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REVIEW

Stimuli-induced Organ-specific Injury Enhancement of Organotropic Metastasis in a Spatiotemporal Regulation

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Abstract The relationship between inflammation and tumorigenesis has been established. Recently, inflammation is also reported to be a drive force for cancer metastasis. Further evidences show that various stimuli directly induced-injury in a specific organ can also promote metastasis in this organ, which include epidemiological reports, clinical series and experimental studies. Each type of cancer has preferential sites for metastasis, which is also due to inflammatory factors that are released by primary cancer to act on these sites and indirectly induce injuries on them. Host factors such as stress,fever can also influence distant metastasis in a specific site through stimulation of immune and inflammatory effects. The five aspects support an idea that specific-organ injury directly induced by various stimuli or indirectly induced by primary tumor or host factors activation of proinflammatory modulators can promote metastasis in this organ through a spatiotemporal regulation, which has important implications for personalized prediction, prevention and management of cancer metastasis.

Keywords Stimuli · Organ-specific injury · Organotropic metastasis · Spatiotemporal regulation

Introduction

Metastasis is the primary cause of mortality from most solid cancers. Understanding the biology of metastasis will be vital for discovering new targets to prevent/slow and treat metastasis. Although great advancements have been made in uncovering cancer metastasis, it still remains a great problem for cancer patients. The relationship between chronic inflammation and tumorigenesis has long been recognized [1–5]. Recently, inflammation is also found to play an important role in the process of metastasis [6–8]. According to this clue, we search for the literatures about the studies focusing on inflammation and metastasis and find that enhancement of cancer metastasis in a specific organ is not only due to chronic inflammation but also link with a variety of injuries on this organ induced by different stimuli. This can be date back to Jones's [9] study in 1914, who showed that secondary tumors grew at points of injury. To get more information on specific-organ injury and organotropism metastasis, we further enlarged the searching strategies by using keywords including inflammation, injury, infection, wound healing, trauma, asthma, fibrosis, bone fracture, skin scar, and metastasis from the databases of the Google scholar and PubMed. We also conducted a secondary searching from these literatures. These searched literatures supported an idea that there was a strong relationship between different stimulus-induced specific organ injury and tissue-specific metastasis. In the following statements, we reviewed the evidence for this idea and discussed its implications in the biology of metastasis and clinical practice.

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Evidences from Epidemiological Studies, Clinical Series and Experimental Studies

Evidences from Epidemiological Studies

Epidemiological studies show that different stimuli such as smoking and asthma-induced lung injury can enhance lung metastases from different kinds of cancers. Smoking is a well

known risk factor for carcinogenesis, especially for lung cancer [10,11]. It can also predict poor prognosis in breast and other cancers [12,13], which may be due to short-term relapse in smoking patients. Shaw et al. [14] found that smoking could induce malignant melanoma metastasis, indicating that smoking not only contributed to carcinogenesis but also metastasis. Recently, it has been testified that smoking can increase lung metastasis from breast and esophageal cancer [15–17]. Smoking-induced lung injury is mainly through increasing the permeability of endothelial cells and assaulting epithelial cells by free oxygen radicals, local immune functions on pulmonary and system effect [10,18–21]. These effects are considered to contribute to enhancement of lung metastasis [15–17]. Padua et al.'s [22] showed that the mechanism of lung metastasis from breast cancer was attributed to the increasing permeability of lung capillaries caused by angiopoietin-like 4 (ANGPTL4). Smoking seems to have a similar effect to ANGPTL4 on increasing the permeability of lung capillaries by its compositions. Asthma is a common pulmonary disease with infiltration of perivascular/peribronchial leukocyte cells, subepithelial fibrosis, increasing mass of airway smooth muscle and secretion of cytokines [23,24]. Among these changes, fibroblasts, macrophage cells, transform growth factor-beta (TGF-β) have been also identified to play important roles in cancer metastasis [25–33]. So Taranova et al. [34] studied the relationship of asthma and lung metastasis from breast cancer and found that breast cancer patients with asthma underwent a high risk of lung metastasis compared with non-asthma patients, which might be due to the pulmonary changes at the cellular and molecular levels caused by asthma. Radiation is a local treatment for breast cancer. However, it can also induce side effects including skin and lung injuries [35]. Unfortunately, it was found that post-operative radiation could also enhance skin and pulmonary metastasis from breast cancer [36]. The lung damage from smoking and radiation is mainly a kind of injury not just inflammation while asthma-induced lung injury manifests itself as a process of airway remodeling and inflammation, which are regarded as different stimuli to induce lung injury through different mechanisms. All of them can enhance lung metastases from the same type of cancer. In this sense, smoking, radiation and asthma seem to have a common status in lung for recruitment of the same type of cancer cells. They have been reported in many literatures to induce structural and functional changes in the lungs, which include injured cells, actively inflammatory cells and their releasing cytokines, chemokines and growth factors. These changes are reported to enhance lung metastasis through the mechanisms of passively enriching cancer cells by structural changes of the lung and actively binding their receptors by cytokines, chemokines or growth factors in the above literatures, which may contribute to the common status. Identify this common status will be a direction to prevent lung metastasis. On the other hand, the same stimulus-induced lung injury can increase lung metastases from different types of cancer, which mean that there is also a common pathway in different cancers. This common pathway can be recognized by the constitutions of microenvironment of the lung injury and is important to develop common target drugs for different cancers.

Other inflammatory sites have been also reported to be prone for cancer metastasis. Peritoneal metastasis is a frequent pattern of recurrence for many solid tumors. The relationship between peritoneal injury, repair and peritoneal metastasis has been recognized [37] . Pancreatic fistula (PF) is a common complication after biopsy or resection of pancreatic cancer. It was reported that PF after surgery of pancreatic cancer was a predictive factor for peritoneal recurrence [38]. PF can induce inflammation around the pancreatic anastomosis, which may be the reason for PF prediction of peritoneal recurrence. Oral metastasis is a rare event. A literature analysis showed that metastatic tumors were more often seen at the gingival than other oral mucosal sites [39]. In the oral cavity, the gingival is prone to be affected by inflammation. This finding may indicate that the chronically inflamed gingiva may serve as a pre-metastatic niche for disseminated cancer cells [39].

Although these clinical studies mainly focused on pulmonary, peritoneal and gingiva metastasis, the following case reports showed that metastases occurred at the sites with injury, trauma, wound infection and chronic inflammation and supported the association between stimuli-induced organ-specific injury and organotropic metastasis.

Evidences from Clinical Series

The injured tissues have been recognized to be preferential sites of metastases since 1960s [36,40–42]. However, there are only case reports in clinical observations. These reports showed that metastases in the skin scars [42–56] such as the flap donor site, radiation dermatitis, unrelated biopsy site [57] and percutaneous gastrostomy sites [58,59], bone traumas and fractures [41,60–66], pulmonary trauma [67], lung fibrosis [68], focal infarction and infection of the brain [69,70], which suggested that injuries in the different sites might favor an environment for tumor locomotion and growth. Unusual metastases should be also noticed. Skeletal muscle metastasis is an infrequent event. Palazzo et al. [71] and Magee et al. [72] respectively reported skeletal muscle metastases mainly at the injury sites of skeletal muscles, indicating that injury and inflammatory oncotaxis contributed to metastasis at this tissue. Synovial metastasis is also very rare. Currall et al. [73]reported a case with synovial metastasis from colorectal adenocarcinoma after total knee arthroplasty, indicating the injury and repair of synovial tissue after operation provided a favorable environment for cancer cells. Dionigi et al. [74] reported a case that was diagnosed of intrathyroidal metastasis from renal clear cell

carcinoma. The patient had been evaluated toxic substernal goiter with chronic thyroiditis for 2 years before diagnosed of renal carcinoma, indicating that chronic thyroiditis could summon up cancer cells to lodge and favor them growth. Table 1 sum up some cases of the above reports. In these reports, some patients showed metastases at the injured sites before diagnosed of primary tumors; others exhibited metastases after resection of primary tumors. They have a common trait that inflammatory sites promote metastases even if corresponding primary tumors rarely metastasize to the organs, which support that different wounds can increase metastases in these inflammatory sites [75]. Walter [62] has proposed two possibilities to explain the mechanism. One is that locally damage tissues create a favorable environment that is permissive for seeding of metastatic cells from distant sites. The other is that micrometastatic foci are already present at the time of injured sites, and trauma initiates changes in the microenvironment that stimulate the proliferation of the metastatic cells. We support that both of them exist. Inflammatory sites can summon cancer cells and or stimulate the preexisting micrometastases at these sites. In clinical practice, doctors should be aware of these circumstances that internal and external inflammation sites may be possible focuses for tumor metastases. These literatures are only case reports and seem to be not enough for supporting this hypothesis. The probable reason may be that similar cases are ignored by clinical doctors or due to publication bias. However, the following experimental studies may further provide evidence for this idea.

Evidences from Experiment Studies

Researchers have investigated whether metastasis preference can be influenced by an injured organ. They have found that injuries on lung, liver, bone, kidney, and other organs can promote occurrences of metastasis in these wound organs no matter in artificial metastasis or spontaneous metastasis. This effect mainly occurs during the healing process. When these injured organs recover to normal status or develop to fibrosis, metastases will rarely occur. This supports that a particular organ undergoing a healing process after stimuli action may promote organ-specific metastasis through a spatiotemporal regulation.

The lung is an organ affected by both primary lung cancers and metastatic tumors from other solid tumors. Chronic inflammation has been testified to be strongly related with primary lung cancer [11]. The following experiments also show that different stimuli-induced lung injury can increase the formation of metastasis in the site. Smoking is a well known factor to induce lung injury. The retrospective reports showed that smoking increased lung metastasis from breast cancer [15,16], which was also testified in Murin et al.'s experiment [76]. The potential mechanism may be related to smoking-associated inflammatory responses including local pulmonary changes and system effects. Protein kinase C (PKC) in activation status is a mediator to induce inflammatory response and cell death in human airway epithelial cells [77]. Gopalakrishna et al. [78]found that catechol and hydroquinone released by cigarette smoke could activate PKC to influence cancer cell invasion and metastasis, which might be the reason for smoking promotion of lung metastasis. Platelet hyperactivity is one of smoking induced system effects [79] and can lead to release aggregation-inducing factor aggrus/podoplanin that has been shown to promote pulmonary metastasis [80]. A lung infection is inflammation in the lungs caused by a virus, fungi or bacteria infection. It is present in about 47 % of cancer patients and often leads them to be death [81]. It has been found that acute lung infections can also promote pulmonary metastasis, which may be due to infections-induced lung inflammation that provides a favorable metastatic niche [81]. Yan and colleagues further find that the mechanistic basis for bacterial-induced lung injury promoting pulmonary metastasis was via the ubiquitin/CXCR4 chemokine axis [81]. The Chemokine CXCR4 has been found to play a critical role in lung metastasis from breast cancer [82], which can be modulated by multiple inflammatory components [83]. Cyclophosphamide is a cytotoxic drug to treat most of solid cancers. Nevertheless, it also has an opposite effect and is found to be able to enhance lung metastasis in experimental studies [84–89]. Multiple mechanisms are involved in the process, which include endothelial cell injuries, elevated vascular endothelial growth factor (VEGF), increased immunoreactivity, and macrophage infiltration [86,88,89]. Another cytotoxic drug, bleomycin is well known for inducing lung injury. Its damages on the lung include alveolar damage, collagen synthesis, macrophage infiltration, injuries of vascular endothelial cells and secretion of cytokines such as TGF-β, tumor necrosis factor alpha (TNF-α), connective tissue growth factor(CTGF) [90–92]. These responses are also reported to be vital for the formation of metastasis [25,26,32,33,93–99]. Thus, the investigations on the relationship between lung metastasis and bleomycin-induced pulmonary injury were also studied and showed that bleomycin-induced pulmonary damage increased lung metastasis [100–103]. Radiation-induced lung injury has been well known. It can also increase lung metastasis in preirradiation of lung of experiment animals [87,104–107]. This effect can be abolished by neutralizing antibody of TGF-β, indicating that the effect is partly through the regulation of TGF-β [108]. Other stimuli such as monocrotaline [109], carbon suspension [110], hyperoxia [100,111], ozone exposure [112] like smoking or radiation have different mechanisms to induce lung injury but have the same effect on enhancing lung metastasis, which is not only related to the status of lung damage but also the process of repair in these reports.

Table 1 Clinical reports of metastasis at the injured sites

Author(Year)	Primary cancer	Diagnostic methods for primary cancer	Metastatic sites and their traits	Interval between primary and metastasis
Cohen (1972) [42]	larynx cancer	Occasionally found PT in anesthesia	skin, bone, and lymph nodes in previously traumatized area	5 months
Marley (1982) [45]	Uterus adenocarcinoma	Routine diagnose of PT	Skin in the area of chronic radiation dermatitis	NA
Ito (1984) [46]	Breast cancer	Routine diagnose of PT	Skin in the areas previously treated by prophylactic irradiation	6 months
Carr (1986) [47]	the retromolar fossa	Routine diagnose of PT	the donor site of a temporalis muscle flap	NA
Betke (1993) [49]	gastric carcinoma	Routine diagnose of PT	a congenital melanocytic nevus	NA
Erol (2008) [53]	cutaneous melanoma	Routine diagnose of PT	skin graft donor site on the contralateral lower extremity	8 weeks after PT excision
Pradhan (2006) [52]	Cervix squamous cell carcinoma	Routine diagnose of PT	skin scar of a previous cesarean section before 26 years	12 months
Marenco (2009) [54]	Melanoma on the right supraclavicular	Routine diagnose of PT	Skin graft donor site at the left thigh	1 month
Shine (1981) [44]	Sigmoid colon adenocarcinoma	Routine diagnose of PT	Metastasis at the site of intradermal skin tests with a marked inflammatory response after operation of PT	3 months after PT and 2 months after skin test
Trefzer (1998) [50]	malignant melanoma on the left scapula (Clark level IV)	Routine diagnose of PT	At the graft donor site with a healing process	8 weeks after removal of PT and receiving grafts
Serrano-Ortega (2000) [51]	Acral lentiginous melanoma (ClarkLevel III, Breslow depth 1.3 mm)	Routine diagnose of PT	At the graft donor site with a healing process	1 month after removal of PT and receiving grafts
Ferguson (2004) [57]	an osteosarcoma of the proximal humerus	Routine diagnose of PT and concurrent with biopsy of the contralateral humerus	At the Remote Biopsy Site with a healing process	NA
Hameed (2009) [59]	squamous cell carcinoma of the oropharynx	Routine diagnose of PT and receiving percutaneous endoscopic gastrostomy	the gastrostomy site with granulation tissue	4 months
El Saghir N (2005) [60]	non small-cell lung cancer	Routine diagnose of PT	At the right lateral side of his head suffering from an accidental trauma	16 month after PT
Fukushima (2010) [61]	Liver cancer	Routine diagnose of PT	At a skull fracture after 2 years diagnose of PT	3 months after trauma and 27 months after diagnose of PT
Walter (2011) [62]	Lung cancer	Lung cancer was diagnosed after trauma	at sites of recent physical trauma	Metastatic tumors firstly showed symptoms
Bergqvist (1978) [63]	Gastric cancer	PT was diagnosed six months after metastasis was found	Calcaneal metastasis at the fractured bone 2 years ago	Metastasis was firstly found the onset of gastric symptoms
Nielsen (1983) [69]	Cervix adenosquamous carcinoma	Routine diagnose and treatment of PT	Brain metastasis at the area of a 4-week-old infarct	10 months
Kukita (1992) [68]	cholangiocellular carcinoma	Pulmonary metastasis was firstly found	At the lungs with marked fibrotic changes	NA
Palazzo (2000) [71]	Colonic carcinoma	Routine diagnose and treatment of PT	At the skeletal muscle and skin with inflammatory oncotaxis	NA
Magee (2002) [72]	8 cases	NA	skeletal metastases at the sites with a documented clinical history of previous trauma	average 28 months after the trauma
Currall (2008) [73]	Rectosigmoid adenocarcinoma	The patient was firstly diagnosed of a metastatic disease after a left total knee arthroplasty.	At the synovial with wound repair after surgery	Metastasis prior to primary tumor
Dionigi (2008) [74]	renal clear cell carcinoma	The patient was also diagnosed of a toxic substernal goiter when PT was diagnosed.	At the thyroid gland with chronic thyroiditis	2 years after PT

However, among these studies, researchers mainly discovered the effect of promoting metastasis by different stimuli-induced lung injury and seldom explored the precise mechanism. Several studies further made endeavor to explore which factors exerted effect in the process. Three reports showed that endothelial injury induced by hyperoxic through neutrophil action contributed to the formation of metastasis at the lung [111,113,114]. When the endothelium recovered to normal status, metastases also decreased to the level of control group. Kennel [115] used monoantibody to directly mediate pulmonary endothelial injury and found lung metastasis increasing, further testifying that pulmonary endothelial injury was an element in enhancing lung metastasis. Oxygen radical and neutrophil cells are the mediators to regulate the process [113,116]. Nature killer cells, macrophage and their releasing proinflammatory factors such as TNF-α, interleukin-6 (IL-6), Toll-like receptors, MMP9 and NF-kappa B are also reported to be responsible for increasing lung metastasis [94,117–125]. Although there were controversies on neutrophils or macrophages and some molecules [101,113,117,121,123], the injured lung did promote lung metastasis. From the external environment, the host lung can be injured by various stimuli. In the host's inner status, the lung produces responses and shows physiopathological changes including endothelial cells injuries, immune and inflammation cells of activation accumulation and aggregation at the injured sites, and subsequently secretion of cytokines such as TGF-β, TNF-α, NF-kappa B and VEGF. From the external stimuli to inner changes of the host, they constitute a hierarchical system and collectively play the role in enhancing lung metastasis. Meanwhile, the lung begins to repair when the organ receives stimuli. From the initial stage to the inflammatory stage after stimuli-induced lung injury, the incidence of lung metastasis begins to increase and achieves peak. When the injured lung recovers, lung metastasis starts to decrease and disappears. Therefore, promoting lung metastasis by different-stimuli induced-lung injury is a spatial and temporal effect.

Bone is a fertile reservoir for a complex array of cells, cytokines and growth factors that are involved in bone turnover, response to injury [126,127] . The above mentioned cases showed that metastatic tumors occurred at sites of bone trauma, fracture and bone graft site [41,60–66]. These bones affected by metastasis have a common trait that they undergo a process of injury and repair and the normal bone homeostasis is disrupted, which may constitute a hospitable milieu for cancer cells. Thus, the bone affected by injury or inflammatory disease may increase bone metastases at the bone sites of wound. Bone trauma has been shown to promote bone metastasis in an experimental study [128]. However, the mechanism was not identified in the report. In the process of bone metastasis from lung cancer, TGF-β plays an important role [129], whose role in metastasis has been considered to be through the inflammatory pathway [33]. Therefore, enhancing bone metastasis by bone trauma may be mediated by inflammatory response. The inflammatory disease of bone is also reported to increase metastasis in the organ. For example, autoimmune arthritis (AA) is a disease with changes of inflammation and deformity of the joints and also has other systemic effects including cellular infiltration and inflammation in the lungs. It was found that bone and lung metastasis increased in an animal model of AA through inoculating breast cancer cells [130,131]. This mechanism was related to neutrophilic and granulocytic infiltration in lungs and bones in the pro-arthritic and arthritic mice and subsequent increasing of circulating proinflammatory cytokines such as IL-6, VEGF and TNF-α, all of which have also been identified to play important roles in cancer metastasis [132,133]. Trauma bone site can also arouse dormant cancer cells to grow overt metastasis [60]. Its possible mechanism may be that dormant cancer cells at the site of bone trauma were exposed to pro-inflammatory mediators, which thereby stimulated to overcome dormancy. Prostate cancers are prone to metastasize to bones, which have been identified to be via the stromal cell-derived factor-1/CXCR4 pathway [134]. It has been also found that the signaling pathway is critical for the recruitment of mesenchymal stem cells to the fracture site during skeletal repair after injury [135], which may provide the molecular basis for bone metastasis from prostate cancer. These studies suggest that an inflammatory microenvironment in the bone is vital for bone metastasis.

Liver is another common site for metastasis. It has been reported that liver regeneration and wound healing also increase liver metastasis. Liver regeneration can accelerate liver cancer occurrence in animal models receiving partial hepatectomy [136], indicating that liver regeneration offer a suitable microenvironment for cancer cells. Several studies also showed that partial hepatectomy enhanced liver metastasis from other types of cancer cells [137–139], suggesting that liver regeneration was also link with liver metastasis. In the process of liver regeneration after partial hepatectomy, there was no underlying liver inflammation, as was the case in humans with liver cancer. DNA damage-response machinery and genomic instability increasing accounted for the major mechanism of partial hepatectomy, which further resulted in hepatocyte apoptosis, cell-cycle arrest, and senescence that might be contributed to cancer cells colonization and growth at the liver [136,140]. Obese mouse can produce a heightened inflammatory response in the liver. Wu et al.'s [141]study showed that hepatic metastasis increased in wild type of obese mouse and rarely occurred in the rats with chronic insulin-like growth factor-I (IGF-I) deficiency. In the process, IGF-I was necessary to activate and sustain the inflammatory response in the liver, indicating that obesity, inflammation response and IGF-I collectively played the role in enhancing liver metastasis. Ischemia/reperfusion-induced liver injury [142–144] had the similar effect, which was mediated by MMP9 [144] that

had been well reported to be vital for metastasis [145]. These studies suggest that the local microenvironment during the processes of liver injury and regeneration after stimuli provides a favorable milieu for cancer metastasis. However, liver cirrhosis is also a kind of injury resulted from different stimuli. In clinical practice, metastases seldom occur in cancer patients with liver cirrhosis [146–148]. It seems that liver cirrhosis with rare metastasis is contradicted with the conclusion of the injured liver promoting liver metastasis How to solve the controversy? Focused this question, Qi, et al. [149] established the animal model of liver cirrhosis by carbon tetrachloride and observed liver metastasis increasing from B16F1 melanoma cells. In Kuriyama's [150] report, hepatic metastasis from hepatocellular carcinoma in an orthotopic mouse was also observed to occur in cirrhotic but not in normal liver. In the two experimental studies, the liver is undergoing a process injury and repair and liver metastasis increases. In clinical practice, the cirrhosis is a result of a long process of injury and repair after stimuli and live metastasis rarely occurs. These indicate that it is the healing process response to injury not the result of injury (cirrhosis or fibrosis) that contributes to enhance metastasis in the liver.

Brain metastases (BM) are common for many types of cancer and lead an increasingly important cause of death in cancer patients. Its mechanism is under exploration. Berghoff [151] investigated 17 human autoptic tissue specimens of BM from some types of cancer and found that inflammatory response existed in BM, which was characterized by profound microglia activation with marked peritumoral accumulation and independent from treatment of methods. Microglia is the main immune effector cell population in the central nervous system and control immune cell recruitment and is rapidly activated and recruited to the site of injury after any type of brain injury, which is also important for formation of BM [152]. However, it is unknown whether metastatic tumors induced inflammatory responses in the brain or inflammatory microenvironment in the brain enhanced brain metastasis. Massagué's group has identified genes to mediate breast cancer metastasis to the brain [153]. These genes are often involved in vascular permeability and leukocyte infiltration during brain inflammatory processes [153], suggest that brain metastasis from breast cancer may be related to brain inflammation mediated by specific genes. The following experiment studies supplied direct evidence that brain injury enhanced BM. The blood–brain-barrier(BBB) permeability is vital for cancer cells to metastasize to the brain [153–155] while disruption of BBB is a common effect in the pathophysiology of various inflammatory conditions of the central nervous system [156]. Acute stress can induce BBB disruption through activating brain mast cells and corticotropin-releasing hormone secreted [157,158] that can resulted in focal brain inflammation and neurotoxicity [159,160]. When acute stress acted on the mice bearing tumor burden, activating mast cells and releasing corticotropin-releasing hormone at the brain statistically significant increased BM through disruption of BBB [161]. Polychlorinated biphenyls(PCBs) contained in fish and meat comprise a ubiquitous class of toxic substances that can lead neurotoxic properties in the brain [162]. When mice were exposed to PCBs and inoculated by melanoma cells and Lewis lung carcinoma cells, the rate of formation of BM was enhanced [155,163]. This effect of PCBs enhancement of BM is facilitated by disrupt blood–brain barrier integrity [155] and proinflammatory adhesion molecules of intercellular cell adhesion molecule-1 and vascular endothelial cell adhesion molecule-1(VCAM1)[163] in the brain, which may further suggest that that avoiding to exposure to PCBs may decrease the incidence of BM in some extent. Although the evidence is few, together with BM occurring at the sites of focal infarction and infection in the brain [69,70], they may suggest that particular stimulus induced brain injury can enhance BM.

Kidney metastasis and kidney injury was also reported. Radiation induced kidney injury was demonstrated to enhance metastasis in the organ [164]. Ammirati et al. [165] also showed that kidney metastasis was enhanced at the trauma site of kidney induced by milliwatt carbon dioxide laser. This type of kidney injury has no obvious inflammation process, implying that it is that the process of wound healing in injured kidney promotes kidney metastasis.

Peritoneal injury can be induced by PF, anastomotic leakage in colorectal surgery, trocar insertion in laparoscopic techniques, etc. It has been reviewed that these causes induced peritoneal injury are negative prognostic factors for some solid tumors in abdominal cavity [37,38]. It has been speculated that these wound sites in abdominal cavity release proinflammatory cytokines to form an inflammatory microenvironment, which promote growth of residual or implanted cancer cells and finally lead to peritoneal recurrence [38]. Although there are controversies on whether the port sites of wound are preferred or contaminated by cancer cells, the following experimental studies testified that inducing peritoneal tissue injury by different causes could also enhance peritoneal metastases [9,166–170]. In contrast, repair of injured peritoneum at trocar sites or minimizing peritoneal trauma could reduce the frequency of wound metastases [37,166,171]. Moreover, there is a temporal effect for peritoneal injury promoting metastasis. For example, Zeamari et al. [172] studied the relationship between a peritoneal wounds and tumor cell seeding and stimulated growth in granulation tissues, and found that tumor seeding mainly occurred at the early granulation tissue. Thus, these experimental studies support that peritoneal injury may potentiate wound metastases and may be a possible reason for peritoneal recurrence after different causes induced-peritoneal injury in clinical reports.

These experimental studies are consistent with clinical observations and further support that different stimulus

directly induced-specific organ injury can enhance metastasis in the injured site. This is a system effect through a spatio-temporal regulation, which includes external stimuli, specific organ and the following inner changes at the cellular and molecular levels with time. From the above statement, different stimulus direct action on the same organ can enhance metastases at the organ from the same type of cancer or different types of cancer, which means that there is a common status to promote organ-specific metastasis. This status can be characterized by an inflammatory status. When a particular stimulus acts on a specific organ in an organism bearing tumor, a healing process of injury and repair occurring as an inflammatory status contributes to the formation of organ-specific metastasis. Moreover, the formation of metastasis is related to the stage of wound healing, which may occur at an acute phase (acute lung infection promoting pulmonary metastasis) or a chronic process (smoking promoting lung metastasis) according to a stimulus intensity and frequency and the degree of specific organ making response to stimuli. When the inflammatory status is mild and quickly recovers to normal status, metastasis also rarely occurs. When the process leads severe endings for the particular organ such as liver cirrhosis or for the organism such as death, metastasis rarely or never occurs. Although the status is hard to be accurately defined, it can be evaluated and detected for the factors from external stimuli to inner changes at the organic, cellular and molecular levels that resulting in the status. Evaluating these factors and identifying the status may be useful to prevent or inhibit the formation of metastasis in distant organs.

Primary Tumor and Its Treatment Influencing on Distant Metastasis Through Activation of Wound and Inflammation Effects

It has been recognized that the status of primary tumor can determine organ-specific metastasis, which is also shown to be related with inflammation. At the cellular level, disseminated cancer cells from primary cancer are the seeds of distant metastasis. Cancer stem cells(CSCs) have been identified in primary solid tumors and are considered to contribute to distant metastasis [173]. Chemokines are a goup of small pro-inflammatory chemoattractant cytokines, which serve as the major regulators of cell trafficking [174]. The SDF-1–CXCR4 Axis can regulate the trafficking of both normal and cancer stem cells [175], which can be activated by the inflamed tissues [135]. Thus, it maybe regulate mesenchymal stem cells and CSCs to recruite at the site of injury. Self-renewal is an important trait of CSCs [176]. The inflammatory cytokines and pathways generate positive feedback loops to drive CSC self-renewal [177]. These cytokine loops and the pathways will be activated during wound healing and chronic inflammation. Thus, CSCs will be droved to proliferate and grow under inflammatory microenvironments. However, the theory of CSCs has been challenged by a study [178]. The study analyzed two subpopulations of CD24+ and CD44+ cells from breast cancer stem cells and revealed genetic difference between the two subpopulations, which questioned the validity of the cancer-stem-cell hypothesis in breast cancer and supported the classical model of clonal evolution [178]. In fact, Massagué's group has separated cancer cells subpopulations for organ-specific metastasis(bone, lung, brain) from the parental MDA-MB-231 cell line through in vivo selection [153,179,180]. They express a set of genes to respectively mediate breast cancer metastasis to the bone, lung and brain. These genes are involved in inflammatory pathway. Although these molecules are not reported whether they can induce organ-specific injury, they result in the changes of targeted organ similar to inflammatory response in corresponding organs (e.g. BBB disruption in the brain) that may be related to organ-specific metastasis. Stromal cells of primary cancer can affect premetastatic organs through indirect injury by their secretion of inflammatory modulators. They include many types of cells, fibroblasts, macrophages, lymphatic cells, all of which have been identified to be involved cancer metastasis [98,123,181–185]. Thus, under the conditions of distant organ with no obvious injury, they can release proinflammatory modulators such as s100A8 and s100A9 [186] to induce injuries on distant organs. At the molecular level, the gene signatures of primary tumor as prognostic factors have been used to predict distant metastasis [187]. Among of them, wound gene signature in primary cancer cells is one of these prognostic factors for predicting distant metastasis in breast cancer patients [188], indicating that the genes regulation of the wound healing process are also involved in cancer metastasis [189]. This is further supported in recent studies. They show that primary tumor cells can secret proinflammatory molecules to induce distant site injury for formation of organ-specific metastasis. For example, endogenous human microRNAs of miR-335 and miR-126 are also identified to be metastasis suppressors in breast cancer through targeting of Tenascin-C [190], a modulator of tissue injury and tumorigenesis [191]. When they are lost in primary tumors, tenascin-C will upregulate to promote lung metastasis [190]while its upregulation can be also induced by lung infections [191]. Primary tumor-secreted miR-21 and miR-29a can bind to receptors of the Toll-like receptor (TLR) family to trigger a TLR-mediated prometastatic inflammatory response, which ultimately lead to tumor growth and metastasis [192]. Nuclear factor-kappaB, a critical proinflammatory molecule, can induce lung injury to potentiate lung metastasis when it is secreted by Lewis lung cancer cells [121]. At the physical and chemical levels, primary tumor microenvironment such as hypoxia and acid ph value can also influence distant metastasis [193–195] through up-regulation of inflammatory modulators including proteolytic enzymes, proangiogenic factors,

and antiapoptotic proteins [196–200]. At the organic level, status of primary organ can also determine the behavior of metastasis. It is well known that primary liver cancer mainly developed from the basis of cirrhosis liver induced by different stimuli and often metastasize to the liver itself. Budhu et al. [201] identified a unique inflammation/immune response-related signature in noncancerous hepatic tissues from metastatic hepatocellular carcinoma was principally different from that of the tumor, indicating that inflammatory status of primary organ can influence the site-specific metastasis. On the other hand, local treatment regimens such as surgery and radiation on primary tumors can also induce distant metastasis through activation of inflammatory cells and signals [202–209]. For example, removal of primary breast cancer can led to a progressive phenotype of lung metastases through upregulated the expression of ITGB3, EGFR, HGF, IGF1, PDGR-B, TNF–α, VEGFA, VEGFC and MMP9 genes and down regulation of Cdkn2a, Cdh1, and Syk genes [210] that are also involved lung inflammation. These suggest that primary tumors and local treatment of them may indirectly induce injuries on distant sites to sustain the process of distant metastases.

Host Factors Increasing Distant Metastasis Through System Inflammation and Immune System

Host factors can increase distant metastasis through activation of immune system and system inflammation, which includes postoperative fever, chronic stress, obesity, particular status such as pregnancy and lactation. Postoperative fever, a frequent event in clinical practice, has been identified to be a poor prognostic factor among patients of colorectal cancer, breast cancer, and soft-tissue sarcoma [6,211,212]. Its mechanism is speculated that postoperative fever is a response to tissue injury or infection of unknown trauma sites in the body, which induce to distant metastasis in these wound sites and result in poor prognosis for cancer patients [6]. Stress, social isolation and other factors can also influence cancer progression and metastasis under the modulation of neuro-endocrine-immune network [213–215]. For example, Wu and cooperators found that social isolation stress promotion of liver metastasis was via suppressed splenic NK cells activity and decreasing macrophage-mediated cytotoxicity at the cellular level [216], TNF-alpha increasing and the proteolytic enzymes such as MMPs and u-PA upregulating in tumor and liver tissues at the molecular level [217]. Sloan et al. [218] found that chronic stress could increase distant metastasis through activation of sympathetic nervous system (SNS) and increasing the expression of proinflammatory and prometastatic genes including COX2, MMP9, VEGF, and VCAM1 that has been identified to be involved site-specific metastasis [120,132,219]. These indicated that stress activated the inflammatory pathway under the modulation of neuro-endocrine-immune network. Stress is also a common complication of operation for cancer patients. Combination of beta-blockers and non-steroidal anti-inflammatory drugs was shown to be correlated with reduced recurrence, metastasis and mortality [220], which further testify that fever and chronic stress can enhance distant metastasis. Obese cancer patients were reported to have high rate of reoccurrence [221,222], which were considered to be due to inflammatory changes [223]. Therefore, host factors such as chronic stress, social isolation, postoperative fever, and obesity activate the inflammatory pathway to indirectly promote distant metastasis.

Host organ is the end point of disseminated tumor cells (DTC) and responsible for organ-selective metastasis. DTC can reach any organ, even if most of them are captured by the first capillary bed in their journey of migration. Whether DTC develop a new tumor in ectopic sites is depended on the results of mutual effects between them [194,224]. On one hand, an inflammatory microenvironment of a host organ can alter the behavior of DTC. Okada [225]found that weakly tumorigenic and nonmetastatic QR-32 cells derived from a fibrosarcoma in C57BL6 mouse could be converted to malignant once they grew in an inflammation microenvironment. In brain metastasis, activation of astrocytes was vital for cancer cells growth [226], which was often related and inflammatory microenvironment of the brain [227]. On the other hand, DTC with strong ability of metastasis can act on host organ through activation of local inflammatory cells and system inflammation. Wang et al. [228] has shown that highly metastatic carcinoma cells can trigger a rapid host proinflammatory response by inducing TNF-α production in resident Kupffer cells once they entry into the hepatic microcirculation while weakly metastastic cells can't. Therefore, the mutual effect mediated by inflammatory pathways between host organ and DTC may contribute to organ-selective metastasis.

Bone marrow is now found to play an important role in distant metastasis [229,230]. Several studies have shown that bone marrow is a reservoir for DTC, which is not only the predictor factor of bone metastasis but also other site's metastasis. Moreover, there are also reports to show that bone marrow-derived progenitor cells can home to pre-metastatic sites such as liver and lung to form a premetastatic niche before the arrival of tumour cells [186,231,232]. Nowadays, it is well known that bone marrow-derived mesenchymal stem cells (BMSCs) can repair injured tissues [233,234]. In the host, liver and pulmonary is easily inflamed by different stimuli and often undergo injury and repair. In the process, BMSCs play an important role [235–237]. This may partly explain why DTC can predict liver and lung metastasis and why liver and lung are the most sites for metastasis from different cancers.

Different Stimuli-induced Organ Injury Enhancement of Organtropism Metastases in a System Effect

From the above analyses, we can see that not only inflammation but also a wide meaning of injuries on a target organ can enhance metastases in this organ. Moreover, it is the process of repair or wound healing response to different kinds of injuries not the result of injury that exerts this effect. For example, the process of development of cirrhosis can enhance liver metastasis while metastasis rarely occurs in the liver when cirrhosis forms. Therefore, organ-preference metastasis enhanced by organ-specific injury is in a spatial and temporal regulation (Fig. 1). At the spatial level, stimuli, host factors, status of primary cancer and its organ, premetastatic organs' microenvironments, state of bone marrow, system and local immune and inflammatory effects including activated immune and inflammatory cells, released chemokines, growth factors and cytokines are all involved in the determining the site of distant metastasis [238]. From the temporal level, at the initial stage of wound healing in an organ after receiving a stimulus, metastasis begins to form. With the inflammatory effects development and repair increasing, metastasis will increase at the injured site. When the injured organ completely recovers or results in a bad state such as hepatic cirrhosis, metastasis rarely occurs. This is a system effect. Only when stimuli-induced organ injury reaches this status at the spatiotemporal effect, organotropism metastasis can be promoted, which may explain why a negative result exists between trauma and an increased rate of breast cancer recurrence in Allawi et al. [239]'s report. Deep understanding the above accurately mechanism has a significance for biological and clinical implications on cancer metastasis.

Firstly, when a patient is diagnosed of cancer, it should be recognized that potentially harmful stimuli are taking effects on his or her whole organism or particular organ. So these stimuli(e.g. smoking, PCBs in a food chain, etc.) should be avoided and the status of the injured organ should be conversed into normal state. Secondly, some inflammatory diseases such as acute lung infections, asthma, inflamed gingiva, autoimmune arthritis lead to inflammatory status in target organs that are preferred sites of metastasis. These diseases should be positively managed in cancer patients. The relationship between other inflammatory diseases such as COPD and cancer metastasis should be also investigated in the future studies. The trauma sites or wound tissues undergoing a process of injury and repair may be preferred by cancer metastasis, which should be aware of and often checked after cancer diagnosis. Thirdly, host factors such as fever related to system inflammation and stress in cancer patients should be adjusted. Inhibition of system inflammation by using aspirin can decrease distant metastasis [240]. Detection of factors of system inflammation such as acute phase protein and IL-6 may be helpful to predict of metastasis [241–243]. It has been shown that beta-blocker can increase the clinical outcome of breast cancer patients through inhibition the activities of SNS, which mainly reduces distant recurrence [244,245]. Thirdly, when a tumor is diagnosed, its primary organ status, and premetastastic organ or metastatic organ status should be evaluated so as to decrease metastasis occurrence (Fig. 1). Finally, because different stimuli induced organ-specific injury can enhance organotropism metastasis from the same type of cancer, it is vital for inhibition organ-specific metastasis to find similar effects on the injured organ produced by these stimuli. A same stimulus can also enhance organ-specific metastasis from different tumors, indicating that there is a common status for lodging in a same organ among these tumors. Discovering the common status will be also to treat different metastasis. These evaluations and measurements for cancer patients will make personalized in prediction, prevention and management of cancer metastasis.

Conclusions

In conclusion, we propose a notion that chronic injury not merely chronic inflammation in an organ can enhance metastasis in this organ through a spatiotemporal regulation. This is a system effect including multiple scales. From the spatial scales, external stimuli (chemical, physical and biological factors) directly act on a specific organ in an organism that makes

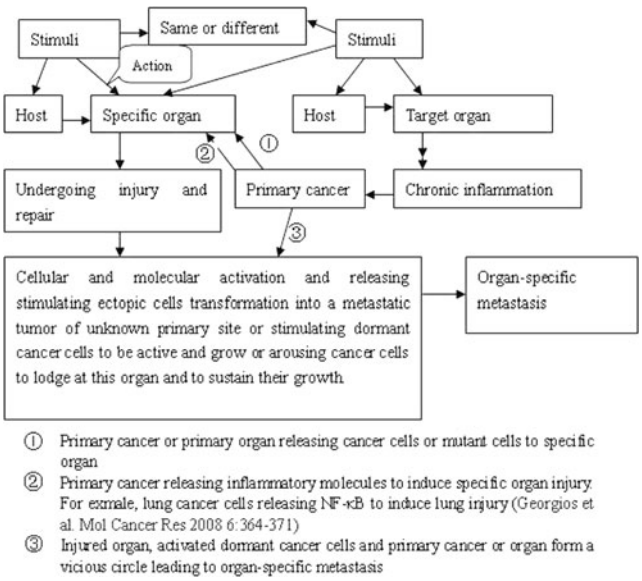

Fig. 1 Stimuli directly or indirectly induced specific organ injury and organotropic metastasis. When human is exposed to internal and external environments, the body will receive stimuli and make response to stimuli. In the reaction, stimuli always act on specific organ and induce organ-specific injury. When a particular organ undergoes persistent and chronic injury, it will occur to cancer. If there is another organ undergoing persistent injury, it will provide a favorable environment for cancer cells, this organ will be a preferred site for metastasis

response at cellular and molecular levels, which finally induce organ specific injury to promote organotropic metastasis. Primary cancer is not only the source of 'seeds' of distant metastases but also can release inflammatory molecules to induce injury on distant sites. Thus, cancer cells interaction with the injured organ contribute to organotropic metastasis. The host factors such as chronic stress, fever, obesity indirectly influence on distant metastases through activation of the inflammatory pathway under the modulation systems of neuro-endocrine-immune and bone marrow. Many factors can be included in each scale. They interact at the time scale and generate an inflammatory status at a particular organ or specific some organs in cancer patients to be suitable for cancer cells growth and proliferation. Finally, cancer metastases occur at one or more specific organs. Therefore, occurrence of organotropic metastasis is a stem effect and management of cancer metastasis should be comprehensively considered at multiple scales in a systems biology view. Evaluation of these factors at each scale using system biology methods and identifying organ-specific injury is vital for understanding the biology of organotropic metastasis and personalized management of metastasis.

Conflict of Interest Dongwei Gao has been recruited by Lanzhou General hospital of PLA but not permitted by the 536th hospital. He now works in the 536th hospital and conducts experimental studies in Lanzhou General Hospital of PLA. We declare no other personal, commercial or financial conflicts.

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