INVITED EDITORIAL

Tumor metastasis, physical sciences and the value of multidisciplinary collaborations

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Metastasis— the spread of cancer from its site of origin to distant organs—is responsible for most cancer deaths [1, 2]. For many tumor types, including breast and prostate cancer, local treatment (surgery, radiation) may be able to eradicate the primary tumor. However, if the tumor has spread beyond the local site, it is much harder to treat with success, and may lead to death due to the physiological damage caused by the tumor growing in distant, vital organs. Thus, improvements in cancer mortality will require better understanding of the metastatic process.

We have come to recognize that metastasis is a complex process, not the product of single gene defects but the result of an interplay between molecular and physical features of cancer cells and the host during cancer progression and the dynamic evolution of these features over time. Much of this understanding has come from multidisciplinary collaborations among researchers with diverse backgrounds in physical, biological and molecular sciences. Recently, our group has reviewed many of the contributions of a physical science perspective to our understanding of the metastatic process [3]. Here I will consider two specific examples where multidisciplinary collaborations have led to improved understanding of aspects of the metastatic process.

Metastasis is an inefficient process, with many cells disseminating from a primary tumor, but few of these going on to form lethal metastases. This has been observed both in experimental mouse models as well as in cancer patients [1, 2, 4–7]. In early work that led to the concept of ‘dynamic heterogeneity’ of the metastatic phenotype, interactions among scientists with backgrounds in cancer biology and computational modeling described how cancer cell lines with a more metastatic phenotype had higher rates of generation of metastatic variants than did more poorly metastatic cell lines, and that these variants were highly unstable and ‘plastic’ [8–13]. Heterogeneity of cancer cells within a tumor are well-recognized confounders to effective treatment, and the fact that properties such as drug resistance, biomarkers and metastatic ability itself can change over time provide considerable clinical challenges. Mathematical modeling of these dynamics holds the promise of shedding light on how cancer cells may change over time and how to approach this challenge of cancer as a ‘moving target’ in the clinic (e.g. [14]).

Another area where physical sciences expertise has been effectively brought to bear on understanding metastasis is in preclinical imaging of tumor dormancy. We previously had provided evidence, from optical in vivo videomicroscopy as well as histology, for large numbers of cancer cells persisting in a dormant state, even from highly aggressive cancer cell lines [15, 16]. Thus, the population properties of cancer cell lines (e.g. ‘highly metastatic’ or ‘poorly metastatic’) are a result of the genomic/epigenetic plasticity of the cell line, coupled with over-all inefficiency of the majority of cells within a population. The presence of dormant cancer cells can lead to failure of cytotoxic chemotherapies that target actively dividing cells (e.g. [17–19]), mirroring the situation often seen in patients, where apparently successful primary treatment and adjuvant chemotherapy can still be followed sometimes years later by cancer recurrence and metastatic disease [2, 20]. These studies were facilitated by the development of novel magnetic resonance imaging (MRI) techniques and hardware (‘Single Cell MRI’) that allow detection of single cancer cells that remain dormant in vivo, detectable due to their retention of iron microparticles loaded into cells prior to their in vivo injection (e.g. [21–24]), reviewed in [25]). Examples of iron-loaded cells in vitro and in vivo, along with in vivo mouse brain MRI images, are shown in figure 1. Development and use of these novel procedures, and their role in clarifying tumor dormancy, depended on interactions among scientists with expertise in cancer biology, as well as in software and hardware development in MRI science.

Overall, appreciation of the metastatic process and how it can be addressed clinically will come from effective collaborations among scientists with diverse and complementary expertise. The journal Convergent Science Physical Oncology is providing a valuable new forum for facilitating these interactions.
References

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