Biological resonance for cancer metastasis, a new hypothesis based on comparisons between primary cancers and metastases

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Abstract Many hypotheses have been proposed to try to explain cancer metastasis. However, they seem to be contradictory and have some limitations. Comparisons of primary tumors and matched metastases provide new insight into metastasis. The results show high concordances and minor differences at multiple scales from organic level to molecular level. The concordances reflect the commonality between primary cancer and metastasis, and also mean that metastatic cancer cells derived from primary cancer are quite conservative in distant sites. The differences reflect variation that cancer cells must acquire new traits to adapt to foreign milieu during the course of evolving into a new tumor in second organs. These comparisons also provided new information on understanding mechanism of vascular metastasis, organ-specific metastasis, and tumor dormancy. The collective results suggest a new hypothesis, biological resonance (bio-resonance) model. The hypothesis has two aspects. One is that primary cancer and matched metastasis have a common progenitor. The other is that both ancestors of primary cancer cells and metastatic cancer cells are under similar microenvironments and receive similar or same signals. When their interactions reach a status similar to primary cancer, metastasis will occur. Compared with previous hypotheses, the bio-resonance hypothesis seems to be more applicable for cancer metastasis to explain how, when and where metastasis occurs. Thus, it has important implications for individual prediction, prevention and treatment of cancer metastasis.

Keywords Primary cancer · Metastasis · Similarity · Difference · Biological resonance (bio-resonance) model

Introduction

Metastasis is one of the most enigmatic characteristics of cancer and causes 90 % of deaths from solid tumors [1]. Understanding of the biological mechanism of metastasis is of importance to unravel the metastatic cascade and may lead to novel interventions for this devastating disease. A reasonable hypothesis plays a vital role in facilitating the biology of metastasis. Since the nineteenth century, many hypotheses or theories on metastasis have been proposed (i.e. seed and soil[2], purely anatomical mechanism[3], clonal evolution and selection[4–6], parallel evolution[7, 8], the theory of cell fusion[9–11], cancer stem cell hypothesis[12, 13], dynamic heterogeneity[14–16], the same-gene model[17, 18]). They provided rational explanations for many phenomena in cancer metastasis and suggested different directions for targeting metastasis. However, they seem to be mutually contradictory [19–21] and haven't made breakthroughs in treatment of metastasis. Metastasis is still a major problem for cancer patients. Moreover, most of these hypotheses are mainly based on observations of cell culture, experiments of transplant animal models, primary cancer tissues. They seldom focus on metastatic tissues because metastatic tissues are difficult to be obtained by biopsy or resection. Thus, they have some limitations for them in understanding the metastatic process. To gain a comprehensive view of metastases, priority should be given to paired analysis of primary tumors and metastases [22–24]. Now this thought has been recognized and some institutions have conducted studies on comparisons between primary tumors and metastases at multiple levels by traditional and modern technologies. These researches provide new insights into biological metastasis than ever before. The following

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statement will describe these results, conclusions and implications in understanding and managing of metastasis.

Comparisons between primary cancer and corresponding metastasis at multiple levels and their implications

Both similarities and differences exist between primary tumors and matched metastases

Although metastatic tumors generally originate from primary cancers, little is known about changes in these second tumors. Thus, comparisons between primary tumors and corresponding metastases will supply direct information on alternations of metastatic tumors compared with their primary tumors. But current studies on these comparisons didn't reach agreements on whether similarity or difference between primary cancers and matched metastases. Tables 1 and 2 sum up the results from these comparisons, which showed identical or discordant at multiple scales from morphological traits to molecular biomarkers.

Similarities between primary tumors and matched metastases and the biological and clinical implications

On the one hand, some studies showed that metastases were high similar to their matched primary cancers at the levels of cytologic features[25, 26], cytogenetic alterations [27–35], DNA changes including aneuploidy, and index[36–42], gene analyses including mutations[43–53], profiles[18, 54–57],

and epigenetic and transcriptive changes[58–62], proteomic profiling[61, 63] and expression[64–73]. These studies often comprised small sample sizes, so the similarities may be due to chance. Researchers performed a computational analysis and found that the similarities within the matching pairs was not due to chance but actually existed between them [18]. In fact, the existing similarities between paired primary and metastatic tumors have important effects on understanding the biological mechanism of metastasis and selecting suitable treatments for metastatic tumors. First, they implies that the matched tumors have a common origin [28, 74–76] and the key biological traits of primary tumors are maintained in metastatic tumors. They also suggest that metastatic capacity is an inherent feature and encoded in bulks of primary cancer [77]. The conclusion of the similarities between primary tumors and matched metastases is compatible with early metastatic model proposed by Virchow[20], purely mechanic model[3], and the same-gene model[17, 18]. Based on this feature, prediction of distant metastasis from primary tumor is available [55–57, 78–82]. Second, current therapies on metastases are relied on their primary tumors because they are considered to be identical. However, this is an imaginary more than a fact. High similarities from comparisons of paired primary tumors and metastases testify that this is a fact and supply direct evidences for rationality of treatment on metastases based on their primary tumors [83]. Third, concordance at the gene level between primary tumors and matched metastases can be used to discriminate solitary metastasis from secondary primary tumor on the same organ after removal of primary cancer [26, 49, 84–86].

Table 1 Morphological and cytogenetic changes between primary tumors and matched metastases

Author	Cancer type	Metastatic site	Pairs	Targets	Method	Results
Schmid	Lung cancer	MS	2	Chromosomal aberrations	CGH	Similar patterns
Korn	Colorectal cancer	Liver	6	DNA sequence copy numbers	CGH	Similar
Jones	Urothelial carcinoma	RLNM	24	LOH X-chromosome inactivation	PCR	Same clonal origin
Al-Mulla]	Colorectal cancer	RLNM and liver	12	chromosomal aberrations	CGH	Frequently same
Fox	Canine Osteosarcomas	MS	48	DNA Aneuploidy	flow cytometry	Quite similar and minor difference
Bissig	Kidney cancer	MS	19	chromosomal aberration	CGH	Different
Baba	Gastric cancer	RLNM	61	DNA content	Flow cytometry	25 pairs same while 36 changing
Flotte	Melanoma	Skin	22	DNA content	Flow cytometry	91 % agreement
Danner	Colorectal cancer	Lung	30	Chromosomal aberrations	CGH	Similar
Liu	Gastric cancer	RLNB M	23	DNA sequence copy number aberrations	CGH	Different
Feichter	Breast cancer	RLNM	80	DNA Index, S-phase	Flow cytometry	Close agreement
Ljungberg B	Kidney cancer	MS	32	DNA content	single-cell cytophotometry	Different
Bäckdahl	Papillary thyroid carcinoma	MS	40	DNA content	Flow cytometry	Similar

Table 2 molecular changes between primary tumors and matched metastases

Author	Cancer type	Metastatic site	Pairs	Targets of detection	Method	Results
Ki	Colorectal cancer	liver	27	Whole genome	cDNA microarray	Major concordance Minor difference
Knijn	Colorectal cancer	Liver	305	KRAS mutation codons 12 and 13	Mutation analysis	Concordance (95 %)
Mariani	Colorectal cancer	MS	38	KRAS mutation	Direct sequencing, SNAP Shot multiplex PCR, Taqman PCR	Concordance (97 %)
Loupakis	Colorectal cancer	MS	53	PTEN, pAKT, KRAS	IHC for PTEN, pAKT Mutation analysis for KRAS	Respectively 60 %, 68 %, and 95 % concordance
Kuramochi	Colorectal cancer	Liver	31	EGFR mRNA	RT-PCR	Concordance
Kobayashi	Colorectal cancer	Liver	31	Cox2, IL-8, VEGF mRNA	RT-PCR	VEGF and IL-8 concordance Cox2 different
Mole	Colorectal cancer	Liver	38	Osteopontin TRC factors	Digital microscopy	Different
Kim	Colon cancer	Lung	6	84 metastatic genes	Quantitative RT-PCR-based PCR Array	Different
Danner	Colorectal cancer	Lung	30	chromosomal imbalances	CGH	No substantial differences
Veenendaal	Colorectal cancer	MS	11	Wnt,Notch, TGFbeta signaling pathways	TMA	Different
Yu	Colorectal cancer	Liver	12	proteome	Two-dimensional gel electrophoresis	Different
Lark	Colorectal cancer	Liver	24	Focal Adhesion Kinase	IHC and RT-PCR	Concordance
Malek	Ovarian cancer	Peritoneal	9	Copy number variations	High-density SNP arrays	Different
Sakai	Ovarian cancer	MS	56	Histological grade, P53, ki-67, CD44	IHC	p53 different ki-67 and CD44 concordance
Rodriguez -Burford	Ovarian cancer	MS	30	P53 erb-2	IHC	No difference
Thongwat-chara	Breast cancer	RLNM	5	678 protein spots	2D-SDS-PAGE, LC-MC/MS	19 spots up and 3 down
Poplawski	Breast cancer	RLNM	13	Genomic profiles	cDNA microarray	157 genes different
Aitken	Breast cancer	RLNM	385	ER, PR, HER2	Quantitative immunofluorescence	Different
Da Silva	Breast cancer	Brain	39	Her3	IHC, gene expression, somatic mutation profiling	Different
Subhawong	Breast cancer	MS	17	Bcl-2	IHC	Up in metastasis
Azam	Breast cancer	RLNM	100	ER, PR and Her2	IHC	91 %, 88 %, 95 % concordance
Ellsworth	Breast cancer	RLNM	20	Gene expression	cDNA TaqMan assays	51 genes different
Li	Breast cancer	RLNM	29	Genomic, proteomic	CGH, 2-D PAG	High similar
Akcakanat	Breast cancer	MS	29	Akt/mTOR signaling	IHC	Discordant
Kowalski	Breast cancer	MS	30	E-cadherin	IHC	Stronger in metastases
Durbecq	Breast cancer	MS	29	Topoisomerase-II α	FISH	Concordance
Monaco	Lung cancer	MS	85	EGFR KRAS	FISH Mutational analysis	22.5 % discordant
Schmid	Lung cancer	MS	96	EGFR KRAS BRAF	Direct bidirectional sequencing	Discordant
Bozzetti	Lung cancer	MS	28	EGFR	FISH	Discordant
Kalikaki	Lung cancer	MS	25	EGFR KRAS	Direct sequencing IHC	>10 % discordant
Sun	Lung cancer	Brain	55	HER pathway	IHC, FISH, PCR-based sequencing	different
Wu	Lung cancer	Brain	20	O(6)-Methylguanine-DNA methyltransferase	IHC, MSCP RT-PCR	Enhanced in Brain lesions

Table 2 (continued)

Author	Cancer type	Metastatic site	Pairs	Targets of detection	Method	Results
Gow	Lung cancer	MS	67	EGFR mutation	Direct sequencing, SARMS	discordant No mutation
Xie	Gastric carcinoma	RLNM	5	Gene, protein expression	cDNA microarray TMA	76genes different
Marx	Gastric carcinoma	RLNM	69	Her2	IHC, FISH	Identical
Kim	Gastric cancer	RLNM	74	11genes methylation	MS-PCR	Different
Alonso	Larynx cancer	RLNM	25	37 genes	multiplex ligation-dependent probe amplification	Identical and different
Turajlic	Melanoma	RLNM	1	global gene copy number alterations, LOH single nucleotide variation	Whole genome sequencing	Highly similar
Bahrami	Melanoma	Epidermo-tropic metastases	9	LOH, X-chromosome inactivation	PCR	Same clone
Cheung	Liver cancer	Liver	5	Genomic profiling	cDNA microarray	Same clone
Paris	Prostate cancer	RLNM	2	Whole genome copy number	Array comparative genomic hybridization	Similar
Bockmühl	Esthesioneuroblastoma	MS	12	Chromosomal imbalances	CGH	A high concordance
Tarkkanen	Sarcomas	Lung	22	Genetic aberrations	CGH	Similar

MS multiple metastasis sites; *RLNM* regional lymph node metastasis; *LOH* loss of heterozygosity; *TMA* tissue microarray; *CGH* comparative genomic hybridization; *IHC* immunohistochemistry; *RT-PCR* Real time polymerase chain reaction; *FISH* fluorescence in situ hybridization; *MS-PCR* methylation-specific polymerase chain reaction

Diversities between primary tumors and corresponding metastases and the biological and clinical implications

On the other hand, differences were also reported on the above level [38, 87–107], especially for particular genes such as EGFR [96, 100, 108–111] and BRAF [97]. Then, some questions need to be pinned down. Which situation is true, concordance or and discordance? How to explain these seeming mutual exclusive results? Do we need biopsies from metastatic tissues when molecularly targeted therapies are used in metastasis? To answer these questions, we first exclude false results from these studies. The possible reasons that produce discrepancies between primary and metastatic tumors have been discussed elsewhere [58, 109, 112, 113]. When these possibilities were excluded, variations still existed between primary tumors and corresponding metastases [114, 115]. Metastasis is quite a complex process including intravasation, transit in the routes, extravasation and colonization at a secondary site [116]. When cancer cells lodge in a foreign organ, the status for them in dormancy, apoptosis, or progression toward frank metastasis is influenced by the secondary site microenvironment[117–120]. To adapt to new environment and overcome the inhibition of the microenvironment of the distant organ, cancer cells must evolve into new traits[116, 120]. These new traits may be the reason of the differences. For example, metastasis progression genes and virulence genes have been identified in recent years. They confer a

selective advantage for metastatic tumors during the adaptation and takeover of a specific organ microenvironment while have little influence on primary tumor growth [121–123]. Witz's group generated two cells lines(lung metastatic NB, MetNB and disseminated neuroblastoma, DisNB) from the same neuroblastoma tumor. They had an identical genetic background but differed in the ability to form macrometastases in the lungs. The differences were due to MetNB cells with a higher migratory capacity, an elevated matrix metalloproteinase (MMP) secretion, and a higher constitutive phosphorylation of extracellular signalregulated kinase (ERK) than DisNB cells[124]. In fact, the differences between paired of primary and metastatic tumors can be explained by current hypotheses. According to the prevailing metastasis model of clonal evolution [4], it suggested that additional somatic genetic alterations could be acquired in the process of metastasis. Thus, the differences of primary tumors and metastases were due to the acquired mutations. The parallel evolution model indicated that early progenitors with metastatic capacity from primary tumor could develop and evolve into a metastatic tumor independently from the late stage cancer cells [7, 8]. Acquired traits during the evolution for these early progenitors might lead to difference between primary tumors and matched metastases [98]. The dynamic heterogeneity model of metastasis implied that metastasis was determined by the frequency of metastatic variants. The variants were in dynamic status of acquired and lost from

microenvironment when they were involved in the process of metastasis [14, 15]. This process was also explained by the epithelial-to-mesenchymal transition (EMT) that epithelial cancer cells acquired the mesenchymal traits and mesenchymal-related genes so as to adapt to the foreign environment at the site of final dissemination [125]. Cell fusion theory was another model of metastasis to explain why cancer cells became so invasive. The idea considered that cancer cells were fused with other cells in the process of migration and became hybrids [9–11]. When they grew into a new tumor, they were different from their progenitors. In fact, genomic instabilities and heterogeneity have long been recognized as importantly inherent features of cancer [126, 127]. After cancer cells dissemination, they still persist and result in ongoing, parallel evolution among different metastases [106, 128]. Therefore, the differences between primary tumors and metastases are inevitable [129]. The conclusion has important implications for management of metastasis. For example, researchers usually hold an idea that identifying differences in primary and metastatic tissues are of importance to develop new targets for metastasis [130–133]. The different genes between primary and metastatic tumors have been identified to be involved in growth factor and signal, cell cycle, cell motility, adhesion and immune response, indicating that metastatic cells need extra signals to sustain growth in foreign organs [99]. Characterization of such variations may lead to identify novel events associated with metastatic dissemination process and develop new targets for different metastases [134–136]. Molecularly targeted therapies are being used to treat many cancers. The differences of corresponding molecular status between primaries and metastases suggest that status of specific molecules in metastatic tumors should be reevaluated when the patients with metastases are about to use the inhibitors [137, 138].

Tissues of primary cancer, corresponding normal organ and metastasis are similar at the genomic level but different from normal tissue of metastatic organ

Further analyses were conducted on primary cancer, matched normal tissue and metastasis, normal tissue of metastatic organ [139–141]. The findings showed that primary cancers, corresponding normal tissues and metastases had a great similarity, but were different from normal tissues of metastatic organs. The results implied the three paired tissues had a common origin. Tissue-resident stem cells seemed to play the role in the transmission from normal tissue to carcinogenesis and metastasis, which was compatible by cancer stem cell hypothesis. Ding et al. [142] also reported whole-genome sequencing on a primary breast cancer tissue, matched metastasis, mouse xenograft tumors and a blood sample as a normal control from the same patient. Although there were some new aberrations in the xenograft and metastatic tumors, the

spectrum of structural aberrations and most of the copy-number abnormalities were shown to be high similar in all three tumors and further indicated that they originated from the same progenitor.

The two basic principles of evolution, conservation and variation are applicable to explain similarity and difference between primary tumors and matched metastases

Therefore, both similarities and differences actually exist between primary tumors and matched metastases [31, 143–146]. The concordance is dominant while the difference is minor. This can also be explained by Darwinian evolution. In the process of cancer evolution, most of inherent features of cancer cells are conservative. When these features are detected by various methods, they show similarities between primary tumors and metastases. However, if disseminated tumor cells (DTCs) develop a new tumor in ectopic sites, they must complete several key steps and conquer many limitations. Thus, cancer cells must evolve into or acquire new traits to conquer these barriers and adapt to foreign microenvironments. From an evolutionary perspective, these gained new traits reflect variation for cancer cells in foreign microenvironments. They will lead to differences when compared primary tumors with matched metastases. Even if some genes in metastatic cells are quite conservative, for example p53 [50, 51, 147, 148], they will also change when they receive extra stimuli in the process of migration, colonization and proliferation in foreign organs. This can explain why these genes as early events in carcinogenesis also change in metastatic tumors. They can be viewed in Fig. 1.

Hematogenous and lymphatic metastases have common and different mechanisms through comparison of regional lymph node metastases and corresponding distant metastases

For most of epithelial cancers, the bloodstream and lymphatic systems are the major two pathways of cancer cells spread [149]. Clarification of the mechanism of vascular and lymphatic metastasis is the prerequisite to identify all the events of metastasis. According to the theory of clonal selection and linear model, metastasis is a late-stage event in the process of cancer development [106]. In clinical experience, vascular spread is thus considered to be secondary from lymphatic system [150]. Thus, target of lymphatic metastasis will be important to inhibit distant metastasis and increase survival rates [151]. However, some cancers can directly develop into distant metastases via hematogenous system without lymph involvement. Meanwhile, most mesenchymal neoplasms generally spread through the bloodstream and seldom transmit through lymphatic system, which are often related to poor prognosis. Pantel [152] proposes a new model to explain the

Fig. 1 Similarity and difference between primary tumor and matched metastasis. Red color representing cells from normal status to cancerous state, yellow color representing bone marrow derived cells, purple color representing various stromal cells and blue color representing extracellular matrix players. Primary tumor (P), metastatic tumor (M) and their corresponding lodging organs (a and b) are all under the modulation of host genetic factors, psycho-neural-endocrine-immune system and system inflammation. Bone marrow not only contributes to the primary tumor but also metastatic tumor. Primary tumor and matched tumor showed similarities because they have a same clone. Disseminated cells progression into overt metastasis need to complete a series of progresses including intravasation, transit, extravasation, colonization at secondary sites. They must evolve into new traits and gain new mutations to overcome the barriers. These new traits and mutations lead to the differences between primary tumors and matched metastases

phenomena. For some patients, if their tumor cells first spread to the regional lymph nodes, they can be cured when removal of the nodes before secondary dissemination into the blood. In contrast with other patients, if the tumor cells directly disseminate into the bloodstream, local therapy would not have an effect on clinical outcome. This model indicates that both of the two pathways are independent, which can be further supported from the comparisons between primary cancers and matched lymph node metastases, distant metastases [132, 150, 153, 154]. They showed that distinct pathways involved lymphatic metastasis and hematogenous metastasis. But, there were still common genes between distant metastasis

and regional lymph node metastasis from these comparisons. Identifying common and different molecules between the two pathways is helpful to develop combination targets for treatment of both lymphatic and hematogenous metastasis.

Comparisons of multiple sites of metastases from the same patient provide new insight into organ-selection metastasis

Organ-specific metastasis is one of the major features of metastasis and remains poor [118, 123]. Comparisons different metastasis sites with their primary cancer in a same patient are helpful to identify differentially expressed molecules for organ-specific metastasis. In these comparisons using human tissues, similarities existed among the paired tumor tissues, indicating that multiple site metastases had a common progenitor. The different genes among them suggest molecular mechanism for site-specific metastasis. For example, Tie et al. [155] compared KRAS mutation among metastases from liver, lung, and brain and found that KRAS mutation was associated with lung relapse. Knosel et al. [156] found more alterations in pulmonary metastases than liver metastases through comparative CGH on primary colon cancers and their corresponding liver, lung metastases, suggesting that colon cancer needed more mutations to succeed in formation of pulmonary metastasis. Landemaine et al. [157] found a "six-gene" signature for lung metastases through comparison of lung metastases versus other metastases in a same patient, which was further testified in 725 patients. The different genes may be regulated by site-specific microenvironment, which have been testified in experiment studies. For example, Massague's group and Witz's group isolated of different site specific metastatic cells from the same tumors through selection in targeted organs [124, 158–161]. There were common mediators to contribute to pulmonary and brain metastases. However, the different genes mediating lung and brain metastasis are regulated by lung or brain microenvironments. These findings indicated that DTCs need specific genes to contribute to organ-selective metastasis. They can support the metastatic theories of the clonal-selection model, seed and soil hypothesis and also imply potential targets to be developed into specific target therapy drugs for organ-selective metastasis.

Detection of the genotype of disseminated tumor cells providing the window of primary tumor and matched metastases

DTCs shed from primary cancers are the seeds of metastatic tumors [115]. With the advancement of technologies, DTC can be detected in peripheral blood (Circulating tumor cells, CTCs) and bone marrow (BM-DTC) [162]. Detection of CTCs represents a relatively noninvasive and repeatable source of primary cancer. Identifying genotypic information of CTCs provides a tool that might influence treatment and

estimation of prognosis [163]. Khan et al. [164] detected p53 mutations in CTCs, corresponding primary colorectal cancers and their metastasis and found that p53 mutations were identical in the matched three samples from a same patient. Gene profiles on CTCs and their primary cancers, matched metastases also showed similar [165]. These studies indicated that some molecular information was invariable among primary cancer, CTCs and metastasis. They provided evidence that genotype information of primary cancer and or metastasis can be acquired from CTC. This has been used on the information of EGFR mutations obtained from peripheral blood to evaluate the response of EGFR inhibitor [166, 167].

Comparing BM-DTC with their primary cancers has been reviewed elsewhere [8, 115, 152]. The genetic alterations between primary tumors and BM-DTCs are heterogeneous for patients with M0-stage cancer while are homogeneous for patients with M1-stage cancer. These are compatible with parallel progression model. DTCs are quite early in cancer progression, independently undergo evolution in an ectopic environment and can grow into a new tumor in secondary organs when the changes are enough to sustain them proliferation. However, they still keep key biological hallmarks of their progenitors. When overt metastases develop from these early DTCs, they are similar to their corresponding primary tumors.

CTC and BM-DTC have been also used to evaluate prognosis of cancer patients. However, only BM-DTC at initial diagnosis is a predictive factor for distant metastasis including not only bone but also other organs such as liver and lung, which suggests that bone marrow, may exert a potential reservoir in cancer metastasis [152]. Comparisons between cancer cells in bone marrow and their primary cancers showed there were extensive distinctions on them; suggested that early spreading cells lodged in bone marrow can independently develop into a new tumor [168]. Further studies testified that these cancer cells in bone marrow had a putative stem cell phenotype [169], which was a strong evidence for cancer stem cells as lethal seeds. This phenomenon was explained by parallel model and also compatible with cancer stem cells model, supporting early and late cells that were enriched and adapted by bone marrow had the stem cell characters and had the capacity to complete the process of metastasis. Moreover, Kaplan [170] found bone marrow stromal stem cells can firstly reach premetastatic site to create a suitable niche for cancer cells arriving. Such niche [171–173] has been recognized in primary cancer. The discovery indicated there was a similar niche for cancer cells survival and proliferation between primary cancer organ and distant organ. Bone marrow stromal cells are major constitutions of the two niches. Therefore, we speculate that bone marrow was not only a reservoir for cancer cells but also a sustain nutrition pool. During metastasis process, bone marrow may be an intermediate station for cancer cell adapting and dormancy (Fig. 1).

Dormancy recognition from comparison of primary tumors with distant metastases decades after removal of primary tumor

Dormancy is another puzzle question in cancer research [174]. DTCs shed from primary cancer are in dynamic process [175]. These cells can be cancer cells, early progenitors [176] and even normal epithelial cells [177]. They can reach, lodge and survive in ectopic organs. However, it is still unknown when and how these cells are activated and regrow into new tumors in second organs. The new information about the interactions of dormant cancer cells and foreign environment can be gained by comparisons between metastatic tissues and their primary cancers. No matter how long metastasis occurs after resection of primary tumor, there is highly homogeneous between primary cancer and metastasis [25, 178, 179], indicating that the metastatic capacity of ectopic dormant cells are determined by primary cancer and these cells need a micro-environment similar to primary cancers so as to sustain their repopulation and regrowth. The difference in specific genes suggests that these dormant cells need further mutations to overcome the limitation of distant organs. Finally, when the milieu of primary cancer and second organ reach concordant at signal level, dormancy cells are activated and grow into a new tumor in second organs. Now studies have shown that the process from dormancy to activation is regulated by foreign microenvironments [180, 181]. The milieus of neoangiogenesis, stromal cells and immune factors on modulate dormant cancer cells have been studied in some institutions [182–186]. However, these cannot completely answer why metastatic tumor are still similar to primary cancer even after a long interval. Thus, such precise memory for these dormant cancer cells urges us to search for the roles of the nerve system on regulation of dormancy. Recently, the role of nervous system in cancer onset and progression has been recognized [187–189]. Thus, tumor dormancy as well as metastasis formation may be switched from the non-angiogenic and non-neurogenic phenotype to an angiogenic and neurogenic [190]. In addition, Eyles et al.'s [191] study showed that DTCs spread into many organs but immunosurveillance keeps them dormancy, indicating that immune system also play an important role in cancer cells dormancy. Their interactions should be further exploration in the future (Fig. 1).

Similar microenvironments between primary and metastatic tumors

Cancer is an ecosystem, which not only composes cancer cells but also microenvironment. “Seed” and “Soil” hypothesis has emphasized the vital roles of host factors also called microenvironments [192]. In tumor microenvironments, inflammatory molecules and cells are the major constitutions [193]. As we all known, the relationship exists between inflammation and

carcinogenesis and the link grows stronger [194, 195]. Some studies also showed that inflammation on certain organs can promote metastases in these organs. It is well known that smoking is vital for carcinogenesis of lung cancer [196]. Epidemiological and experimental studies showed that smoking can induce to a locally inflammatory microenvironment on pulmonary to enhance lung metastasis from breast cancer [197–199] and esophageal cancer [200]. Asthma is also reported to contribute to lung cancer due to persistent chronic inflammation occurring in asthma. Lee et al. [201] found allergic respiratory inflammation can lead to the recruitment of breast cancer cells to the lung and promote lung metastasis. Experimental studies showed that different stimuli induced lung [202, 203], liver [204–207] and peritoneal injuries [208–210] can enhance organ-specific metastasis. These studies indicated that chronic persistent inflammation not only contributes to carcinogenesis in primary organ but also to the formation of metastatic tumor in the distant site. Moreover, the molecular players in normal wound healing and those in tumor progression and metastasis are also found to be similar [211], which indicates that biomarkers of inflammation or wound healing can be used to monitor and predict the risk of distant metastasis. This view has been testified in other studies [212–214] and is putting into clinical practice [215–217].

Unravelling the complexity of metastasis-identify common players for metastasis among different primary tumors and specific perpetrators for different metastasis sites from the same cancer

Cancer is a complex disease and is looking for simplicity. To find common molecular targets may be a direction of simplicity. Ramaswamy et al. [218] compared the gene-expression profiles of an extensive adenocarcinoma metastases of multiple tumor types to unmatched primary adenocarcinomas and found there was a molecular signature of metastasis in these different kinds of adenocarcinomas. This finding was confirmed by applying the expression signature on 279 primary solid tumors of diverse types. Massagué group studied different carcinoma cell lines located in different site of metastases from a same patient through comparing genes of these cells and found that some genes were common for metastases to all sites, whereas others were specifically relation to growth in a given tissue [158, 219]. More importantly, they found common genes combined specific genes were required for successful metastasis to each site while a single molecule hardly exerted effect, which suggested that inhibition of both common genes and specific genes decrease metastasis and offered a new direction for target different metastasis from a same disease. Witz's group also identified common genes and different genes for site-specific metastasis using the cell lines with an identical genetic background [160, 161]. These studies give us an clue that searching for common molecules playing

key roles in different metastases from a same cancer or the same organ metastasis from various cancers is a direction of simplicity to treat cancer metastasis.

A new hypothesis, biological resonance (bio-resonance) model for cancer metastasis based on the above statements

A new model, bio-resonance, for cancer metastasis, bio-resonance and its illustration

In conclusion, similarities exist at different levels from macroscopic studies to microscopic researches between primary cancer and metastasis (Fig. 2 illustration). It can be also concluded from the above statements that metastasis is a complex process involved random (the same gene model suggest that most cells of primary bulk can spread and form metastatic tumor) and selective (clone-selection model indicating that only rare cancer cells can regrow in distant organs), not only passive (spreading through vascular system to reach other organs) but also active (distant organ can promote organ tropism metastasis). In the process of cancer cells migration, bone marrow plays an important role in enriching and adapting cancer cells. The processes of DTCs shed from different stages of primary cancers, lodgment, and dormancy or proliferation at distant sites are in dynamic state no matter in space or time, and modified by several intrinsic and extrinsic factors. So the differences between primary and metastases do also exist to some extent. In fact, the differences are vital for DTCs to grow into overt metastasis. However, migration cancer cells still keep key biological traits of their progenitors no matter where they lodge. When they are aroused or stimulated by similar stimulus or same signals to primary cancers, they will develop a second tumor that resembles primary cancer. Thus, we propose a new metastasis model, biological resonance (bio-resonance) model to explain how, when and where metastasis occurs.

The new model can explain how, when and where metastasis occurs

We first answer the question of how metastasis occurs. The bio-resonance model means two aspects. One is that primary and metastatic tumors have a same clone. That is to say that the cells from a cancer or its derivation tissue must disseminate into premetastatic organs. The other is that primary and metastatic sites must have same or similar conditions such as similar microenvironments, same or similar signals. Metastatic tumor growth is determined by the interaction of the two aspects. Now we can overview a whole history of a cancer from carcinogenesis to metastasis. According to current studies, primary cancers are in dynamic status in space and time.

Fig. 2 Primary tumor and matched metastasis show similar at multiple levels. The biological resonance model has two basic principles. One is that they have a same ancestor or common clone (Described by Level IV) between primary tumor(PT) and matched metastasis(MT). This clone receive same or similar signals (describe by Level V) in primary and metastatic sites. The other is that primary and metastatic organs must have same or similar conditions including similar injury response induced by different stimuli, similar embryological derivation or congenial soil, similar microenvironment (illustrated by Level I-III). PT or MT is a interaction result from the organism level to molecular level. Thus, its mathematical formula should be: (1) $P=f(x, y, z, t)$, (2) $M=f(x', y', z', t')$ Among of these variables, P: primary cancer, M: metastasis, x: primary

cancer cells, x' : metastatic cancer cells. x and x' have the same progenitor. y and y' represent local microenvironments or and same signals in primary organ and premetastatic organ. z and z' represent stimuli, which can be same of different. t and t' represents time. f (function) represents the rules of tumor initiation and growth. Their relationships are: When time changes, the host receive the stimuli (z for P, z' for M), x' , y' and their interaction will be reach the status of x , y and their interaction, M will be nearly equal to P . That is to say: In a person's whole life, z and z' (stimuli) take effect on the host in space and time and are hardly evitable, There will be the following conditions: (3) Sufficient and necessary conditions: $x' \approx x$; $y' \approx y$, $x'y' \approx xy$, (4) Final Result: $M \approx P$

Invasion and migration are basic traits of cancer. At the initial stage of carcinogenesis, mutant cells, early progenitors or even normal cells of a cancer derivation tissue are shed into circulation and lodge in congenial organ or enriched in bone marrow. With gradually development of cancer, tumor cells are in succession separated from primary cancer. Through circulation system, they reach, lodge in secondary organs, and keep dormancy, apoptosis or proliferation. According to this hypothesis, when the dormancy cells receive same signals or its lodged organs reach similar microenvironments that sustain primary cancer cells to grow and develop, metastasis will occur. Otherwise, they will continue to keep dormancy or undergo apoptosis.

Therefore, cell migration from a specific organ is the prerequisite for metastasis formation while same or similar conditions to a primary tumor are essential for migrated cells to develop a new tumor in secondary sites.

When primary and metastatic tumors are considered to take together in one patient's whole life, there are five possibilities:

- I) They are synchronous. About 60 % of cancer patients (including lymph node metastasis).
- II) Primary cancer is before metastasis occurrence, about 20–25 %.

- III) Primary cancer is after metastasis occurrence [220–222], very rarely.
- IV) Only metastasis occurring {This phenomena called metastatic carcinoma of unknown primary site (CUP) [223] in clinical practice} about 3 %–5 %.
- V) Only primary tumors (locally and be cured) <10 % in cancer patients.

For cancer patients, the fifth possibility is the best. Under the second possibility, the case that metastasis occurs several decades after removal of primary cancer is also better. However, this proportion among cancer patients is very low because 90 % of them will die for metastasis no matter primary cancer first showing or metastasis first manifestation. From the above statements, metastasis is certainly to occur unless cancer cells do not migrate (For example, basal skin cancer rarely metastasizes and its curative rate is the highest). In fact, migration is a common phenomenon for cancer cells and even normal cell [224, 225]. It is the first prerequisite for metastasis. In other words, ectopic cells can lodge and survive in foreign organs. When they are irritated by various stimuli, they can evolve into a new tumor called metastasis in foreign organs. The process is to some extent like carcinogenesis in primary organ. Thus, if cell migration occurs in an organism, metastasis like carcinogenesis is inevitable. The key question is when metastasis occurs. To answer this question, we first understand how cancer develops. It is well known that cancer occurrences are due to chronic persistent inflammation in primary organs that are stimulated by temporal or permanent factors called stimuli. Thus, cancers can be viewed as the results of interactions between stimuli and tissue specific resident progenitor cells in an organ. These stimuli have different traits when acting on organisms. For example, smoking can influence many organs but mainly produce injury on the lung while hepatic virus mainly insults the liver and seldom acts on other organs. For primary and metastatic organs, they can receive the same stimuli or although they receive different stimuli, they have the similar response and reach same or similar microenvironments for cells transformation and growth. In general, particular stimuli are often acting on specific sites. Thus, primary organ usually received more stimulations than metastatic organ. In this case, primary cancer often occurs earlier than metastasis. Therefore, early stage tumors often mean that their primary organs are assaulted by specific stimuli. In the development of these early stage tumors, tumor cells continue to shed into circulation and lodge in other organs. If these organs don't receive stimuli and keep normal conditions, they can make these cells dormancy or drive them to be dead. In this situation, metastasis hardly occurs. If these ectopic sites receive more stimuli and produce persistent injuries or same signals as primary cancer grow, metastasis will occur. The interval between metastasis occurrence and resection of primary tumor is dependent on the status of migrated cells and distant sites. If the

cells lodged in an ectopic organ are normal or early progenitor cells, it will take a long time for these cells to develop a new tumor when the lodged organ receives stimuli and reach similar status to primary tumor. If these cells are fully evolved tumor cells in a distant site, they soon develop metastatic tumor when the lodged site forms a suitable milieu under similar or different stimuli. If primary tumors are indolent and don't release cells into other organs, they can be viewed to be curative and never have secondary tumors even after several decades after removal of these primary tumors. For late stage tumor, it means that the whole organism receive stimuli. Thus both primary and metastatic organs will simultaneously make response to these stimuli and be easy to reach similar environments. Thus, synchronous metastases are often detected at initial diagnosis. If the distant site firstly suffers from persistent stimuli, normal cells or early mutant cells from other ectopic tissue will independently evolve into an ectopic tumor named CUP in a foreign organ.

The last question is that we focus on where metastasis occurs. According to the above statements, which organ is affected by metastasis tumor is not only depended on intrinsic state of primary cancer, its derivation organ, spreading routes, but also relation to target organs. In general, each tumor has preferred organs for metastasis. These organs are often congenial to primary organ. The congenial trait can be considered to be isogenesis in the levels of embryological derivation and development, and or similar microenvironments described in the above statement. For example, Monte et al.[226] investigated primary sites and metastatic organs in melanoma patients and found that they had similar embryological derivation. So they can be compatible with ectopic cells or enriched cancer cells. When these organs receive stimuli and produce injury, ectopic cells will develop a metastatic tumor in foreign organs. It is well known that the lymph node, lung, liver and bone are the most sites of metastases from many kinds of solid tumors. These organs have common traits. They are in dynamic balance between new cells generation and apoptosis and are also easily affected by various stimuli. When they are irritated, they will undergo repair and produce injury. Moreover, they are the first bed for many organs efferent vascular system so that they can capture many types of tumor cells of various tissues. Therefore, they are easily influenced by metastatic tumors. For heart and skeletal muscles, although they receive large amount of blood supply and seem to be lodged by disseminated tumor cells, these tissues are stable even if they receive stimuli, metastasis hardly occur. The above phenomena are mainly based on the first capillary bed met by cancer cells. However, recent studies indicate that cancer cells can be equivalently distributed into all other organs in a host [191, 227]. If these organs undergo injury by extrinsic and intrinsic stimuli, metastasis can be formed, which have been supported by cases reports and experimental studies. This may explain why infrequent sits of metastases are often observed in clinical practice.

Commonality and difference between our model and previous hypotheses

This hypothesis is similar to the hypothesis of “seed” and “soil” in some extent. However, although the “seed” and “soil” emphasized the interaction of the cancer cell and host factors, it is uncertain when metastasis occurs. Early model and purely mechanism model, clone selection, dynamic heterogeneity, cancer stem cells and EMT model mainly focus on the intrinsic traits of cancer cells, fusion models only studied the metastasis capacity of cancer cell. Now their limitations and reconciliations have been recognized [19, 122, 125]. Takahashi et al.[228] compared whole-genome allelic imbalance and mutational analysis of the p53, EGFR, and KRAS genes on eight pairs of primary and metastatic lung cancers and found the similarity was major(>67 %) between primary and metastatic lung cancers while there were still variations that genetic alterations were accumulated only in metastatic tumors in seven eight of cases and four cases showed genetic alterations detected only in primary tumors. When nature history of each case was considered, the process of metastasis varies among cases and some genes. Thus, they draw a conclusion that clonal evolution, parallel evolution and same-gene models were applicable to lung cancer progression. In fact, taking together previous studies on cell culture in vitro, transplantation animal model and primary cancer tissues and these comparison between primaries and metastases, metastasis seems to be the combination of the above models. Talmadge [125] focused on recent data and new models and gave a new explanation using clonal evolution hypothesis. Finally, he posited that other models represented subsets of the clonal evolution hypothesis when considering the context of natural history of a tumor. Our model is not mutual exclusive with the clone evolution model. In the sixth paragraph, we also use this model to explain similarities and differences between primary and metastatic tumors. However, clonal evolution model seems not to explain when and where metastases occur. Bio-resonance model merge these merits of the previous metastatic hypothesis, supply a comprehensive view of cancer metastasis and seems to be more applicable to explain how, when and where metastasis occurs. Its mathematic formulate is listed in Fig. 2 legend.

The limitation of our new model and further works to solve the limitation

This model can easily explain why non-small-cell lung carcinomas often spread to the contralateral lung [122]; primary liver cancer often has metastases in the liver itself. However, it also has a limitation. For example, it can't explain why breast and kidney cancer scarcely metastasize to contralateral breast or kidney. The reason may be due to unrelated vascular spread system. This is like two same tuning forks in the Earth. When

their distance is no more than 10 cm, resonance will occur. But when one is in china and the other in America or British, resonance hardly occurs between them. The organism like the Earth not like the vacuity environment has substantial connection. From the route of cancer cells migration through vascular circulation, the distance between contralateral organs is no more shorter than that between primary organ and other distant organ. Thus, the incidence of metastasis in the contralateral organ is also low. Another reason may be that normal microenvironment in the contra-lateral organ can inhibit proliferation and growth of DTCs[229]. In fact, renal cancer can also have a high incidence of contralateral kidney metastasis [230, 231]. Moreover, second primary cancer also increases in the contra-lateral organ when one organ occurs to primary cancer [232]. From the supplemental formulate, stimuli (z) can act on both organs, y'(microenvironment of premetastatic organ) is easily equal to y(milieu of primary organ). x (progenitor of primary cancer) and x' (ancestor of secondary primary cancer) are similar at tissue derivation) but don't have a same clone. Thus, P' (secondary primary cancer) will also occur. From this point, the model is still to some extent true.

To further testify the model, the following working should be done. First, the nature history of cancer should be noticed. A cancer is initiating at mutant cells and ends with metastasis. This is a process. It is noticed only after it is diagnosed of cancer which accounts for no more than 1/4 in the whole cancer history [125]. Cancer history should be considered to be a whole process from the beginning to the end. From the initiation of primary tumor to metastasis occurrence, stimuli, host, primary and metastatic organs, cancer cells and surrounding stromal cells and many molecules are collectively involved the whole process, which can supply more information for this hypothesis. Second, in the whole process, the regulation is so precise and subtle that metastasis tumors resemble their primary tumors even after several decades from complete resection of primary tumor. Cancer cells have so good memory so as to grow a nearly identical tumor. There must be a system to regulate. Moreover, the bio-resonance model emphasize that there are same or similar signatures when primary and metastasis occurrences. Who produce and modulate the same signals? We speculate that the nerve system may play an important role in this process, which has received attention and need to be further studied. Third, when a individual patient is considered to how, when and where metastasis occurs, current mathematics models cannot answer these questions and need to develop a more powerful math tool to make complexity of cancer metastasis be simplicity and easily operated.

Clinical implications of the bio-resonance model

This hypothesis has important implications for individual prediction, prevention and treatment of metastasis. Traditional

approaches mainly aim at primary cancer cells and try to eliminate all these cancer cells. From the above statement, we can conclude that it is impossible to achieve this aim. According to this hypothesis, treatments on cancer not only focus on cancer cells but also pay attention to the microenvironments of primary organs and distant sites. The stimuli are often omitted in clinical practice. When a host is diagnosed of cancer, it means that he or she is suffering from stimuli. In the following treatments, stimuli must be recognized and try to eliminate them or decrease their injuries at the least. For example, smoking habits in cancer patients should be abandoned while asthma should receive treatment to decrease lung inflammation. Moreover, future directions should interrupt the communications of interactions between primary and secondary tumours, evaluate the risk organs for metastases and try to decrease their incidence. Distant metastases have been reported to be predicted from the primary cancer tissues. Base on the theory and chronic inflammation relation to cancer and metastasis, inflammation markers can also be used to evaluate when metastasis occurs. If these biomarkers increase, it may indicate that patients with cancers are undergoing injuries by intrinsic and extrinsic stimuli and are in risk of metastases. They need proper adjuvant therapy to decrease the risk. Combination therapies of common and specific molecules may exert this effect.

Conclusions

In summary, we proposed a new hypothesis of bio-resonance model through comparisons between primary cancers and matched metastases. When taking consideration of all the pheromones from the nature history of cancer, cancer cell culture in vitro and vivo, transplant animal models, huge information of primary cancers and their metastases, the hypothesis seems to be applicable in various of metastatic phenomena. This hypothesis needs to be testified in nature history, nerve system and mathematics model. If it is correct, it will supply new insights to prevention and treatment of metastasis.

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