FOREWORD

Charting a course to a distant site

Abstract | The rules governing metastasis remain enigmatic, as molecular pathways exercise the freedom to operate in an unregulated manner resulting in patient morbidity and mortality. As researchers generate incremental titbits of information regarding the evolution of the metastatic process, we can begin to assemble a new arsenal of novel therapeutic strategies.

Historically, cancer biologists have oversimplified the metastatic process by presenting an orderly, step-by-step sequential progression from local invasion to colonization at distant sites. Surprisingly, recent evidence indicates that metastasis might not occur as a late event in the progression of tumour growth and the acquisition of aggressive traits, as discussed by Christoph Klein. The heterogeneous nature of how different tumour types arise and spread to specific organs has prompted awareness of the gaps in our knowledge of the acquisition of metastatic competence. Joan Massagué and colleagues highlight recent advances in elucidating organ-specific infiltration, implicating metastasis gene signatures and the parameters governing the latency potential of disseminating tumour cells. A better understanding of the factors within the tumour microenvironment that promote latency and activation will yield new clues to more effective anti-metastatic therapies.

Indeed, the complex and reciprocal interactions of tumour cells with their microenvironments are coming into focus, supported by substantial new insights into the pre-metastatic niche and metastatic homing mechanisms, as highlighted by Joyce and Pollard. Further characterization of the metastatic niche model is offered by Psaila and Lyden and delineates significant changes that occur in the local parenchyma at distant sites, thus facilitating engraftment. Some tumour masses contain more than 50% non-cancerous cells, including various bone marrow-derived cells and Pollard and Joyce focus on the crucial contribution(s) to malignant progression of these cells, which include macrophages, neutrophils, mast cells, myeloid-derived suppressor cells and mesenchymal stem cells. This body of evidence compels us to rethink the merits of simplistic approaches to studying single tumour cell types and their molecular signatures in the absence of their biological ecosystem(s) — the heterogeneous tumour mass.

There has been a great deal of excitement over the emerging role of microRNAs in metastasis and how this new information may affect the design of new therapies. Calin and colleagues provide a comprehensive summary of the recent evidence supporting the significant involvement of microRNAs as metastasis activators, metastasis suppressors, prognostic markers of metastases and promoters of angiogenesis. Particularly fascinating is the connection drawn between microRNA-driven pathways fundamental for cell stemness in embryonic stem cells and tumour cells with stem cell properties. The notion that microRNAs might affect cancer stem cells and metastasis through regulation of epithelial–mesenchymal transition (EMT) and mesenchymal–epithelial transition (MET) is further promulgated by Polyak and Weinberg in their Review of the plastic tumour cell phenotype. They highlight the molecular pathways underlying activation of EMT and MET in tumours and illuminate the influence of the microenvironment in triggering these transitions during cancer progression. Moreover, they provide compelling evidence that EMT and MET are quintessential regulators of cancer cell plasticity and are important in therapeutic resistance, tumour recurrence and metastatic progression.

The study of the metastatic cascade would not be complete without the current overview of metastasis suppressor proteins contributed by Smith and Theodorescu. Until recently, few metastasis suppressor genes had been characterized; however, the field has benefited from new findings generated by genomic analyses, including a new class of microRNAs that suppress metastasis. Novel therapeutic strategies may be exploited on the basis of these emerging new findings, including the reintroduction of expression of metastasis suppressors or the targeting of molecules regulated by the suppressor gene(s).

Targeting metastasis remains a major challenge. The content of the articles in this issue challenges former paradigms and provides new perspectives on the molecular pathways underlying the multistage process of metastasis, hopefully resulting in novel therapeutic strategies based on substantial biological findings. As each article illuminates particular intricacies of the metastatic cascade, one cannot but feel excited about the promise of exploring new avenues of scientific inquiry in targeting cells with metastatic potential. Are they transformed stem cells? Are they tumour cells with stem cell properties? Is the microenvironment the major culprit? As the research community develops additional strategic approaches to the study of metastasis, our ability to predict, target and ultimately pre-empt this process will come into better focus.

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