Letter to the Editor

Is metastasis predetermined?

One depiction of the multi-step invasion-metastasis cascade indicates that this process can be broken down into two major steps: the first subsumes all the steps that are required in order for cancer cells to move physically from the heart of the primary tumor to the parenchyma of distant organs, resulting in micrometastatic deposits. The second involves the growth of micrometastases into macroscopic metastases—the process termed colonization. This second step requires the adaptation of micrometastatic cells to the microenvironment of the tissue in which they have landed, which is invariably quite different than the microenvironment of the tissue and primary tumor from which they originated.

This depiction bears on the interpretation of a recently published report in this journal by Suzuki and Tarin (2007), who describe microarray analyses revealing that the gene expression patterns of primary breast tumors differ from those of their respective lymph node metastases, and that a set of genes exists that is characteristically changed in all of these metastases when compared with their primary tumors. This evidence was described as rebutting the proposals of others, including the present author (Bernards and Weinberg, 2002), who argued that metastatic outcome is partly governed by events occurring early in the development of a tumor, rather than being dictated exclusively by events that occur many years or decades later at the culmination of tumor progression.

In fact, the recent observations of Suzuki and Tarin do not and could not critically test the earlier proposal that metastatic predisposition is determined by events occurring early in tumor development. This raises the question of how the recent evidence by these authors “rebuts” the notion of early determination.

As was actually proposed in 2002, the early events do not per se create invasive or metastatic phenotypes or, indeed, necessarily have any immediate effects on cell-biological phenotypes related to invasion and metastasis; instead, these early events simply set the stage for the subsequent development of these malignant phenotypes many years later. Suzuki and Tarin write that the earlier speculation proposed that “early conversion is the rule” and that the “metastatic proficiency is preprogrammed from the beginning”. Such statements are difficult for the present author to defend, since they were not made in the first place.

If anything, research in this author’s laboratory in the ensuing 5 years has bolstered and extended the proposal of 2002 that events and factors operating early in the process of multi-step tumor progression are critical determinants of the eventual development, much later, of invasion and metastatic traits. This more recent research has revealed a second factor that operates early as an important determinant of later metastasis: the differentiation program of a tumor’s normal cell-of-origin.

Thus, when two different subtypes of normal human mammary epithelial cells are transformed in parallel through introduction of an identical set of oncogenes, the resulting transformants yield primary tumors of strongly differing metastatic powers (Ince et al., in press). An even more dramatic and extreme difference was found when comparing the metastatic tendency of transformed human epithelial cells with transformed human melanocytes; once again, both types of cells were transformed through introduction of the identical set of genetic elements. The transformed melanocytes were vastly more metastatic than the transformed epithelial cells although the two were equally competent to form primary tumors of comparable size (Gupta et al., 2005). In both cases, the differentiation program of the normal cells-of-origin was clearly a key determinant of eventually developed metastatic powers.

Taken together with the earlier speculation, this now makes it possible that two distinct types of early factors can strongly influence the eventual development of metastatic behavior: the differentiation program of normal cells-of-origin that exist prior to the tumor-initiating event and the subsequent early events in tumor progression, including initially acquired mutated alleles as well as promoter methylation events that shut down gene expression.

Because Suzuki and Tarin examined a set of 10 human breast cancers, all of which metastasized, they could not possibly have tested the earlier proposal that the primary tumors examined by them shared a common set of genetic/epigenetic
changes that were already present relatively early in tumor progression and that subsequently determined predilection to generate metastases years later. The only way to critically evaluate this notion would be to compare the gene expression patterns of matched groups of primary breast tumors that did metastasize with the patterns of those that did not. (In reality, such a comparison could only be undertaken in matched sets of tumors that contained far more clinical samples than were undertaken by Suzuki and Tarin).

These authors did indeed demonstrate that the lymph node metastases shared a distinct, characteristic set of gene expression changes that were not present in the respective primary tumors. The need of disseminated micrometastatic breast cancer cells to adapt to a foreign microenvironment – the draining lymph nodes – clearly creates great selective pressure on these cells, requiring them to develop an appropriate repertoire of adaptive responses that allow their growth and survival in these nodes. Thus, independent of the mechanisms underlying all preceding steps that enabled physical dissemination from the primary tumor, the requirement for such adaptation at a site of metastasis readily explains why metastases share a set of expressed genes that are not similarly expressed in primary tumors. So, it still seems likely to the present author, as it did 5 years ago, that the first phase of the invasion-metastasis cascade – physical dissemination – is strongly influenced by processes operating early in tumor progression, while the second – colonization – requires evolution and selection occurring at the end of this cascade.

REFERENCES

Ince, T., Richardson, A., Bell, G.W., et al. Transformation of different human breast epithelial cell types leads to distinct tumor phenotypes. Cancer Cell, in press.

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