

NEW HYPOTHESIS ON THE ORIGIN OF METASTASES

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ABSTRACT

A new hypothesis for the origin of metastases is presented. It assumes that a cancer-transformed gene in a primary tumour is incorporated in its identical form via a virus-vector function into biologically potent recipient cells in other organs, such as stem cells, multipotent cells or cells in an early phase of division. The origin of metastases may thus possibly occur via a genetic pathway.

Key Words: viruses, genes, stem cells, multipotent cells, bone marrow, lymph nodes

INTRODUCTION

While there are many ambiguities in terms of explaining the behaviour of metastases, the theory of cell migration for the origin of metastases remains accepted today. Convincing evidence in favour of this is the cytological identity of the metastatic cells and the cancer cells in the primary tumour. However, no evidence exists that explains the known uncertainties. With its focus on charting the genetic background of the origin of tumours and their more effective treatment, research has relied on the cell migration theory. The easily understandable process of cell migration is favoured over processes that would help to explain the extremely complex events that have been observed, reflected in the broad panorama of knowledge of the genetic pathogenesis of malignant tumours.

While the current concept of the migration theory carefully describes certain pathophysiological actions in the metastasizing process, there are several aspects of the phases of the multifaceted course of the process that are unclear^{1,2}.

In the parts of the process that have yet to be explained, we use a logical interpretation of certain phenomena that occur in the metastatic process, while we use assumptions to shed light on others. The phenomenon of different cancer forms preferring to metastasize in certain organs, i.e. they show a pattern of priority, has still not been explained². Some authors assume that anatomico-circulatory conditions can play a role, as well as metabolic properties in the recipient organ, adhesion characteristics of the vascular endothelium, and the histogenic properties of the tumour¹.

Received: April 20, 2012; accepted: September 19, 2012

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The lymphogenic metastases also fail to comply with strict rules, and lymph nodes located relatively far from the primary tumour are often invaded by metastases. An example is the so called Virchow's metastases in stomach cancer. As evidence for their origin is lacking, it is assumed that they are signs of haematogenous metastases via the *ductus thoracicus*¹⁾. Furthermore, it is not known why the spleen and the skeletal musculature are extremely infrequently affected by metastases. Because of the many uncertainties in the process of metastasis, together with the mostly unsolved riddle of cancer³⁾, one is encouraged to look beyond the current theories.

It has been shown that cancer cells are found in the blood of cancer patients but, remarkably, only in 5% of these patients²⁾. Similarly, cancer cells are found in the *ductus thoracicus*²⁾. This is not surprising, but it is hardly sufficient as evidence for cell migration as the origin of metastases. Cancer cells are also found in pleural fluid and abdominal fluid, for example, although in these cases probably via an implantation mechanism.

Before I arrived at the hypothesis presented below, I thought in particular about two phenomena (see below) that have to do with ambiguities in the origin of metastases and that are in violation of the concept of cell migration. The two phenomena prompted me to consider other possible paths for the origin of metastases, namely at the subcellular level.

Lack of the microembolism phenomenon in the clinical picture of lung cancer

The microembolism phenomenon is clearly not a part of the clinical picture in most forms of cancer with an intravascular invasion into the venous system. If the cancer cells have reached the lungs and been able to survive, metastases are formed, with resulting symptoms. The cancer cells may pass further into the pulmonary circulation via arteriovenous shunts, but it must be noted that these are open only under certain haemodynamic conditions.

The situation is different in the case of lung cancer, however. From the perspective of biology and pathophysiological microcirculation, the clinician would expect to observe an episodic microembolism syndrome in lung cancer, as released cancer cells enter the arterial system (see two well-known phenomena below). One arrives at this reasoning by considering the relationship between the diameter of the capillaries (from 4–10 μm ⁴⁾), the diameter of the arterioles (less than 50 μm ⁴⁾), and the size of the cancer cells (varying from 14 μm to 40–60 μm , and in some cases up to 180 μm ⁵⁾). In addition, it has been noted that cancer cells are bound to thrombocytes, lymphocytes, and other blood corpuscles¹⁾, i.e. their joint diameter exceeds the diameter of the capillaries and in certain cases also that of the arterioles.

Thus, with an incidence of cancer cells in the arterial blood that are of the size given above, a clinician would expect a microembolism syndrome of the type sporadically encountered in e.g. mitral valve prolapse and atrial fibrillation as well as in *amaurosis fugax* or cerebral microembolism phenomenon – TIA (transitory ischemic attack). Note: the *fundus* of the eye has a specific microcirculation.

In addition to the above, it is important to consider what we have learned in biology and respect the strict criteria in the biological system. The sinusoids in the bone marrow release blood cells such as erythrocytes, leukocytes, monocytes, and thrombocytes to the circulatory system under normal conditions. The size of these cells ranges from 7–15 μm . Somewhat larger blood cells can sometimes occur – in diseases such as leukaemia, such as myeloblasts (12 μm – 20 μm), promyelocytes (15 μm – 24 μm), and metamyelocytes (14 μm – 20 μm). However, larger blood cells such as megacariocytes (30 μm – 100 μm), megacarioblasts (≥ 30 μm), and promegaloblasts (26 μm – 35 μm) are not released from bone marrow. These blood cells are not found in the peripheral blood⁵⁾. Neither are Sternberg cells (30 μm – 75 μm – 80 μm) in the case of lymphogranulomatosis released from the bone marrow or from lymph nodes. The size of the cancer cells far exceeds the biological criteria. Thus the lack of microembolism syndrome

in lung cancer should be considered remarkable. There are two alternatives: either cancer cells are released from a lung tumour and in the clinical picture should belong to the microembolus phenomenon or, if cancer cells are not released, we must ask what pathway according to the cell migration theory metastases take from a lung cancer, for example to the vertebrae, pelvis etc.

The concepts discussed above clearly lead to thoughts of a subcellular mechanism for the formation of metastases.

Krukenberg metastases in stomach cancer

Krukenberg metastases in the ovaries, which are characterized by so called signet ring cells that are abundant in mucin, occur in most cases of stomach cancer but can also originate from the colon, appendix, or breast⁶⁾. These authors point out, "For some unclear reason, the usual type of gastro-intestinal cancer, which lacks signet ring cells, does not have anything like the same tendency to metastasize to the ovaries. It was stated that the signet ring type of stomach cancer spreads to the ovaries in 41% of cases, whereas common stomach cancer does so in only 17% of cases"⁶⁾. It was also claimed that, in the signet ring cancer form, both ovaries were involved in over 80% of cases.

This is remarkable. These two facts show two separate metastasizing patterns to the ovaries by different cancer cells from cases of stomach cancer. As there is no clarity in this phenomenon, assumptions are made. This then provokes the thought that, in the light of the cell migration theory for the origin of the metastases, there cannot exist different migration rules so that signet ring cells from this type of stomach cancer metastasize to the ovaries in 41% of cases while cancer cells from an ordinary stomach cancer do so in only 17% of cases. Further, the signet ring cells lodge in both ovaries in 80% of cases. This is another phenomenon that clearly provokes consideration of a possible subcellular mechanism behind the origin of metastases.

All the facts in the two phenomena described above provoke a strong suspicion of the migration theory indeed offering the absolute truth; at the same time, they are a challenge to search in other areas for the origin of metastases.

Over the years, the literature has raised doubts about whether the origin of metastases actually depends on cell migration. As early as 1993, Professor Michael Baum began to question whether metastases instead depend on a subcellular transfer with the help of a mechanism for *in vivo* transfection⁷⁾. He considered this a rich area of research and suggested antiviral therapy. His new paradigm was prompted by the limited success of the established scientific methods for breast cancer treatment that were used for two decades. Professor Baum⁸⁾ issued a further report in 1995 and again in 1996⁹⁾. In these recent reports, he discusses the problem of breast cancer, stating that, although the apparent progress in diagnosis and treatment was often emphasized, only modest success in reducing mortality had been observed in the preceding 20 years. He offers another conceptual revolution and repeats that it is probable that not all metastases are a cellular phenomenon. He writes: "Therapeutic interventions that may control rather than 'cure' breast cancer using biological specific modalities rather than non-specific cytotoxic drugs could provide some of the answers."

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The lack of the microembolus phenomenon in the clinical picture of lung cancer and Krukenberg metastases in stomach cancer, which cannot be explained by the theory of cell migration, were the basis for considering subcellular agents as the origin of metastases. The concept of the subcellular level is particularly associated with the first phenomenon, which must obey

the strict biological rules for limits for the size of cells in the arterial system. The reasoning in the hypothesis is that the subcellular substrate is gene transformation in a primary tumour, i.e. that cancer genes are transferred to recipient cells. Thus, the origin of metastases probably has a genetic background mechanism. This cancer gene transferral must, however, take place via some transport mechanism, and the hypothesis points to what is known from medical practice, the so called virus-vector function. It is important to remember that the goal of the virus is to survive in infected, active cells¹⁰. Further, cancer itself has a cancer-related inflammatory component¹¹. In this case, the cancer cells in a primary tumour are in an excellent environment for this purpose; they can multiply in a primary tumour and, with their capacity to steal genomes, the hypothesis proposes that they participate in the metastasis process as vector bearers. Humans already use viruses as vectors – but it should not be neglected that humans do nothing that nature has not done before! Here we can consider viruses of different kinds, such as many of the human retro, adeno, herpes viruses and human papillomavirus (HPV). To develop metastases in recipient cells, these cells must have a regenerative potential. Examples include stem cells, multipotent cells, or cells in an early phase of division which, in incorporating gene material, further develop in these different cell types. Moreover, such cells are found in the favourite locations for metastases, namely bone marrow, vertebrae, lymph nodes, liver, lungs, ovaries etc. American researchers have recently identified pluripotent stem cells in the lungs¹².

Fig. 1 shows a schematic picture of such a hypothetical process.

In summary, the change in the cancer cell that lodges in e.g. a stem cell must be replicated in the subsequent stem cell division, with its malignant character, and form a metastasis. The stem cell thus develops to become a tumour cell that is a copy of the primary tumour's cell. It must carry all the characteristics of the primary tumour's cells and have a continuous, uninhibited cell division as a result of a strong interaction between oncogenes and tumour suppressor genes,

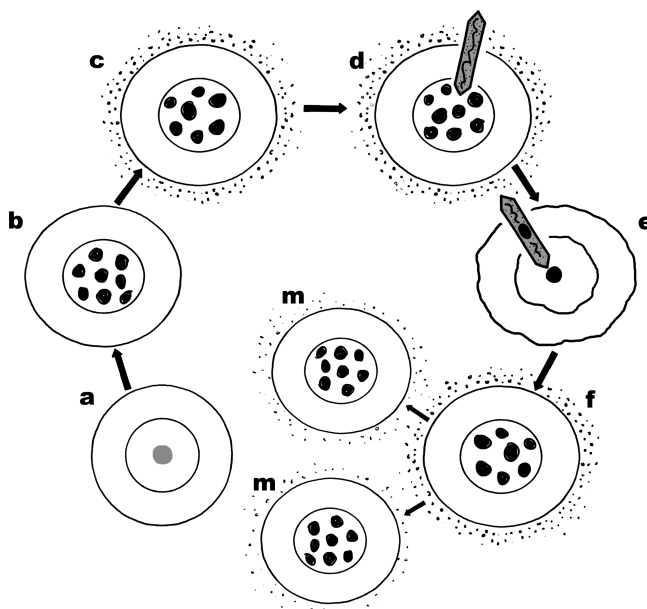


Fig. 1 a) normal cell, b) cancer cell, c) cancer cell with cancer-related inflammation element, d) virus attracted into the cancer cell, e) virus incorporates a cancer gene in a stem cell, f) stem cell is transformed into a cancer cell, m-m) metastatic cells.

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which genetics has demonstrated^{10,13}). The tumour suppressor genes will probably be of the same kind and have the same inactivation competence as in the primary tumour because they have specific tissue effects¹⁰.

Two background concepts can be perceived through the unpredictable biological phenomenon in Krukenberg metastases described above: selection and/or attraction. The hypothesis also offers other perspectives, including whether the occurrence of signet ring cancer in the stomach may be caused by viruses that have gastric mucosa cells as a goal, similar to HPV in genital cancer. Of these, HPV is also more prolific – more than 15 variants are known and they show clear tropism to the genitalia. Stina Syrjänen¹⁵) writes: “The probable goal of the papilloma virus infection is the basal cells of squamous cell tissue. HPV exploits the receptors on the surface of the target cell to infect the cell. The receptors on HPV are as yet not completely known...”. Two primary alternatives in the hypothesis are whether the origin of stomach signet ring cell cancer can have any viral mechanism of origin, as in genital cancer, or whether a virus has found its means of replication in an already developed signet ring cancer and been infected with an oncogenic genome. However, as the infection travels further and is directed especially to the ovaries to build metastases there, there is a third alternative: that Krukenberg metastases are possibly also directed by specific receptors in the cells of the ovaries to cells that can be used by the virus-vector bearers with a cancer-transformed gene in them in order to replicate themselves. Consequently, in the case of the origin of Krukenberg metastases, it should also be suspected in the virus-vector explanatory mechanism that there is some participation of specific receptors, as in the case of HPV. Such reasoning can also support the well-known but still unclear phenomenon that certain cancer forms give metastases in specific organs. The assumptions made call of course for research. Krukenberg metastases should be a challenge to science.

With the constellation of concepts in the hypothesis, it would appear more credible to seek an explanation for the origin of metastases in remote, non-regional lymph nodes via the virus-vector function. However, metastases in regional lymph nodes would also according to the hypothesis have the same path of origin. It has been reported that, when metastases occur in the lymph nodes, the cancer cells are seen first in the cortical zone of the nodes¹⁾. The explanation offered for this is that the afferent lymph nodes exit peripherally via the capsule and that the incoming cancer cells would lodge there first. I would like to emphasize, however, that this phenomenon does not conflict with my hypothesis: quite the opposite, it can support this theory owing to the fact that the follicles, whose central section consists of cells in the division phase, are also found in the cortical zone of the nodes¹⁶⁾.

It is not surprising that there are cases of breast cancer and an occurrence of metastases in the regional lymph nodes, especially as the distance to the regional lymph nodes is so small, and can be considered as an almost prime example of the migration theory. However, it is not clear what mechanisms exist allow migration to the axillary lymph nodes. Three driving components exist in this mechanism for the migration of cancer cells to the regional lymph nodes in this cancer form: a) the cohesion between the cancer cells in the tumour, b) the pressure in the lymph node, and c) the lymph flow rate. Primarily glycoproteins, but also several other factors, have been discovered to maintain adhesion between cells in all the organs of the body to the extent that no cell can liberate itself during its lifetime. The migration theory claims that cohesion is somewhat weaker. But how much weaker? Research on this topic is ongoing today. In the case of breast cancer, there is extremely low pressure in the lymph capillary in the surrounding healthy tissue. Lymph fluid enters the lymph capillary system *Vis a tergo*, and the flow speed is very low. Thus, no dynamic force exists in lymph flow that allows it to contribute to loosening and taking along cancer cells for migration. If this nevertheless does take place, i.e. cancer cells do follow the lymph flow, then we must accept that the breast cancer cells are completely loose without

reasonably competent adhesion components, which cannot be the case. Thus the involvement of two components of the above named triad – flow rate and pressure – has no decisive function and lacks sufficient dynamic effect in the context, and the third (the necessary action of adhesion) is not involved. There is thus a constellation of physiological facts that complicates the acceptance that, in the case of breast cancer as well, the metastases in the axillae nodes are there simply via the cell migration theory. There further appears a factor that is of interest and that is not in lymphodynamic harmony, namely: a histopathological fact (mentioned above) that, in the building of breast cancer metastases in axillae lymph nodes, the cancer cells lodge first in their cortical zone¹⁾. Why do they lodge there instead of following the easier flow into the large lymphatic labyrinths and sinuses of the glands as would logically be expected? It should be observed that the cancer cells lodge first in the lymph nodes' cortical zone, where the follicles exist, and there are large numbers of cells in an early phase of division. This again supports the reasoning in the hypothesis that there is possibly a genetic pathway for the origin of metastases, also in the case of the regional lymph nodes in breast cancer: that viruses carrying a cancer-transformed gene from the primary tumour exploit replicating themselves in the cells of the follicles in an early phase of division that have a regenerative potential.

Metastases exhibit a certain cyclic phenomenon. In addition, they can occur long after the discovery of the primary tumour, sometimes many years after. The concept of “cancer cells in dormancy” is used. No explanation for these remarkable phenomena has yet been found. Viruses also have life cycles, and it is known that some of them can become dormant in some organs.

The fact that metastases seldom occur in the spleen can be due to characteristics of viruses. It is known that antibodies to antigens are manufactured in the white pulp of the spleen¹⁶⁾. Apparently, the spleen's terrain makes the viruses' existence more difficult.

DISCUSSION/CONCLUSION

There are a great many metastatic phenomena that cannot in any way be explained by cell migration, either by any haemodynamic or physiologic mechanism. Two such phenomena are presented in the article: the lack of the microembolus phenomenon in the clinical picture of lung cancer and Krukenberg metastases in stomach cancer. They were also a basis for the present hypothesis, namely that the origin of metastases would take place on a subcellular level. The teachings of biology, with the strict rule that cells that exist in the arterial blood must be of a certain limited size, is evidence for the first phenomenon that supports the subcellular concept for the origin of metastases. Migration of cancer cells from lung cancer that come into the arterial blood and whose size far exceeds the biological limitations should cause the microembolus phenomenon, which is lacking in the clinical picture of that form of cancer. In the case of the peculiar phenomenon of Krukenberg metastases, which can absolutely not be explained by cell migration or by any physiological or haemodynamic mechanism, the reasoning in the hypothesis is that there would almost be a transfer of subcellular substrate in their origin as well. As such, the hypothesis discusses transfer of a cancer-transformed gene, namely substrate, that differentiates the cancer cell from a normal cell. Consequently, the origin of metastases occurs in a genetic pathway. As regards the transport mechanism, the hypothesis calls upon something that is known in medical practice, the so called virus-vector function, that is, a virus of some type carries out this cancer gene transfer. The capacity of the virus to steal a genome is known in genetics. The specific aspect of the reasoning in the hypothesis is that this cancer-transformed gene is incorporated in stem cells, omnipotent cells and multipotent cells, and cells in an early phase of division, which are transformed into cancer cells and in each special case of gene type

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become identical to that which exists in the primary cancer. Finally, a supporting fact in the reasoning in the hypothesis is that the places in which the above named immature-regenerative cells exist are favourites of metastases: bone marrow, lymph nodes, liver, ovaries etc. Specific receptors in this mechanism, as in HPV, should also be suspected. However, consideration must be given to the occurrence of some metastases via the transplantation mechanism. This is a part of nature – biology.

The subcellular concept for the origin of metastases in this hypothesis should be a challenge to research. As long as there are ambiguities in the origin of metastases, new research steps should be taken to find a way to break the path for the building of metastases and open new paths for treatment. Hopefully in the spirit of these new ideas, there will be a development of safer antiviral agents to be used for early discovery of a malignancy, safer vaccines and vaccination programs, probably primarily against virus forms in a dormant state in the human body.

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