METASTASIS

New paradigms to explain metastasis

The primary cause of cancer mortality is distant metastasis. Patients with distant metastases are generally not considered curable and are given systemic treatment with hormonal therapy, targeted therapy or chemotherapy. However, metastasis does not always signify a dismal prognosis; for instance, surgical resection of liver metastases in patients with colorectal cancer can result in cure. This observation led Samuel Hellman and Ralph Weichselbaum in the mid-1990s to postulate the existence of an intermediate state of metastasis—limited in number and site—termed oligometastasis.

In this special focus on metastasis spanning two issues, Hellman and Weichselbaum examine the clinical and laboratory data indicating that oligometastasis is a distinct entity that is more frequently being identified. Opportunities for earlier detection of metastases with advanced imaging and diagnostic techniques could identify patients with limited metastases at a stage when treatment with curative intent is possible.

In terms of paradigm-shifting ideas, perhaps the most important recent concept was proposed by Larry Norton and Joan Massagué when, in 2006, they introduced self-seeding to explain the enigmas associated with cancer metastasis not clarified by existing models. In this issue, they (with Elizabeth Comen) expand the self-seeding model and correlate it with clinical observations from patients with breast cancer. They highlight the limitations of Halsted's model of metastatic spread; he proposed that tumor cells originating in the breast pass through the lymphatic system into the circulation, and that surgical removal of whole breast surrounding the tumor prevents metastatic spread—the success of radical mastectomies seemed to confirm this theory. But, this model does not account for the development of distant metastasis in patients without axillary lymph-node involvement. Bernard Fisher and colleagues subsequently suggested the need for systemic therapy owing to alternative processes besides lymphatic spread. However, both models are inadequate in terms of reconciling observations in the clinic—namely, why local control is needed if surgical resection with clear margins has eradicated the tumor, and why different outcomes are observed between preneoplasia and cancer despite their gross morphologic similarities.

A small fraction of cancer cells, so-called circulating tumor cells (CTCs), acquire the properties needed to invade and seed to a distant organ and alter the microenvironment. The self-seeding model challenges the traditional tenet that CTCs leave the primary tumor and then seed to distant organs in a unidirectional process. CTCs can also seed and then colonize the tumor they originated from. Self-seeding is therefore a multidirectional process whereby CTCs can seed to distant organs as well as self-seed the primary tumor. Minor differences in self-seeding capacity might explain the varied clinical outcomes between preneoplasia and cancer. If the self-seeding ability of some breast tumors was high, this might increase their stromal component, explaining why mammographic breast density is a poor prognostic feature. Importantly, while the ability of a tumor to seed correlates to some extent with its ability to colonize, these two processes are not identical. Some tumors might be very efficient self-seeders while others seed mainly to distant sites, explaining why some tumors remain stable or dormant while others are very aggressive.

The therapeutic implications of the self-seeding model are significant. If CTCs are attracted to the primary breast tumor, subsequent radiotherapy may alter the tumor microenvironment preventing CTCs from thriving at the site owing to the altered stroma. Self-seeding could explain why radiation therapy given after adjuvant chemotherapy can be more effective than when given before adjuvant treatment. Comen *et al*. suggest that screening for compounds that have anti-seeding or anti-colonizing properties would increase the armamentarium of available drugs to treat metastases, and that drugs that do not affect proliferation might still be useful as antimetastasis agents. Assessing only tumor shrinkage as a trial end point may need to be revised in light of self-seeding.

In another paradigm-challenging article, Lida Mina and George Sledge highlight why the assumption that micrometastases and overt metastases will respond to the same interventions is incorrect. The primary tumor does not behave in the same way as the metastatic cancer, illustrated by agents that have failed to work in the adjuvant setting despite showing success in the metastatic setting. The pathway to regulatory approval for all adjuvant therapies is similar, with safety and efficacy trials performed in patients with overt metastases. Mina and Sledge explain why the current drug approval approach may not be realistic for agents that do not benefit patients with overt metastasis, but might help in the micrometastatic setting. Targeting the right steps in the metastatic cascade will be critical for future clinical success. They comment that clinical trial testing of metastasis inhibitors should also monitor micrometastasis, the duration of therapy (maintenance), and how we define clinical benefit in these settings. We believe these articles and others in this focus provide new insights regarding metastasis.

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Competing interests
The authors declare no competing interests.