Cancer and Metastasis Reviews (2023) 42:1057–1059
https://doi.org/10.1007/s10555-023-10130-1

EDITORIAL

Metastasis suppressors: a paradigm shift in cancer biology

Danny R. Welch[1,2,3,4]

Published online: 3 August 2023

It was when I visited Lance Liotta's lab at the NCI in the mid-1980s that I met his postdoc, Patricia Steeg. Pat had hypothesized the existence of a class of genes that block metastasis. As readers of *Cancer & Metastasis Reviews* already know, she discovered Nm23 (non-metastatic clone 23; now designated NME1) [1]. By chance, I happened to be in the lab on the day that she harvested the colonies from the subtractive hybridization experiment that discovered the first metastasis suppressor. One of the colonies identified was branded Nm23. So, one might say I watched the metastasis suppressor gene (MsG) field grow since its very genesis.

Her work was heralded as a breakthrough by many, but skeptics were vocal. Still, the doubters could not ignore her data. By transfecting Nm23 into metastatic melanoma cells, metastasis was reduced by half when injected into syngeneic hosts. She and many of her collaborators have subsequently made inroads into understanding the mechanism(s) of action and demonstrate that Nm23 has some prognostic value in some, but not all, human cancers.

Unfortunately, excitement waned because siblings of Nm23 were not found in the decade following. Pat had been at the cutting edge of molecular biology to identify the first MsG. It was not until the mid-1990s that two additional MsG were identified—KISS1 [2] and KAI1 [3]. At that point, a family of genes was born. In subsequent years, the number of metastasis suppressors grew to more than 30. This issue updates the state-of-the-art regarding this exciting family of molecules. This editorial seeks to provide some perspective on metastasis suppressors relative to the field of cancer biology and, hopefully, identify areas for future research. It also highlights how knowing the existence of MsG has shifted thinking about how cancer metastasis occurs.

When Hanahan and Weinberg first published the *Hallmarks of Cancer* [4], they provided a framework that has proven helpful in explaining what cancer is. Their hallmarks, however, bundled invasion and metastasis, which caused some to be confused. Some interpreted that singular hallmark as meaning that all cancers metastasize. Not true! While local invasion is certainly the hallmark that distinguishes malignant neoplasms from benign tumors, not all invasive cancers metastasize [5]. The discovery of MsG provided the first incontrovertible genetic proof that cancer and metastasis are distinct phenotypes.

By their very definition, metastasis suppressors reduce metastasis *without blocking growth of a primary tumor* [emphasis added]. Please note: occasionally metastasis suppressors exhibit effects on the primary tumor; however, they still permit growth of cancer cells at the orthotopic site. So, even the word *block* is used in order to add precision to the definition. Disappointingly, literally hundreds of publications invoke the term "metastasis suppressor" without testing orthotopic tumor growth. The ~30 molecules referred to above are functionally characterized. A big hurdle in the field of metastasis genetics is the misuse of terminology, something that must be guarded against assiduously.

While this issue focuses on genes (and gene products) that inhibit metastasis, it is important to emphasize that the process of metastasis requires coordinated expression of multiple genes. Some genes promote metastasis, while others suppress dissemination or colonization. Since secondary tumor formation requires completion of a sequential series of steps, blockade of any one step prevents subsequent steps. As a result, metastasis suppression is technically easier to study. To illustrate, assume six genes (designated A-B-C-D-E–F) are required to metastasize with each gene being key for a single step in the metastatic cascade. If a cell is defective for any one of those genes (e.g., A-b-C-D-E–F), then that cell would be non-metastatic because it could not complete every step of the

✉ Danny R. Welch
dwelch@kumc.edu

1 Departments of Cancer Biology, The University of Kansas, Medical Center, Kansas City, KS 66160, USA

2 Pathology & Laboratory Medicine, The University of Kansas, Medical Center, Kansas City, KS 66160, USA

3 Internal Medicine – Hematology/Oncology, The University of Kansas, Medical Center, Kansas City, KS 66160, USA

4 The University of Kansas Cancer Center, The University of Kansas, Medical Center, Kansas City, KS 66160, USA

process (even though it is fully capable of completing some of them). Restoration of that defective gene in that particular cell would render the cell metastatic. However, if a cell had two (or more) non-functional metastasis promoters (e.g., A-B-c-D-e–F), it would likewise be non-metastatic. But restoration of metastatic potential would require both defective genes to be repaired/replaced (e.g., A-B-**C**-D-**E**–F since A-B-**c**-D-**E**–F or A-B-**C**-D-**e**–F would still be non-metastatic). As a result, experiments to test for metastasis promoting genes would require knowledge of all defects in order not to experience false-negative studies.

MsG do not always encode proteins, something assumed in the early days. In the 1980s and 1990s, all genes were assumed to encode proteins. However, "Junk DNA" has subsequently proven that one man's junk is another's treasure. Several non-protein coding RNA have been added to the metastasis suppressor repertoire [6, 7]. Expanding evidence demonstrates that some of these ncRNA can be transferred between cells or alter signaling pathways critical for regulating metastasis. Some metastasis suppressors work coordinately, while others appear to function independently [8–10].

Some metastasis suppressors have very distinct mechanisms of action. For example, CD44 and E-cadherin are membrane associated and differentially regulate cell–cell or cell–matrix interactions; MKK4, RKIP, RhoGDI2, and DRG1 are involved in signaling cascades, and BRMS1 functions as a component of histone deacetylase complexes. However, the mechanisms of action for other metastasis suppressors (e.g., KISS1, Nm23) remain a bit more enigmatic. In the case of KISS1, it is paradoxical that there is metastasis suppression in cancer cells lacking the KISS1 receptor [11]. In the case of Nm23, a substantial step forward in understanding mechanism of action was the discovery of the role of Nm23 in dynamin-mediated membrane remodeling during endocytosis and mitochondrial dynamics [12]. But, for both of the latter two molecules, other functions make ascribing a single mechanism of action somewhat challenging. Insights into the mechanisms of action of each suppressor are provided in the articles in the special issue. However, how the individual suppressors work independently as well as coordinately remains a key priority for future study.

Strikingly, not all metastasis suppressors function in every tumor type. Some suppressors appear to work more ubiquitously. Why is that? While there are certainly diverse ways for cancer cells to spread and colonize different tissues, it is unclear why the overlap is not greater.

There are several other questions related to metastasis suppressor function that remain unanswered. Are there convergent signaling nodes in the pathways controlling metastasis promotion or suppression? If so, could the latter become targets for treatment, and would they be effective against all histotypes or only select cancer types? Why are there data that metastasis suppressors in some cancer types actually promote malignant behavior? Or are positively correlated with tumor progression? Do metastasis suppressors work for all sites of metastatic colonization? Or do some metastasis suppressors only inhibit metastasis in an organ-selective manner? If the latter exist, could they be an explanation for the organotropism described by Stephen Paget [13]? What is the physiological function of metastasis suppressors? Do those functions explain how the metastasis suppressors work? In the case of KISS1, for example, the answer is no. KISS1 is a neurotransmitter that mediates signaling in the hypothalamic-pituitary–gonadal axis to control puberty and, in some cases, pregnancy [14]. How those functions are involved in metastasis is not self-apparent. Perhaps, recent data linking neuronal infiltration into tumors [15, 16] may provide an answer.

I believe that the answer to these questions will be found in the requirement of coordinated gene expression in complex phenotypes, i.e., different cassettes of genes are required for each cell type to metastasize and for metastases to different organs. While this makes logical sense, supporting data are limited. Metastasis is a complex phenotype and systems biology approaches will be required. While discovery of MsG was transformational to the field, it emphasizes how the one gene-one phenotype paradigm has been replaced. Their discovery also changed the paradigm of how cancer biologists think about metastasis.

We owe a great deal of credit to Pat Steeg who took on the challenge to discover metastasis-regulatory genes in the first place. Remember, in the late 1980s, the now well-established notion of tumor suppressor genes was not even accepted. The existence of genes regulating metastasis was near heretical at the time. Yet, she persisted as did a growing number of investigators who established a solid foundation from which to build future studies. Of course, there are many new questions to answer—some of which are mentioned here. Like any biological system or clinical observation, the number of experimental variables makes progress slower than desired. However, we are at an exciting time in metastasis research, as metastasis suppressors are providing insights that are helping focus attention on aspects of metastasis that will hopefully help patients soon.

References

1. Steeg, P. S., Bevilacqua, G., Kopper, L., et al. (1988). Evidence for a novel gene associated with low tumor metastatic potential. *Journal of the National Cancer Institute, 80*, 200–204. https://doi.org/10.1093/jnci/80.3.200
2. Lee, J. H., Miele, M. E., Hicks, D. J., et al. (1996). KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. *Journal of the National Cancer Institute, 88*, 1731–1737. https://doi.org/10.1093/jnci/88.23.1731

3. Dong, J. T., Lamb, P. W., Rinker-Schaeffer, C. W., et al. (1995). KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. *Science, 268*, 884–886. https://doi.org/10.1126/science.7754374
4. Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell, 100*, 57–70. https://doi.org/10.1016/s0092-8674(00)81683-9
5. Welch, D. R., & Hurst, D. R. (2019). Defining the hallmarks of metastasis. *Cancer Research, 79*, 3011–3027. https://doi.org/10.1158/0008-5472.CAN-19-0458
6. Hurst, D. R., Edmonds, M. D., & Welch, D. R. (2009). Metastamir: The field of metastasis-regulatory microRNA is spreading. *Cancer Research, 69*, 7495–7498. https://doi.org/10.1158/0008-5472.CAN-09-2111
7. Edmonds, M. D., Hurst, D. R., Vaidya, K. S., et al. (2009). Breast Cancer Metastasis Suppressor 1 (BRMS1) coordinately regulates metastasis-associated microRNA expression. *IJC, 125*, 1778–1785.
8. Beadnell, T. C., Scheid, A. D., Vivian, C. J., et al. (2018). Roles of the mitochondrial genetics in cancer metastasis: Not to be ignored any longer. *Cancer and Metastasis Reviews, 37*, 615–632. https://doi.org/10.1007/s10555-018-9772-7
9. Bohl, C. R., Harihar, S., Denning, W. L., et al. (2014). Metastasis suppressors in breast cancers: Mechanistic insights and clinical potential. *Journal of Molecular Medicine (Berlin, Germany), 92*, 13–30. https://doi.org/10.1007/s00109-013-1109-y
10. Cook, L. M., Hurst, D. R., & Welch, D. R. (2011). Metastasis suppressors and the tumor microenvironment. *Seminars in Cancer Biology, 21*, 113–122. https://doi.org/10.1016/j.semcancer.2010.12.005
11. Nash, K. T., Phadke, P. A., Navenot, J.-M., et al. (2007). KISS1 metastasis suppressor secretion, multiple organ metastasis suppression, and maintenance of tumor dormancy. *JNCI, 99*, 309–321.
12. Boissan, M., Montagnac, G., Shen, Q., et al. (2014). Membrane trafficking. Nucleoside diphosphate kinases fuel dynamin superfamily proteins with GTP for membrane remodeling. *Science, 344*, 1510–1515. https://doi.org/10.1126/science.1253768
13. Paget, S. (1889). The distribution of secondary growths in cancer of the breast. *Lancet, 1*, 571–573.
14. Harihar, S., & Welch, D. R. (2023). KISS1 metastasis suppressor in tumor dormancy: A potential therapeutic target for metastatic cancers? *Cancer and Metastasis Reviews, 42*, 183–196. https://doi.org/10.1007/s10555-023-10090-6
15. Barr, J. L., Kruse, A., Restaino, A. C., et al. (2021). Intra-tumoral nerve-tracing in a novel syngeneic model of high-grade serous ovarian carcinoma. *Cells, 10*(12):3491. https://www.ncbi.nlm.nih.gov/pubmed/34944001
16. Madeo, M., Colbert, P. L., Vermeer, D. W., et al. (2018). Cancer exosomes induce tumor innervation. *Nature Communications, 9*, 4284. https://doi.org/10.1038/s41467-018-06640-0