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Targeting dormant cancer

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An important challenge for oncologists is to treat overt metastasis, the major source of cancer-related deaths¹. Adjuvant therapy should prevent distant recurrences by targeting residual disseminated tumor cells (DTCs) that give origin to metastasis, as well as existing undetected micrometastasis. Whereas in some cases, such as breast cancer, patients can show delayed metastasis after hormonal therapies (for example, in estrogen receptor–positive tumors) or treatment with trastuzumab, for HER2 (also called ERBB2)-positive tumors², adjuvant therapy is for the most part ineffective in fully blocking metastasis development and improving overall survival.

This may be explained by the fact that the biology of residual DTCs seems to diverge from that of the primary tumors and overt metastasis³. The usually unpredictable timing of metastasis can be due to the ability of DTCs to enter dormancy¹. Dormant DTCs can in turn be refractory to targeted or conventional therapies², further limiting treatment responses. Notably, more than 67% of deaths in patients with breast cancer occur after the 5-year survival mark, showing that residual disease can be dormant for very long periods¹. This further argues that targeting dormant DTCs is crucial. Unfortunately, compared to other areas of cancer, our understanding of the biology of dormant residual DTCs is highly limited. Thus, 'bedside' clinical management of dormant disease will be a reality only after rigorous understanding of its molecular and cellular basis.

There is compelling evidence that the presence of DTCs in the bone marrow of patients with breast or other cancers is a poor prognosis indicator¹. However, although some DTC-positive patients recur 3 years after surgery, others do so up to a decade later¹. Characterization of DTCs from patients may be the shortest path to determine which and when patients might relapse and identify DTC-specific mechanisms to target. A study in esophageal cancer showed that direct genetic analysis of DTCs predicted outcome and therapy selection³. An amplification of the region harboring *HER2* was found in the primary tumors and DTCs; however, the *HER2* amplification was only predictive of poor patient survival when detected in disseminated tumor cells. Notably, esophageal tumor cell lines with *HER2* amplification were sensitive to commonly used therapies designed for breast cancer (for example, trastuzumab)³.

DTCs in the bone marrow of patients are largely nonproliferative² and DTCs—but not circulating tumor cells—can persist in the target organs for long periods (up to a decade)¹, suggesting that DTCs probably enter cellular dormancy through quiescence². Although eradicating dormant DTCs or keeping them dormant could be a new strategy to prevent metastasis², achievement of such a goal in the clinic requires answering at least two important questions. First, can DTCs serve as a biomarker when typified during recurrence

or dormancy? And second, can we identify dormant DTC-specific or microenvironment-dependent mechanisms that could be manipulated to maintain or eradicate dormant disease?

Microenvironmental signals that cause a low-mitogenic and high-stress signaling and trigger quiescence may constitute dormancy mechanisms^{2,4,5}. For instance, blockade of the urokinase receptor (uPAR) inhibits fibronectin-dependent mitogenic signaling by reducing the activation of $\alpha 5\beta 1$ integrin and epidermal growth factor receptor (EGFR)², resulting in extracellular signal-related kinase (ERK) deactivation and subsequent p38 activation, which further antagonizes ERK to induce quiescence^{2,4}. Interestingly, uPAR^{low/-} DTCs in the bone marrow of patients with gastric carcinoma were associated with longer disease-free survival⁴, suggesting that this mechanism could induce DTC dormancy. Along these lines, high-density collagen (fibrotic) microenvironments in the lungs and liver promote exit from dormancy by activating ERK signaling². These data suggest that reciprocal tumor-stroma crosstalk can regulate dormancy.

More recently, bone morphogenic protein 7 (BMP7) in the bone marrow was shown to trigger dormancy of prostate DTCs by activating p38 signaling, upregulating the metastasis suppressor gene *NRDG1* and inducing reversible growth arrest⁵. Also, the lysophosphatidic acid receptor *EDG2* has been identified as a breast cancer metastasis promoter⁶, and its pharmacological inhibition induced dormancy of solitary or micrometastatic lesions through activation of p38 signaling⁶. Recently, the BMP4 inhibitor COCO (also known as DAND5) was found to prevent the onset of solitary-cell dormancy of 4T1 tumor cells by activating a self-renewal program and restricting quiescence⁷. These data suggest that microenvironment- and DTC-specific markers may be needed to identify DTCs and their tissue milieu as pro-dormancy. This also offers markers beyond proliferation regulators (such as Ki-67 and p21^{cip1}) to stage DTCs and host microenvironments as prone to dormancy or recurrence (Fig. 1).

How can this be applied in the clinic to identify patients with dormant disease? Translational studies have focused mostly on using gene expression profiles in primary tumors and dormancy-associated genes to predict metastasis-free survival. For example, both BMP7^{high}- and COCO^{low}-associated signatures predicted delayed metastasis to bone and lung in prostate and breast cancer, respectively^{5,7}. Also, a study of individuals with estrogen receptor-positive primary breast tumors that were enriched in p38-induced and angiogenic dormancy gene signatures showed delayed time to metastasis⁸. Interestingly, several genes included in these dormancy signatures⁸ can limit self renewal (*NR2F1* and *TGFB2* (ref. 9)), predict delayed recurrence in breast and prostate cancer (*NR2F1* and *SHARPI* (also called *BHLHE41*)^{2,10}), induce tumor cell quiescence (*p38* (ref. 11)) and suppress breast cancer metastasis (*SHARPI* (ref. 2)). If tested on DTCs in patients, these new markers could produce a set of clinically testable dormancy markers.

Whereas an analysis of 'dormancy signatures' may inform about the time to metastasis, only molecular and phenotypic characterization of DTCs will allow weighing their prognostic and staging value for dormant disease. But in what clinical setting could DTC isolation and dormancy profiling become useful? Ideally, they should be useful in the adjuvant setting, during asymptomatic stages of the disease or both (Fig. 1). However, this might require yearly follow up for long periods (more than 5 years). This is a difficult task, as patients may be deemed cured or not closely followed. Whereas this strategy may require a change in clinical monitoring and research, a new clinical trial scenario may allow for the determination of whether DTC profiling is informative¹². In phase 2 trials, time to the first metastasis and time to a new metastasis could be potential measures for dormancy¹²; detection of recurrence markers in DTCs in this temporal window may allow correlating DTC phenotype with therapy response (Fig. 1).

Epigenetics drugs (such as 5-azacitidine or histone deacetylase (HDAC) inhibitors) can induce low self-renewal states by regulating similar dormancy pathways^{2,8,11,13}. Thus, these drugs, along with inhibitors or activators of other metastasis-related targets such as lysophosphatidic acid receptor 1 (EDG2, also called LPAR1) antagonists⁶ or BMP7 (ref. 5), could be used as a strategy to reprogram residual disease into dormancy. Targeting dormancy-specific survival mechanisms, such as eukaryotic translation initiation factor 2 α kinase 3 (PERK, also called EIF2AK3), chaperone heat shock 70-kDa protein 5 (GRP78, also called HSPA5) or c-Src^{2,14}, could be used to eradicate DTCs. We envision that therapies that induce or maintain dormancy of DTCs followed by or combined with other drugs that block survival mechanisms may be successful in the treatment of dormant residual disease (Fig. 1). As the dormancy mechanisms become clearer, translational efforts will be key. This will require a close relationship between physicians and researchers to correlate marker detection with patient outcome and the design of new trials. Despite the challenges posed by this approach, the benefits would be so substantial that it only makes sense to push these studies further and make this therapeutic window of opportunity one that can be offered safely to patients.

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Figure 1.

Hypothetical scheme for DTC monitoring to treat dormant residual disease. Patients first have their bone marrow analyzed for DTC content. Those patients negative for DTCs (that is, a good prognosis) are monitored for symptoms and DTC content only. If patients are DTC positive at the time of surgery, after surgery or both, their DTCs would be profiled to determine their proliferative status and whether they are in dormancy (set A (DTC eradication profile) and set B (dormant DTC maintenance profile) markers) or recurrence (recurrence markers) mode. If recurrence markers are found, patients are treated with available conventional or targeted anti-proliferative treatments alone or in combination with a dormancy-inducing therapy, when available. If patients show markers of dormancy maintenance, they could be treated with potential drugs to prolong this state. DTC profiling could reveal whether specific pathways are also activated to attempt a DTC eradication strategy (using set A markers) immediately or shortly after anti-proliferative plus dormancy-inducing or dormancy-maintenance treatment schedules. MRD, minimal residual disease.