Melanoma Controls the Metastatic Process only in Terms of Metastatic Cell Dissemination – What Is Responsible for Metastatic Cell Proliferation?

Čabrijan, Leo; Lipozenčić, Jasna

Source / Izvornik: **Acta Dermatovenerologica Croatica, 2021, 29, 30 - 34**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:354497

Acta Dermatovenerol Croat 2021;29(1):30-34 CLINICAL ARTICLE

Melanoma Controls the Metastatic Process only in Terms of Metastatic Cell Dissemination – What Is Responsible for Metastatic Cell Proliferation?

Leo Čabrijan[1], Jasna Lipozenčić[2]

[1]Department of Dermatology and Venereology, Clinical Hospital Centre Rijeka, Rijeka, Croatia; [2]Croatian Academy of Medical Sciences, Zagreb, Croatia

Corresponding author:
Leo Čabrijan, MD, PhD
Department of Dermatology and Venereology
Clinical Hospital Centre Rijeka
Krešimirova 42
51000 Rijeka
Croatia
leo.cabrijan@ri.t-com.hr

Received: January 8, 2019
Accepted: March 1, 2020

ABSTRACT The process of melanoma metastasis can be divided into two stages of metastatic cell dissemination and proliferation. The whole process should be observed and distinguished through the variable or prism of time. The fact that melanoma metastases are detected in visceral organs at the stage when they are macroscopically visible does not imply that their onset has occurred much earlier. Additionally, it is quite obvious that the entire process is not driven by melanoma but rather only the initial stage of metastatic cell dissemination, whereas the later stage of metastatic cell proliferation is driven by other factors, firstly by mutated genes in the presence of melanoma or without it. Dissemination of metastatic cells occurs at approximately the same time in all melanomas, at MIS transition to MM, but is not immediately followed by metastatic cell proliferation; instead, some time has to elapse for a particular gene mutation to occur, and this timing varies among melanomas. Following dissemination of metastatic cells to visceral organs, they remain inactive, and in this period the presence of melanoma is not necessary anymore for metastatic cell proliferation, as they are waiting for a signal to start multiplying. This is clearly discernible from the fact that melanoma is today detected and removed frequently and early, but visible metastases then develop in the absence of melanoma, which may also regress spontaneously. Accordingly, MM is no longer necessary for metastasis later on. Finally, let me rephrase the title: melanoma is only responsible for initial dissemination of metastatic cells, whereas subsequent proliferation of metastatic cells is driven by other factors, most probably mutated genes.

KEY WORDS: melanoma, dissemination and proliferation of metastatic cells, time period

INTRODUCTION

The process of melanoma metastasizing has recently been increasingly tackled in literature reports (1-4). New molecules responsible for metastasizing of malignant melanoma (MM) as well as respective antibodies have been discovered on a daily basis and used as biologic therapy to block MM targets (5-7). However, the problem is that not every step or sequence of events in the process of MM metastasis has yet been elucidated.

Our current position is that MM should be surgically removed to prevent it from metastasizing; thus, MM metastasis is addressed as a future event. When

Acta Dermatovenerol Croat
2021;29(1):30-34

MM metastases become visible, they can be detected and verified by computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), or as visible and detectable skin MM metastases that may also be found in visceral organs. The process of MM metastasis has not yet been characterized properly, because we tend to present all those phenomena that we cannot otherwise explain as MM unpredictability. One of the assumptions is that "patients die from MM", which is completely wrong because nobody dies from MM, namely, the true question of MM is the question of the scar. The claim that patients die from MM metastases is only partially correct, because people live with MM metastases and die when metastases proliferate and destroy visceral organs, which is associated with complications, hemorrhage, thrombosis, etc., answering the question what the patients with MM die from. The process of MM metastasizing has two important stages, i.e. initial dissemination of metastatic MM cells and proliferation of metastatic MM cells.

Some other claims regarding the perception of MM and MM metastasizing also are quite disputable. In some clinical discussions, melanoma located between nevi is frequently referred to as "a wolf hiding among the sheep". If we compare the behavior of a wolf which destroys (kills) due to being hungry, what does MM do? MM also destroys (kills) its host, but this is not its end goal, because eventually MM destroys (kills) itself. Thus, both destruction and self-destruction are implied in the case of MM, which is never the case with a wolf. This may not be crucial, but we "condemn" the wrong agent (wolf), thus resulting in an erroneous perception of MM behavior.

HYPOTHESIS

Our hypothesis on the process of MM metastasis should include a variable without which modern life would not be possible, i.e. time. The timeframe of MM metastasis dissemination greatly precedes the timing of their proliferation; there is a period of time between them, since proliferation of MM metastases occurs later, when it is detectable. Transition of melanoma in situ (MIS) into MM is the time when dissemination of MM metastatic cells occurs, i.e. the time when MM "breaches" the dermoepidermal junction, thus enabling hematogenous transfer of MM metastatic cells to visceral organs. Therefore, dissemination is presumed to occur at nearly the same time in all melanomas, whereas proliferation of MM metastatic cells has different individual timing. It is beyond doubt that the main determinant of our individuality are genes. Proliferation of MM metastases is driven by mutated genes, irrespective of the MM metastatic cell proliferation and the presence of MM, whether they are absent in excised MM or if it has regressed spontaneously. However, the process of metastasis proliferation is driven by mutated genes (1-4). MM is responsible in the initial stage of dissemination, i.e. MM cell metastasis; later on, proliferation of MM metastatic cells is led by other factors that are independent of primary MM.

DISCUSSION

There still are many unanswered questions regarding MM, e.g., using the same criterion and "logic" of MM thickness, how to explain that MM Breslow 0.5 mm metastasizes earlier than Breslow 5 mm, or the fact that patients operated on for MM Breslow 10 mm have no visceral metastases and die from other diseases (8). We are inclined to explain it by a "platitude" that "the only fact that is predictable in MM is that it is unpredictable". We are in fact hiding behind this "unpredictability" of MM because we have no real explanation. This could be viewed through the prism of time. The timing of MM metastasis detection is not the same as the time of their onset, however, and we now believe that dissemination and proliferation of MM metastatic cells occur consecutively (Figure 1).

We used to say that MM should be operated on so as to prevent metastasis. The onset of MM metastatic cells refers to some future time, as demonstrated by MM metastases visualized on CT, MRI, or PET/CT. However, what is the exact timing of the process of metastasis? We know and can verify the time of MM metastatic cell proliferation, but can we be sure that it is also the time of their dissemination, i.e. whether their dissemination is immediately followed by proliferation. There is no evidence for this, and it is therefore quite likely that there is a certain period between cell dissemination and cell proliferation (Δ t in Figure 1, the time that is variable in individual melanomas). Accordingly, the very process of MM metastasis has

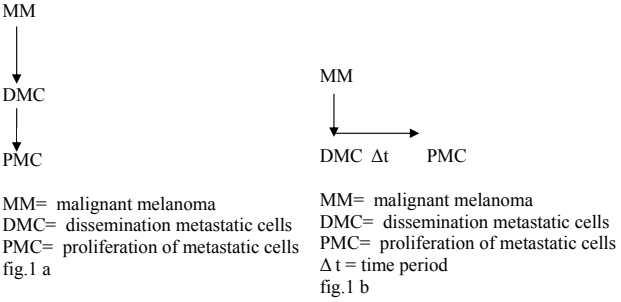

Figure1. Malignant melanoma metastasis in a time period.

Acta Dermatovenerol Croat
2021;29(1):30-34

not been properly defined in relation to the time of onset, in that timing of MM metastatic cell proliferation is well known but timing of their dissemination is not, as it occurs much earlier. Additionally, MM is only responsible for dissemination of MM metastatic cells into visceral organs but not for their proliferation, which quite commonly occurs years after MM excision and re-excision or spontaneous regression. All this provides indirect evidence that MM cannot control the process of MM metastatic cell proliferation to visceral organs because MM is mostly detected and removed early, so it does not physically exist anymore during the process of MM metastasis. Furthermore, currently available methods of dermoscopy and reflectance confocal microscopy enable patient monitoring after MM surgery, thus ruling out the possible development of another primary melanoma. According to the previous concept of the process of metastasis, MM metastasis dissemination is immediately followed by their proliferation and possible detection. The question is: what is responsible for the MM metastatic process control and course, if not MM itself? This process is individualized, implying that metastasizing of MM cells is driven by the mutated genes *via* encoding and signaling disseminated metastatic cells that may have been present silently in visceral organs for years, behaving like normal cells while waiting for the signal to start multiplying. This period varies individually, taking months or even years until triggering the process of proliferation of MM metastatic cells (Figure 2).

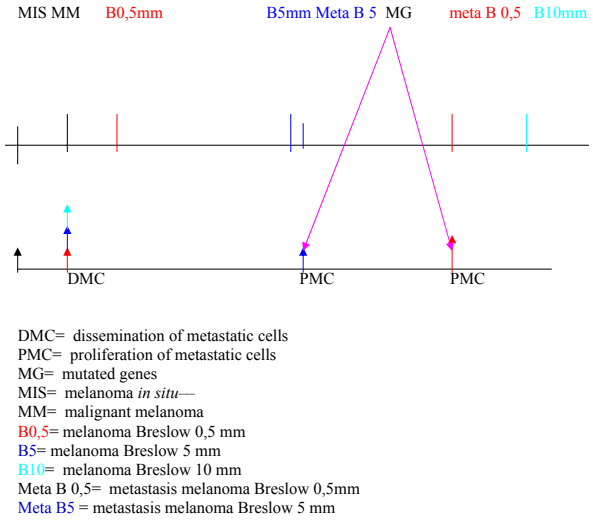

Figure 2. MM metastasis according to depth of MM and mutated genes in time period

Figure 2. MM metastasis according to depth of MM and mutated genes in time period

Involvement of mutated genes in the process of MM metastasis has been confirmed in a number of literature reports (1-4). Epigenetic alterations are also crucial in the process of MM cell metastasis (4).

The relationship of MM and the blood stream is also important. Endothelial cells and their ligands are also implicated in melanoma progression, as is MM metastasis as signal transducer activators of STAT3 transcription, which can trigger cellular adhesion molecules E-selectin and P-selectin in experimental animals (5). The CXCR4 chemokine receptor may also play a role in the expression of MM metastases in the liver (6). The SOX4 transcription factor has been experimentally demonstrated to be involved in MM cell migration (7). BRAF mutations are known to be associated with sentinel lymph nodes as well as with pulmonary and liver MM metastases (9). Cytoskeleton or related proteins may also undergo mutation and have a role in carcinoma mutagenesis (10). Circulating tumor cells are important for melanoma cell dissemination and can be identified in the circulation (11). Some promising treatment modalities currently investigated include cancer-killing viruses (12) and oncolytic viruses (13), the herpes simplex virus (13), and tanapox virus (14). According to some studies, gene mutation or gene signalization is important in differentiating melanoma and benign lesions (15); however, in these studies there were numerous melanomas displaying no gene mutation, suggesting that some time must elapse until mutation occurs, i.e. that it is an individualized process. Owing to the multitude of novel concepts, there are new and useful tools emerging daily (dermoscopy, reflectance confocal microscopy, etc.), which enable melanoma detection at an early stage, followed by melanoma excision and re-excision. Although the melanoma no longer exists (after being diagnosed and removed), the process of metastasis progresses to proliferation of metastatic cells, thus demonstrating indirectly that the mere presence of melanoma is not necessary in the later stage of melanoma cell metastasis. In many cases, in spite of MM being diagnosed and then excised and re-excised, the process of metastasis proceeds and results in visceral metastases. Visceral metastases may also develop after complete melanoma regression and melanoma cells being replaced by fibrosis; visceral metastases may occasionally be found first clinically, while the primary seat of melanoma does not suggest complete regression of primary melanoma. In these cases, dissemination of MM metastatic cells has taken place previously in all melanomas at approximately the same time, i.e. at the time of MIS transition to MM, while the timing of dissemination varies individually from case to case.

Acta Dermatovenerol Croat
2021;29(1):30-34

Therefore, we believe that there must be some other factors driving the process of metastatic cell proliferation after dissemination of MM metastatic cells (either because melanoma does not exist anymore or even in its presence) in visceral organs, where metastases are visible and diagnostically verifiable. This process of proliferation is probably driven by mutated genes because it occurs individually in each melanoma within a time frame needed for gene mutation to occur (Figure 2). The time to detect visceral metastases on MRI, CT, etc., is the time that corresponds to proliferation of the MM metastatic cells, which have previously existed in visceral organs for some time, where they were inactive and behaved like other normal cells.

We ignore the fact that dissemination of MM metastatic cells occurs long before their proliferation, with a certain period elapsed between these two processes (Δ t in Figure 1). This implies that the cells, having disseminated into visceral organs, exist there in an inactive form for some time, in the stage preceding the process of cell proliferation, when they are detectable and undergo the stage of fast and intensive multiplication, which is later difficult to stop. The common histopathologic finding of clear dysplastic nevus cells, which are melan-A positive immunohistochemically, represents indirect evidence indicating that melanoma cells can look like normal or atypical melanocytes, and MM metastatic cells could thus be hiding in visceral organs and appear like normal cells.

There are only a few literature reports voicing suspicion about the current concept of melanoma metastasis and promoting this idea of earlier metastasis of malignant cells such as breast cancer cells, where the same of very similar process occurs as in melanoma (16). Thus, we presume that metastatic cell dissemination takes place much earlier than their proliferation, in the period of transition of MIS to MM. When melanoma cells cross the dermo-epidermal junction and reach the bloodstream, they are transferred to visceral organs where they stay inactive for some time before receiving the signal for multiplication.

Accordingly, future studies of therapeutic modalities for melanoma metastases should be focused on identification of disseminated melanoma cells in their inactive form and trying to block or destroy them, thus preventing their subsequent proliferation and multiplication and saving the patient's life.

The entire process of melanoma metastasizing should be placed within a strictly defined time frame and treatment of patients with melanoma should start much earlier than is done today, which would greatly increase the chance for patient cure. These statements should be more precise, and the whole process should be defined in the context of an exact time sequence, clearly distinguishing previous and future events and identifying the entities driving them. It should be once again noted that melanoma is driving the process at the initial stage of MM metastatic cell dissemination. Metastatic cells stay in visceral organs in an inactive form for some time, and their activation, i.e. the signal for multiplication or proliferation, is triggered from another, independent source, most probably mutated genes. This part of the process of metastasis is individualized; as our individuality is determined by genes, they must play a major role in the subsequent stage (proliferation and multiplication) of MM metastatic cells.

This indicates that melanoma thickness according to Breslow(B) is not substantial for proliferation of metastatic cells, because the process of metastatic cell dissemination has already been completed, probably following the same timing in all melanomas (Figure 2). This explains why melanoma B 0.5 mm can metastasize earlier than melanoma B 5 mm. This also explains why melanoma B 10 mm never "metastasizes". In fact, all melanomas are responsible for metastatic cell dissemination; melanoma B 10 mm (8) is only responsible for dissemination of metastatic cells, which may never undergo proliferation before the patient dies from some other disease or a natural cause (Figure 2). This scenario implies that MM metastatic cells stay inactive as long as it takes for a particular gene mutation to occur, which then drives the process of metastatic cell proliferation, i.e. triggers their proliferation in the presence or absence of melanoma. Of course, the longer the melanoma has been present, the longer is the time needed for gene mutation to occur; metastatic cells will more frequently proliferate in "thicker" melanoma, although this does not depend directly on the process of metastatic cell multiplication.

The answer to the question why melanoma B 0.5 mm metastasizes earlier than melanoma B 5 mm, or why melanoma B 10 mm does not metastasize at all has a logical explanation, but it does not correspond to the theory on melanoma "unpredictability".

Of course, early detection of melanoma, in the MIS stage or earlier, is of utmost importance to avoid metastasis, and efforts should be continuously invested to develop tools for earliest possible accurate diagnosis of melanoma and all lesions that may precede or are suspect of melanoma.

Finally, it should be reiterated that all melanomas begin the process of metastasis in the form of

metastatic cell dissemination at the same time, i.e. at MIS transition to MM, and this stage of the process is driven by melanoma; then, metastatic cells stay inactive for some time required for gene mutation, which then leads the process of metastatic cell proliferation irrespective of the presence of melanoma. This process of metastatic cell proliferation may fail to occur due to the absence of gene mutation or some "error" in the process of proliferation due to which it does not occur or is suddenly interrupted. Once initiated, the process of metastatic cell proliferation is uncontainable; therefore, efforts should be focused on early detection of metastatic cells while they stay inactive in visceral organs. Of course, this may seem like looking for a needle in a haystack, but that does not mean that there are no needles in the haystack.

References:

1. Kunz M, Hölzel M. The impact of melanoma genetics on treatment response and resistance in clinical and experimental studies. Cancer Metastasis Rev. 2017;53-75.
2. Katona F, Murnyák B, Marko-Varga G, Hortobágyi T. Molecular background of the melanoma and the brain metastasis. Orv Hetil. 2017;1083-1091.
3. Hegedüs L, Padányi R, Molnár J, Pászty K, Varga K, Kenessey I, *et al.* Histone deacetylase inhibitor treatment increases the expression of the plasma membrane Ca²⁺ pump PMCA4b and inhibits the migration of melanoma cells independent of ERK. Front Oncol. 2017;7:95.
4. Chatterjee A, Stockwell PA, Ahn A, Rodger EJ, Leichter AL, Eccles MR. Genome-wide methylation sequencing of paired primary and metastatic cell lines identifies common DNA methylation changes and a role for EBF3 as a candidate epigenetic driver of melanoma metastasis. Oncotarget. 2017;8:6085-101.
5. Kim KJ, Kwon SH, Yun JH, Jeong HS, Kim HR, Lee EH, *et al.* STAT3 activation in endothelial cells is important for tumor metastasis via increased cell adhesion molecule expression. Oncogene. 2017;36:5445-59.
6. Mendt M, Cardier JE. Activation of the CXCR4 chemokine receptor enhances biological functions associated with B16 melanoma liver metastasis. Melanoma Res. 2017;300-8.
7. Cheng Q, Wu J, Zhang Y, Liu X, Xu N, Zuo F, *et al.* SOX4 promotes melanoma cell migration and invasion through the activation of the NF-κB signaling pathway. Int J Mol Med. 2017;447-453.
8. Gishen K, Maria DJP, Khanlari M, Cho-Vega HJ, Thaller S, Moller MG. Giant malignant melanomas and their clinical implications: review of literature and case report. Clin Surg. 2016;1:1096.
9. Adler NR, Wolfe R, Kelly JW, Haydon A, McArthur GA, McLean CA, *et al.* Tumour mutation status and sites of metastasis in patients with cutaneous melanoma. Br J Cancer. 2017;117:1026-35.
10. Segarra DT, Yavorski JM, Blanck G.Protected cytoskeletal-related proteins: towards a resolution of contradictions regarding the role of the cytoskeleton in cancer. Biomed Rep. 2017;163-8.
11. De Souza LM, Robertson BM, Robertson GP. Future of circulating tumor cells in the melanoma clinical and research laboratory settings. Cancer Lett. 2017;392:60-70.
12. Zhang T, Suryawanshi YR, Woyczeszyk HM, Essani K. Targeting melanoma with cancer-killing viruses. Open Virol J. 2017;11:28-47.
13. Du W, Seah I, Bougazzoul O, Choi G, Meeth K, Bosenberg MW, *et al.* Stem cell-released oncolytic herpes simplex virus has therapeutic efficacy in brain metastatic melanomas. Proc Natl Acad Sci U S A. 2017;114:E6157-E6165.
14. Zhang T, Suryawanshi YR, Szymczyna BR, Essani K. Neutralization of matrix metalloproteinase-9 potentially enhances oncolytic efficacy of tanapox virus for melanoma therapy. Med Oncol. 2017;34:129.
15. Ko JS, Matharoo-Ball B, Billings SD, Thomson BJ, Tang JY, Sarin KY, *et al.* Diagnostic distinction of malignant melanoma and benign nevi by a gene expression signature and correlation to clinical outcomes. Cancer Epidemiol Biomarkers Prev. 2017;26:1107-13.
16. Harper KL, Sosa MS, Entenberg D, Hosseini H, Cheung JF, Nobre R, *et al.* Mechanism of early dissemination and metastasis in Her2⁺mammary cancer. Nature. 2016;540:588-592.