Review Article

Role of traditional chinese medicine and its chemical components in anti-tumor metastasis

ABSTRACT

Tumor incidence has become higher and higher in recent years, and it has also become the first killer jeopardizing human health. Tumor metastasis is the major barrier for tumor treatment. Some metastases occur in 5 or 10 years and some even in 20 years after tumor is controlled, but the metastases are impossible to defend effectively till now. Therefore, controlling tumor metastasis is critical in determining tumor patients' outcomes. In consideration of the limitations, toxicity and side effects of chemotherapeutic drugs for antitumor metastasis at present stage, seeking for drugs among traditional Chinese medicines (TCM) that share high safety and can effectively prevent and control metastasis is being paid more and more attention. This article is to expound the mechanisms of tumor metastasis and summarize the researches on antitumor metastasis with TCM.

KEY WORDS: Molecular target, signal pathway, traditional Chinese medicine, tumor metastasis

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INTRODUCTION

Tumor metastasis refers to a process that tumor cells extend and spread to the surrounding tissues directly from the primary sites or settle down in distal tissues and progress to form new tumors through blood channel or lymphatic channel.[1] In most cases, tumor cells of all sources have their fixed target organs *in vivo*, demonstrated by the *in vitro* experiment that this bunch of metastatic tumor cell was vulnerable to form tumor sites in specific locations in a sophisticatedly controlled condition.[2] There are four stages of tumor metastasis process: (1) Cell detaching or intravasation: When tumor *in situ* grows to a certain size, tumor cells can secrete some active molecules which can regulate the characteristics of cells *in situ* on gene level and thus lead to reduction of pH value, increase of tumor cell surface charge and modification of glycoprotein structure on the cell surface. These changes enable tumor cells to release a subset from tumor tissues to the surrounding blood vessels or lymph vessels. (2) Cell transportation or migration: Detached tumor cells are transported or migrated to other normal organs with movement of blood or lymph: (3) Cell attaching or extravasation. Tumor cell mass in blood or lymph is blocked in the tiny blood vessel and thus stays there. Then tumor cells release bio-enzymes that can destroy epithelial cells of normal tissues or peripheral connective tissues. After these bio-enzymes destroy the surrounding tissues gradually, tumor cells can enter into the impaired tissues and combine with tumor matrix such as fibrous protein. (4) Angiogenesis or neovasculization: In oxygen deficit situation, matrix of the attached tumor cells can produce angiogenesis promoting factors with the effects of self-regulatory mechanism, such as epithelial growth factor (EGF) and vascular endothelial growth factor (VEGF), which can promote formation of new vessels (generally speaking, it initiates obviously when the tumor diameter is up to 2 mm). Tumor cells are then led to rapid growth via the nutrition transported by blood in the new vessels.[3]

Traditional Chinese medicine (TCM) contains various chemical components with extensive pharmacological activity, and thus its effects on intervening tumor metastasis are versatile with complicated mechanisms. In recent years, the intervention of TCM on tumor metastasis has been studied from various approaches, diverse steps and different action spots worldwide. This article will make an overview on the molecular mechanisms of antitumor metastasis of TCM separately.

BIOLOGICAL NATURE, MOLECULAR BASIS AND DRUG TARGETS OF TUMOR METASTATIC CELLS

Although metastatic cells come from tumor *in situ*, their biological nature has changed a lot

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during metastasis, including cell surface charge and motility, deficit in connectivity among cells, enhancement of matrix catabolic enzymes activity, increasing level of variant surface glycoprotein, reduction of cell immunogenicity, lack of hormone, growth factors and vitamin D receptors on tumor cells surface, and modification of cellular morphology (noncircular and irregular).[4,5] All the above processes are correlated with cell metastasis potential. We will mainly overview tumor metastasis related molecules in this part.

Cell adhesion molecules

Cell adhesion molecules play roles in cell detaching, and closely correlated with the adhesive capacities among cells,[6] which include integrin family of transmembrane receptors,[7] the superfamily of transmembrane cadherin proteins,[8] connexins,[9] the transmembrane glycoprotein CD44,[10] selectins,[11] vascular cell adhesion molecules (VCAM)-1[12] and platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31).[13]

Cell membrane-related molecules

Cell membrane-related molecules mainly include laminin (LN), fibronectin, keratin and tenascin, which play roles in tumor cell detaching and attaching.[14]

Cell matrix degrading enzymes

Cell matrix degrading enzymes include matrix metalloproteinases (MMPs), tissue inhibitors of matalloproteinases (TIMPs), plasminogen, collagenases IV, transformed growth factor (TGF) and tumor necrosis factor α (TNF-α).[15-19] MMPs and TIMPs are a series of inhibitors of matrix proteinases. So far, over 20 categories have been found. MMPs can combine with zinc to synergistically degrade tumor matrix. MMPs can also bind to their specific receptors to generate other effects.[20,21] In general cases, TIMP can compete with MMPs for Zn ion, consequently decreasing the activity of MMP.[22] Hence, elevation of MMP and TIMP levels in tumor cells indicates the enhancement of tumor malignancy.[23,24]

MMPs are mainly divided into four categories: Collagenase (MMP-1, -8, -13, -18), stromelysins (MMP-3, -10, -7), gelatinases (MMP-2, -9) and Elastases (MMP-12, -19, -20). Others include RXXR secreted type (MMP-11) and RXKR membrane type (MMP-14, -15, -16, -17, -21).[25] TIMP-1 mainly acts on MMP-9, and others include MMP-1, -2, -3.[26] TIMP-2 mostly interacts MMP-2, and others include MMP-1, -3, -9.[27] TIMP-3 has influence on the MMP-1, -3, and others include MMP-2, -9.[28] TIMP-4 shows inhibitory effect on MMP-2, and others include MMP-1, -3, -7, -8.[29] Neovascularization is mainly divided into three steps: Epithelial cell proliferation, extracellular matrix degrading and epithelial cell migration.[30] MMP participates in these three steps and ultimately promotes the angiogenetic process.[31,32] For example, MMP-3, -7, -9, -13 can degrade plasminogen into angiostatin.[33-35] Further, plasminogen and endostatin are inhibitors of neovascularization.[36] Based on these results, directly researches on the inhibiting effects of new compounds on the activities of related matrix-degrading enzymes such as MMPs can also screen drugs of antitumor metastasis.

Cell motility and tumor angiogenesis

Cell motility and tumor angiogenesis involve vascular epithelial growth factor (VEGF), basic fibroblast growth factor (FGF), endothelin, IL-2, IL-12 and EGF, which are confirmed to play key roles in tumor metastasis and new vessels and different molecules act on different phases of tumor metastasis.[37-41] Tumor angiogenesis is an important process and pathway that metastatic tumor tissue changes from a state difficult to observe with naked eyes into a state with obvious tumor metastasis.[30] Nowadays, compounds screened to inhibit tumor angiogenesis are provided with antitumor metastasis effects. Some models not only can be observed from histomorphology,[42] but also there are some neovascularization-related epithelial cell promoting factors, such as EGF,[43] VEGF,[44] FGF-2,[45] platelet-derived growth factor (PDGF),[46] platelet derived-endothelial cell growth factor-thymidine phosphorylase (PD-ECGF/TP)[47] and endothelin,[48] among which VEGF presents the most significant promoting effects on new vessels epithelial cells.[49] Normal epithelial cells can secrete these cell factors and so do some tumor cells. At present, the level of VEGF in tumor cells is regarded as the criterion for evaluating patients' outcomes.[50] Compounds targeting above mentioned cell factors exhibit strong anti-tumor activities, especially metastasis.[51]

MECHANISMS OF TRADITIONAL CHINESE MEDICINES AND THE ACTIVE INGREDIENTS ON TUMOR METASTASIS

Functions and the molecular mechanisms of TCMs and the active ingredients exerted on different phases of tumor metastasis will be illustrated in this part.

Degradation of extracellular matrix by traditional Chinese medicines and the active ingredients

In the process of infiltration and metastasis, tumor cells invasion through extracellular matrix mainly includes adhesion, degradation and motility.[3] When tumor cells stick to extracellular matrix, with the participation of a series of proteolytic enzymes, they can migrate to other parts after basement membrane and extracellular matrix are degraded. Therein, matrix metalloproteinases (MMPs) and urokinase plasminogen activator (u-PA) are the two major proteolytic enzymes promoting tumor cells metastasis.[52] It is reported that resveratrol could inhibit the activities of MMP-2 and MMP-9 by down-regulation of the mRNA and protein expressions level.[53] Furthermore, resveratrol inhibited invasion and metastasis of cervical cancer not only by increasing TIMP-1 expression, but also by stimulating HMP-2 activity and its mRNA and protein expressions level.[54] Extractives of Chinese tallow tree could reduce the expressions of MMP-2, MMP-9 and u-PA in high metastatic A549 and Lewis lung cancer cells in a dose-dependent manner.[55] Hyperforin can inhibit the expressions of MMP-2, MMP-9 and u-PA so as to inhibit tumor

invasion and metastasis.[56] Baicalin can inhibit MMP-2 protein expression so as to promote TIMP-2 expression and inhibit invasion and metastasis of liver cancer BEL-7402 cells.[57]

Influence of traditional Chinese medicines and the active ingredients on tumor cells migration and motility

Tumor cells begin to move to the distance after degrading matrix. The potential of tumor cells migration and motility is necessary not only for the invasion to the surrounding tissue, but also for the piercing of blood vessels, which is the prerequisite of tumor infiltration and an important step of tumor metastatic spread.[58,59] Tumor cells migration and motility is activated by exercise factors, which trigger cancer cells motility via information conduction after combined with receptors.[60] The stronger the potential of tumor cells migration and motility, the easier metastasis occurs. It is found that some ingredients in TCM can reduce the potential of tumor cells migration and motility through affecting the activity of exercise factors and inhibiting the adhesion of tumor cells with fibronectin. Resveratrol can inbhibit the motility of ovarian cancer cell strain HO-8910PM *in vitro*.[61] Recently, a group of researchers demonstrated that resveratrol prevented the occurrence of cisplatin-induced EMT in ovarian cancer cell lines and exhibited a promising role as an adjuvant to traditional chemotherapy.[62] Extractives of *Angelica sinensis* can reduce the migration of B16-BL6 cells and inhibit the metastases.[63] Jasmine can inhibit the motility of B16-, F10 cells and the progress of experimental pulmonary metastasis.[64] Besides, water extract of *Curcuma zedoary* can significantly inhibit the invasiveness and chemotaxis motility of high metastatic melanoma cell B16 in mice with high concentration.[65]

Influence of traditional Chinese medicines and the active ingredients on tumor cells adhesion effects

Adhesion plays a dual role in tumor cells invasive movement.[66,67] Tumor cells must detach from the originally adhered primary lesion so as to initiate the invasion. Meanwhile, adhesion facilitates tumor cells the capability of movement. Tumor cells can obtain impetus to move in the process of continuous adhesive contact and de-adhesive contact.[68,69] Therefore, the process of tumor cells metastasis can also be considered as a process of adhesion and de-adhesion.[70,71] Researches showed that some TCM could lower the adhesive effect on tumor cells through inhibiting the expression of cell adhesion molecules and their activities. Curcumin significantly inhibited the expressions of CD44V6 in nude mouse transplanted with MCF-7 cells, which further inhibited breast cancer infiltration and metastasis.[72] Tubeimoside can reduce the adhesion of PGCL3 cells to laminin and fibronectin and lower the secretion and activities of Collagenase IV secreted by PGCL3 cells so as to inhibit adhesion and invasion of these cells.[73] Norcantharidin can lower adhesive capacities via downregulation of the expressions of desmogleins, N-cadherin and α, β-catenin.[74] Liu Jingbing *et al*., reported that arsenic trioxide could regulate the expressions of adhesion molecule CD44 and lower the adhesion effects of pancreatic carcinoma so as to inhibit metastases.[75]

Inhibiting effects of traditional Chinese medicines and the active ingredients on tumor angiogenesis

Tumor angiogenesis is the prerequisite and foundation for tumor cells metastases, which supplies nutrition for tumor cells proliferation and growth.[76,77] Therefore, without formation of new vessels, tumor cells will grow slowly and are difficult to form metastases. Tumor angiogenesis depends on the balance between pro-angiogenesis and anti-angiogenesis molecules in local microcirculations.[78] Therein, VEGF is the most common tumor pro-angiogenesis molecule. It is found that many TCM can exert effects of inhibiting tumor angiogenesis. For example, eleutheroside can inhibit mRNA and protein expressions of VEGF in human liver cancer cell strain HepG2 and VEGF-induced tumor angiogenesis and thus inhibit tumor metastases.[79] Evodiamine can inhibit the phosphorylation of ERK to reduce the expression of VEGF and inhibit tumor metastases.[80]

Influence of traditional Chinese medicines and the active ingredients on tumor metastasis-related gene expression

Occurrence of tumor metastasis is regulated and controlled by many related genes, such as cancer gene, metastasis-related gene and relevant metastasis suppressor gene.[81] When these related genes were modified in some conditions, either activated or inactivated, tumor cells metastases would be induced. It is found that some TCM can inhibit tumor metastases through affecting these genes. Arsenic trioxide upregulated the expression of metastasis suppressor gene mn23 and downregulate the expression of metastasis-related gene N-myc so as to inhibit tumor metastasis.[82] Berberine strengthened the inhibiting effects of arsenic trioxide on the expression of tumor metastasis-related genes myc and jun, consequently inhibiting the invasion and metastasis of glioma cells.[83] Norcantharidin facilitated the expression of tumor cell metastasis suppressor gene mn23 and inhibit the metastasis of human gallbladder carcinoma.[84] Zhong *et al*., reported that allicin decreased the expression of VEGF, uPAR, and HPA, and inhibited the invasion and metastasis of human colon cancer cells *in vitro*.[85]

INFLUENCE OF TRADITIONAL CHINESE MEDICINES AND THE ACTIVE INGREDIENTS ON TUMOR METASTASIS-RELATED SIGNAL TRANSDUCTION PATHWAY

Further molecular studies found that all steps of tumor metastasis are regulated by different signaling pathways. TCM and the active ingredients exert antitumor metastasis just via regulating these signal pathways. We will make a brief introduction to the interactions between TCM and metastasis-related signal pathways in this part.

Influence of traditional Chinese medicines and the active ingredients on nuclear factor-κB (NF-κB) signaling transduction pathway

The transcription factor NF-κB presents overexpression in various human tumors and plays an important role in tumor

infiltration and metastasis.[86-88] NF-κB can accelerate the adhesion of tumor cells to epithelial cells and matrix, induce tumor cells to generate protease so as to degrade extracellular matrix, and promote vascularization.[89,90] Sliva *et al.*, found that lucid ganoderma exerted the inhibiting effects on the migration of high invasive non-estrogen receptor-dependent breast cancer cell via inhibiting NF-κB signal pathway.[91] Bharat *et al.*, reported that curcumin inhibited paclitaxel-induced NF-κB signaling pathway and pulmonary metastasis of human breast cancer cells in nude mice.[92] Dykellic acid inhibited NF-κB transcriptional activity and thus influence the expression of MMP-9.[93]

Influence of traditional Chinese medicines and the active ingredients on AP-1 signaling transduction pathway

Activation of AP-1 signaling transduction pathway is closely associated with tumor invasion and metastasis, which can accelerate abnormal expressions of downstream target genes such as MMP, integrin, CD44 and VEGF.[94] AP-1 participates in various invasion and metastasis steps such as cell matrix degradation, abnormal adhesion, and metastatic tumor angiogenesis.[95] Thyagarajan *et al.*, reported that lucid ganoderma could inhibit transcription factor AP-1 activity and thus affected human breast cancer MCF-7 cell metastasis induced by oxidative stress.[96] Curcumin can reduce MMPs expressions via decreasing AP-1 activity so as to inhibit nude mice hematogenous breast cancer metastasis.[97] Tea polyphenols can inhibit the activity of breast cancer cell AP-1 and adhesion, migration and infiltration of cancer cells.[98]

Influence of traditional Chinese medicines and the active ingredients on ERK signaling transduction pathway

ERK is critical for signals transducing from cell membrane surface receptor into nucleus. After receiving stimulus, ERK is activated through phosphorylation and then passes through nuclear membranes to act on some transcription factors such as AP-1 and NF-κB so as to regulate gene expression.[99] These transcription factors further regulate the transcriptions of their target genes respectively and thus modify the activities of tumor metastasis related proteins.[100] Nobiletin directly inhibited MEK activity, reduced phosphorylation of ERK, and thus inhibited the expression of MMPs in human fibrosarcoma HT-1080 cell line, all of which ultimately inhibited tumor metastasis.[101] *Lucid ganoderma* inhibited phosphorylation of ERK1/2 in accompanied with lowering DNA-binding activities of AP-1 and NF-κB and down-regulation of the expression of MMP-9.[100] By inactivating ERK 1/2 and p38 (MAPK), Flavanone could reduce the expressions of MMP-2 and u-PA in human lung adenocarcinoma cell line A549 and lewis lung cancer cell strain LLC, thus inhibiting tumor infiltration and metastasis.[102]

SUMMARY

In conclusions, tumor metastasis is a complicated cascade process with many steps and procedures regulated by various factors. The interventions of TCM and the active ingredients on tumor metastasis manifest multi-target spots and multi-efficacy effects. At present, studies on TCM and the active ingredients in intervening tumor metastasis begin to take shape both at home and abroad. Meanwhile, studies on tumor metastasis are increasingly deepening. Emerging and developing of cutting-edge disciplines such as bioinformatics, genomics, proteomics and systems biology has provided great platforms for studies on TCM in tumor metastasis. With the unceasing efforts of researchers, studies of the effects and mechanisms of TCM will gain greater development and promote lucubrating new drugs for antitumor metastasis.

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