is released into nucleus where it binds to target DNA promoters [74]. EMT in cancer is suggested to involve NF-κB interacting with a promoter of Snail to increases Snail RNA [75]. Upregulation of NF-κB on Zeb have been reported as well [76]. Therefore down-regulation of NF-κB may be a promising pathway for inhibiting promising way to inhibit EMT in carcinomas.

Tumor microenvironment and various inflammatory factors within it are thought to be activators of NF-κB [77]. ShaoYao decoction, a Chinese traditional medicine for curing enteritis, is extracted from a common plant *Paeonia lactiflora* Pall has been shown by Xiao's group to be therapeutic in an AOM/DSS model on mice. AOM/DSS model is an inducible mouse model of colon carcinogenesis. AOM (azoxymethane) is a mutagenic agent that alkylates DNA and DSS (dextran sodium sulfate) is an inflammatory-induced reagent [78]. Researchers indicate that colitis symptom in the animals was reduced by ShaoYao decoction. Additionally, the immunohistochemical-staining of animal tissues revealed inflammation-induced increases of NF-κB and Snail that were reversed by ShaoYao decoction. These effects were accompanied by greater E-cadherin, the marker of EMT, expression. Thus ShaoYao decoction may down-regulate NF-κB and inhibit EMT [68].

TNF-α, an inflammatory factor, activates NF-κB [69,71]. Lu's group induced EMT with TNF-α in Hela cells and reported that anthocyanins extracted from *Vitis amurensis var. glabrescens* suppressed IκB phosphorylation in this cell line, causing inadequate accumulation nuclear NF-κB. Anthocyanins also reversed the EMT phenotype induced by TNF-α [32]. Zhang and colleagues also developed an EMT model using TNF-α in bladder cancer cells, BLX-211 and BLS-211, and they reported that the flavonoid butein inhibited EMT in these cells [30].

Growth factors also initiate the NF-κB pathway [72], and TAK1 is documented to be a significant mediator of signaling between growth factor and NF-κB. TAK1, a MAPKKK family member, regulates the TGF-β-induced pathways [79]. TGF-β induces binding of NF-κB to the Snail promoter and leads to EMT in A549 lung cancer cells. Luteolin, a chief compound of *Lonicera japonica* Thunb, attenuated interaction between NF-κB and a promoter of Snail and inhibited TGF-β-induced EMT [33]. Also anti-EMT effects of baicalin, extracted from *Scutellaria baicalensis*, were reported to modulate Snail and NF-κB cross talk in MDA-MB-231 breast cancer cells [26]. Interestingly, all flavone compounds mentioned here influence the NF-κB activity, so it is reasonable to speculate that other flavones inhibit EMT via inactivation of NF-κB.

Hypoxic tumor microenvironments also activate NF-κB. Hypoxia induces pancreatic cancer cells to acquire invasive phenotype via NF-κB [73]. Liu's group reported that triptolide from *Tripterygium wilfordii* attenuates binding activity of NF-κB and reverses the hypoxia-induced EMT while downregulating Twist and Slug [58].

2.2. JAK/STAT pathway

The JAK/STAT pathway is a fundamental signaling mechanism for multiple cytokines and growth factors [80]. When specific cytokines combine with corresponding receptors, STATs are subsequently activated by JAK tyrosine kinase family members, and then they translocate to the nucleus and interact with target genes [81].

Interleukin (IL) is an important inflammatory cytokine abundant in the tumor microenvironment [77]. IL-6 is reported to induce EMT in head and neck tumor cells via upregulation of Snail and in breast cancer cells via upregulation of Twist [82,83]. Zhao's group have discovered that wogonin, an active compound in scutellaria (*S. baicalensis*), inhibited IL-6-induced EMT by blocking expression and phosphorylation of Stat3, thereby reducing invasiveness and migration of tumor cells in an A549 lung cancer cell line and in an animal model of lung cancer [27].

Honokiol (*Magnolia officinalis* Rehd.) has been shown to have antithrombotic, anti-anxiety, anti-viral, anti-inflammatory and anti-tumor activity and it may suppress tumor cell proliferation, inducing apoptosis and inhibiting metastasis in multitude cell lines [84,85]. Dimiter's group recently reported that honokiol inhibits breast cancer cell invasion and migration and that it decreases phosphorylation of Tyr-705 of Stat3 and then suppresses the binding between Stat3 and the Zeb-1 promoter,