OPINION ARTICLE

Hypothesis: Cancer alloustasis [version 1; peer review: 1 not approved]

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Abstract

Despite decades of study, there are still many unanswered questions about cancer metastasis. One of these questions is about the origin of the tumor cells that give rise to metastases. The currently accepted models of cancer metastasis are inconsistent with some clinical observations of the natural history of cancer and its response to therapy, challenging our understanding of the nature of metastasis. Here, we coin a term 'cancer alloustasis' to describe the tumor that forms *de novo* in secondary sites, but is not originated from primary site derived cells. Moreover, we present a complementary hypothesis suggesting that the progenitors of alloustasis are distinct with those of primary tumors and the outgrowth of alloustases is promoted by primary tumors.

Keywords

Origin of metastasis, Cancer alloustasis, Complementary hypothesis

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1

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1. **Christoph A. Klein** , University of Regensburg, Regensburg, Germany

Any reports and responses or comments on the article can be found at the end of the article.

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The Primary Site Derived hypothesis

Since the days of the German pathologist Rudolf Virchow (1821–1902), the prevailing view for the origin of cancer metastasis has been the assumption that the anatomic progression of a malignant cell population is a stepwise movement of cells from the primary tumor to the regional lymph nodes and thence to more distant organs. Cancer metastases are believed to be the end result of a multistage process that includes local tissue invasion by primary tumor cells, intravasation into blood vessels or lymphatic system, survival during transit in circulation, arrest within a distant organ, extravasation, survival in the new tissue environment, and proliferation to produce metastatic colonization (Gupta & Massague, 2006).

In line of this hypothesis, Nowell proposed the clonal selection model, where only small sublines of cells within primary tumor acquire genetic permits grow as metastases under stepwise selection (Nowell, 1976). Whereas Weiss emphasize on dynamic or compartmental heterogeneity, stating that the primary tumor is composed of a heterogeneous population of cells with metastatic capability, but metastatic phenotype is only a property of a given tumor cells due to epigenetic changes (Weiss, 1990). Other major models of metastatic growth include the clonal dominance model (Kerbel *et al.*, 1988), metastasis gene transfer theory (Garcia-Olmo *et al.*, 2004), the fusion model (Pawelek, 2005; Pawelek & Chakraborty, 2008) and the parallel progression theory (Klein, 2009). All these models share the common belief that metastasis emerge from primary tumor or primary lesion. I nominate these models for the origin of metastasis as the Primary Site Derived hypothesis (PSD hypothesis).

The phenomena that challenge PSD hypothesis

There are several complex biological phenomena that challenge this assumption of metastatic progression. One important clinical observation is of metastatic tumors from an unknown primary source. It is estimated that 2–6% of cancer patients (according to various literature reports) presenting to oncology units have cancer metastases in the absence of an identifiable primary tumor.

In these clinic cases, the patient is considered to have ‘unknown’ or ‘occult’ primary tumor and characterized as unknown primary origin (CUP) or unknown primary tumors (UPT) (Ettinger *et al.*, 2011). The existence of CUP suggests that metastases may not always be derived from primary tumors (Greco, 2014; Oskarsson *et al.*, 2014; Vanharanta & Massague, 2013).

Moreover, several studies show that the formation of metastatic tumors is not definitely rely on the formation of primary tumor. The morphologically normal breast cells from genetically engineered mice were injected into the tail veins of other female mice. The results showed that tumors were formed resulted in the lungs but not in the breast after oncogene induction (Podsypanina *et al.*, 2008). In addition, the cultured metastatic cells may even be detected in the primary organs rather than secondary sites, for example, the kidneys and heart (Friberg & Nystrom, 2015). Another uncertainty is whether metastasis is really the result of cancer cell dissemination to a secondary

organ through the bloodstream or lymphatic vessels as circulating tumor cells (CTCs). For example, a study has estimated that the probability of not detecting any CTCs in blood from metastatic breast cancer patients is 0.6 (Shahriyari, 2016). Although this finding may be due to technical issues to detect CTCs in all patients, it may also suggest that other mechanisms may operate to create tumors in other organs.

Doubts about the PSD hypothesis

The above experimental or clinical observations generate a follow-up doubt: Do the tumors in secondary sites develop always from the cancer cells preexisting within a primary tumor or absolutely from premalignant cells originated from primary lesion? It is important to note that our current understanding of the biology of cancer metastasis is strongly influenced by experimental models including *in vitro* and *ex vivo* systems, mimic *in vivo* models developed on *Drosophila Melanogaster*, zebrafish, fertilized chicken eggs and mice (van Marion *et al.*, 2016). These models contribute to study the tumor progression especially combined with whole body imaging techniques, which enables the early detection of small metastases and track longitudinally their fate in the same animal. However, the clinical observations is frequently not consistent with the metastatic process in the animal models.

In this regard, the ideal model about the origin of secondary tumors should be summarized solely from clinical observation. Clinically, most secondary tumors occur later when the primary tumor is larger. Nevertheless, secondary tumors can occasionally form early in tumor progression when the primary tumor is still small or even undetectable. The parallel progression model (Klein, 2009) explain this phenomena as tumor cells depart the primary lesion before the acquisition of fully malignant phenotypes to undergo somatic progression and metastatic growth at a distant site. This model well illustrates the characteristic biology of early dissemination (Hosseini *et al.*, 2016; Husemann *et al.*, 2008; Klein *et al.*, 2002) while remaining questions are left open. If parallel progression hypothesis is applicable for all secondary tumors, we would expect that the ever-increasing ability to detect secondary tumors at earlier stages should certainly lead to a major reduction in mortality. In fact, despite earlier diagnosis and improved treatment modalities and supportive care, age-adjusted mortality rates have not appeared to decrease.

Cancer is a complex disease and our current understanding of systemic cancer is insufficient. Unfortunately, neither prevailing models about the origin of secondary tumors is supported by direct and incontrovertible evidence. Therefore, I address the possibility that some tumors formed *de novo* in secondary sites are not coming from the primary tumor or primary lesion. These particular tumors, in a sense, grow up like ‘primary tumors’ and according to their own principles.

The OSD hypothesis

I propose a model to describe the origin of cancer metastases in some patients and nominate this model as Own Site Derived hypothesis (OSD hypothesis). The major points that involved into the OSD hypothesis are:

Cancer metastasis is replaced as cancer alloustasis in some patients

Metastasis is a Greek word meaning ‘displacement’, from μετά, meta, ‘next’, and στάσις, stasis, ‘placement’. It was coined in 1829 by Jean Claude Recamier and is now defined as ‘the transfer of disease from one organ, or part, to another not directly connected to it’ (Fidler & Balch, 1987). Since cancer metastasis is commonly considered as the secondary tumors derived from primary tumor, we create a term ‘cancer alloustasis’ to define the tumors developed from particular cancer cells that are not coming from primary tumor. This idea is inspired by changing μετά, meta, ‘next’ to άλλού, allou, ‘elsewhere’. Accordingly, ‘cancer alloustasis’ means ‘elsewhere placement of tumor’. ‘Alloustasis’ is a singular noun. Its plural, adjective and transitive verb is denoted as alloustases, alloustatic and alloustasize, respectively.

The progenitors of primary tumors and cancer alloustases are different

Cancer is a systemic disease. The origin of cancer cells is the result of clonal selection and evolution. It is possible that there are transformed cells arising from both primary and secondary organs before the occurrence of primary tumor. The fate of these progenitors of cancer is determined by their adaptability for the host environment. The tumor that acquires sustainable growth capability will continue to grow as a malignant lesion.

Otherwise the transformed cells will maintain their premalignant state or be eliminated by their own microenvironment (Figure 1). According to the OSD hypothesis, the first malignant lesions are defined as primary tumors and the organ where they emerge from is described as primary organ. The transformed cells located into primary organ are distinct with those transformed cells located into secondary sites. Even after the outgrowth of primary tumor(s), the transformed cells in secondary sites do not emerge from a subpopulation of cells present within a primary tumor but rather selected out by their own microenvironment.

Primary tumors promote the progress of alloustases

The host environment of the patient is dynamic. The successful growth of the primary tumor may remodel the host environment of the patient’s whole body by excreting humoral factors (such as hormones or cytokines) or by an immune response against those tumor cells. It follows that primary tumors change the microenvironment of secondary site and induce the outgrowth of alloustasis which, in the same manner, produces secondary alloustases (so-called ‘alloustasis of alloustases’) (Figure 2). Thus, in a short time, a small primary tumor may produce a cascade of alloustases. This mechanism reveals why cancer exponentially increases the clinical impact to the host and causes severe diseases, for example paraneoplastic syndrome (Finora, 2003; Torrielli *et al.*, 1971) and cachexia (Fearon & Moses, 2002).

Figure 1. Hypothesis for the progenitors of primary tumors and cancer alloustases. The premalignant cells arise from both primary and secondary organs before the outgrowth of primary tumor. The fate of these progenitors is determined by their adaptability for the host environment and their own microenvironment. **a.** The transformed cells arise from multiple organs of patient. **b.** The special transformed cell acquires priority selection. **c.** The selected transformed cell continues to grow as primary tumor and other transformed cells maintain their premalignant state or are eliminated by their own microenvironment.

Both primary tumors and alloustases have multiple lesions

As I mention before, cancer is a selective and evolutionary process. It is possible that there are multiple transformed cells arising from multiple sites among various organs. These transformed cells will influence the host environment of the whole

body and directly or indirectly cooperate with each other to promote the progression of primary tumors. Finally, only part of them acquire the ability to continue growing as malignant lesions (Figure 3) which is observed clinically as a result of a 'field effect' (Freireich *et al.*, 2005).

Figure 2. Hypothesis for the progression of alloustasis. **a.** The transformed cells arise from multiple organs of the patient. **b.** The special transformed cell acquires priority selection. **c.** The selected transformed cell continues to grow as primary tumor. The outgrowth of primary tumor promotes the formation of alloustasis. **d.** The outgrowth of alloustasis promotes the formation of alloustasis of alloustases.

Figure 3. Hypothesis for the mechanism of multiple malignant lesions. **a.** The transformed cells arise from multiple sites of different organs. **b.** Multiple transformed cells into the same organ are selected out and continue to grow as multiple primary tumors. **c.** The outgrowth of multiple primary tumors promotes the single or multiple alloustasis.

Both primary tumors and alloustases have cancer regression

According to the OSD model, the particular pre-cancerous cells are kept evolutionary and equally selected by host environment of the whole body prior to the formation of primary tumor. Moreover, we propose that the growth of malignant lesions (including primary tumors and alloustasis) is dynamically regulated by the fluctuation of host environment in some patient. After the outgrowth of malignant lesions, they may even be destroyed by their local environment (Figure 4). This can be applied for explanation of the CUP behavior and phenomena of regression of human cancers without treatment (spontaneous regression) which is first reported more than 100 years ago and is well documented

for many types of cancer, albeit with low frequency (Harada *et al.*, 2010; Kumar *et al.*, 2010; Onuigbo, 2012; Strub *et al.*, 2013).

Concluding remarks

Here I challenge the prevalent hypothesis of cancer metastasis, and consider that, in some patients, the ancestral cells of secondary tumors do not necessarily have to be cancer cells originating from a primary site. I propose a complementary OSD hypothesis to indicate that some tumors formed *in situ* into secondary sites (defined as alloustases) resulting from clonal selection and evolution for adapting the dynamic environment (tumor microenvironment and host environment of the whole body).

Figure 4. Hypothesis for cancer regression. **a.** The transformed cells arise from multiple organs of patient. **b.** The outgrowth of primary tumor promotes the formation of alloustasis. **c–e.** The malignant lesions of patient are dynamically regulated by the host environment and their own microenvironment. The primary tumor and alloustases are gradually eliminated or even promoted by the host.

According to the OSD hypothesis, the relationship of primary tumors and alloustases is mutually independent but interrelated. In a sense, the origin of alloustasis seems like that of a primary tumor. However, the hypothesis highlights that the progenitors of alloustases differ from those of the primary tumors and the progress of alloustasis is promoted by the formation of primary tumor. Meanwhile, the primary tumors and alloustases may exhibit parallel evolution, and they will cooperate or even compete with each other during the progress of cancer.

I also emphasize the central significance of environment. The local microenvironment and systemic host environment of malignant lesions (both primary tumors and alloustases) are not stable but rather very dynamic. Hence the cancer lesions may be diminished or eliminated by the environment. Notably, we

consider cancer alloustasis as a systemic disease. In that case, I think it is necessary to treat cancer as a systemic illness. More attention should be focused on systemic treatment and prevent of cancer as they relate to etiology. Perhaps the identification of systemically-acting carcinogens based on the systemically therapeutic strategies might be targeted clinically and would have a substantial impact on overall cancer mortality.

Data availability

No data is associated with this article.

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The opinion article by Wu Zhou provides an interesting hypothesis about the origin of systemic cancer. It starts by opposing the Primary Side Derived (PSD) hypothesis of systemic cancer with the Own Side Derived (OSD) hypothesis. In a nutshell, the OSD hypothesis suggests that there is no migration from one side to another but that tumors arise in different organs in parallel. The first diagnosed tumor is then called the "primary tumor" whereas the other growths are called alloustasis, which means that there is another tumor at another site.

Thereby, the author provides a different concept of systemic cancer, in which the migration inherent to the standard metastasis model is replaced by growth promoting factors of the first, i.e. the leading lesion, which may support progression and diagnosis of the alloustasis. In a way, this is similar to the parallel progression model suggested some years ago (Klein NRC, 2009¹), in which early disseminated cancer that are genetically too immature to autonomously grow into a metastasis receive systemically acting, growth-promoting support from the primary tumor.

Criticism:

While the concept is interesting and thought provoking, I think the paper needs some more work before being listed in pubmed, since students and scientists in training need more information to fully judge its content.

1) Text and nomenclature:

- I strongly recommend that the author revise the text with help of a native speaker. The understanding of such an article fully depends on a precise language. For example the sentence "The transformed cells located into primary organ are distinct with those transformed cells located into secondary sites" is unclear, imprecise and grammatically incorrect. There are numerous sentences like this, which reduce the clarity and scientific vigor of the concept.
- I also strongly recommend that the author spend some more thinking on how to adapt his nomenclature. For example, the term "malignant" indicates in the standard model that a

proliferating lesion seeds cells to other sites and generates systemic cancer. Dissemination is defining malignancy. What would be the meaning of malignant in the alloustasis model? Since invasion and dissemination do not exist, how would the author differentiate malignant vs. benign tumors?

- My school knowledge about ancient Greek has become minimal, however I wonder whether "alloustasis" should be replaced by allestasis. "Stasis" is feminine and "alle" would be the corresponding form of the adjective.

2) References / state of the art

- For several statements, the author should provide the references. For example, I would not agree that early detection and local therapy does NOT impact on outcome. As such the statement that "... the ever-increasing ability to detect secondary tumors at earlier stages should certainly lead to a major reduction in mortality. In fact, despite earlier diagnosis and improved treatment modalities and supportive care, age-adjusted mortality rates have not appeared to decrease" is at best misleading if not incorrect. References should be provided to justify this view.
- As mentioned above, the arguments in favor of a metastasis model should be summarized. This includes a careful analysis of CUP. Recent work on the epigenetic tracking of tumor origin (see the Lancet Oncology paper of the Esteller group²) has generated some evidence in favor of a metastasis model. In fact, consideration of the genetic and epigenetic comparisons between primary tumours and what is currently judged as metastases, may be a useful starting point to define the need of an alloustasis concept.

3) Explanatory power of the concept

- Scientific theories and concepts aim to properly describe reality. Any change needs to be evaluated by its contribution to better explain observed phenomena. The author provides some arguments in this direction, however, this part needs to be substantially improved. For example, cancer of unknown primary is the major argument in favor of alloustasis so far. However, early dissemination and regression of the primary lesion explains CUP equally well. I would suggest that the author generates a table of all arguments in support of alloustasis. The article should also contain a list of arguments that support the "metastasis" concept. What is then needed is that the alloustasis model explains all/most metastasis-supporting phenomena equally well. Such an approach will reveal, for which cancer cases alloustasis may indeed provide a reasonable explanation and which cases would be better explained by a metastasis model.
- In line with this point, it would extremely helpful if the author provides a clear separation of the two models. For example, estrogen receptor expression in a breast cancer and in a metachronous brain lesion is currently taken as evidence for a brain metastasis from a hormone receptor positive breast cancer. How would the alloustasis model explain this? Or would the author agree that in this case metastasis has occurred? Similarly, epithelial growths in mesenchymal organs like lymph node or bone marrow: how are these explained in an alloustasis model given the fact that these organs do not contain epithelial cells that could give rise to an alloustatic epithelial cancer?
- When such confrontation of the two models has been elaborated, the author should check, which model is simpler, i.e. he should apply Ockham's razor.
- Finally, I would greatly appreciate, if the author could provide his thoughts about data that would falsify alloustasis. Would there be any experiment or finding that would lead to rejection of the concept? Falsification criteria are extremely helpful to generate new research, even if methods for such falsification are currently not available.

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Is the topic of the opinion article discussed accurately in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Partly

Are arguments sufficiently supported by evidence from the published literature?

Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: I am member of the scientific advisory board of HiberCell, New York.

Reviewer Expertise: cancer biology, metastasis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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