Abstract

Systemic minimal residual disease after primary tumor treatment can remain asymptomatic for decades. This is thought to be due to the presence of dormant disseminated tumor cells (DTC) or micrometastases in different organs. DTCs lodged in brain, lungs, livers, and/or bone are a major clinical problem because they are the founders of metastasis, which ultimately kill cancer patients. The problem is further aggravated by our lack of understanding of DTC biology. In consequence, there are almost no rational therapies to prevent dormant DTCs from surviving and expanding. Several cancers, including melanoma as well as breast, prostate, and colorectal carcinomas, undergo dormant periods before metastatic recurrences develop. Here we review our experience in studying the cross-talk between ERK1/2 and p38α/β signaling in models of early cancer progression, dissemination, and DTC dormancy. We also provide some potential translational and clinical applications of these findings and describe how some currently used therapies might be useful to control dormant disease. Finally, we draw caution on the use of p38 inhibitors currently in clinical trials for different diseases as these may accelerate metastasis development.

Background

Origin and fate of disseminated tumor cells

The inherent complexity of metastasis biology has proved difficult to unravel (1). Metastasis treatment with conventional chemotherapy is mostly ineffective because at the time of diagnosis these lesions are already large [i.e., 10^{10–10^{11}} tumor cells (2)] and heterogeneous (3). Moreover, the biological and genetic divergence between primary tumors and metastasis (4) further complicates treatment. Thus, a constant catch-up game is played against the robust genetic and epigenetic resourcefulness of metastases, where treatments are given sequentially until lesions become completely refractory.

Clinical tumor dormancy is the asymptomatic period between the time of primary tumor detection and treatment and its local or distant metastatic relapse. However, this time does not necessarily imply the presence of dormant disease and may be explained simply by tumor doubling times (1). This argues for the need for better markers to define truly dormant residual disease. We distinguish tumor cell dormancy (i.e., of disseminated disease) from tumor latency, which is mostly used to define the time from the carcinogenic event to the clinical diagnosis of the primary tumor (5). Dormancy of a micrometastatic mass in which the proliferating population is balanced by a dying one may be due to failure to induce an angiogenic switch and/or to immune cell–mediated mechanisms (5). In contrast, cellular tumor dormancy, which most likely explains solitary disseminated tumor cell (DTC) dormancy, can be explained by quiescence programs (a reversible growth arrest state) in which DTCs remain nonproductive until lesions become completely refractory.

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By the time of diagnosis, a large number of patients already have disseminated disease lodged in target organs in the form of solitary DTCs (1). These DTCs can be found in secondary organs such as the liver and sentinel lymph nodes (LN), as well as in BM (7). DTCs are commonly studied in BM aspirates because of the easy access to this compartment. However, the bone is not the only place where they reside. In fact, DTCs most likely occur in multiple organs simultaneously, and sampling of the BM provides a snapshot of what their behavior and characteristics might be systemically. It is widely accepted that these single DTCs are the seeds for later tumor metastases.
been proposed that circulating tumor cells (CTC; i.e., isolated from peripheral blood) become DTCs when they lodge in a secondary tissue (e.g., lung or liver), but for the most part, these are short-lived tumor cells in the circulation that primarily provide a snapshot of recently intravasated tumor cells (8) and, therefore, of primary or secondary tumor masses that shed cells. However, once the tumor is surgically removed, CTC numbers commonly decrease, whereas DTCs can be detected for long periods (1). Thus, these cells carry information on both their origin and how the target organ affects them. Unfortunately, because DTC biology is poorly understood, we are currently unable to eradicate these tumor cells and prevent metastasis (5). Further, because nonproliferative DTCs (see below) may evade conventional therapies (5), a completely different approach may be needed to eradicate these cells.

Dormancy of DTCs may be explained by 2 complementary hypotheses, which propose that during cancer progression, dissemination represents either early or late events. The first hypothesis is supported by the frequent detection of BM DTCs in patients with noninvasive lesions (e.g., atypical ductal hyperplasia or ductal carcinoma in situ; ref. 4). In MMTV-Neu (Neu) mice, in which p38 antagonizes tumor development (9), premalignant lesions contained microinvasive cells, and dissemination to lungs and BM occurred early (10). In uveal melanoma, a cancer with a 50% incidence of late liver recurrence (>10 years) in humans (11), analysis of tumor doubling times led to the conclusion that dissemination had occurred at least 5 years before diagnosis. In a mouse model of uveal melanoma (12), it was shown that dissemination occurred early and dormant (i.e., growth-arrested) DTCs were commonplace. In a Drosophila melanogaster CSK null cancer model, early dissemination required Src activation without loss of E-cadherin or apparent EMT induction (13). Early DTCs can carry robust survival signals but still lack key genetic and epigenetic changes to sustain proliferation (10). Consequently, prolonged growth arrest with interspersed division might explain the clinical dormancy, during which slow accumulation of genetic and/or epigenetic alterations gives rise to malignant DTCs and relapse. For an excellent recent review, see the article by Klein (1).

Finally, late DTCs that progress in the primary tumor may reprogram into quiescence and coexist with early DTCs in patients with invasive cancers (5) who can display long metastases-free periods. This may be regulated by metastasis suppressor genes (MSG) that can respond to microenvironmental stress responses (14). Investigators have identified a number of genes that selectively affect growth at secondary sites, including KISS1, MKK4, MKK6, BHLHBL3/Sharp-1, and Nm23-H1, among others (for a comprehensive review, see ref. 14). These genes may inhibit metastasis by inducing DTC growth arrest, preventing the formation of overt metastases (14). Of interest, MKK4 and MKK6 are upstream activators of p38 (14). BHLHBL3 is a target of p38 required for quiescence induction (ref. 15; see below), and Nm23-1H1 appears to function via the downregulation of EDG2 LPA receptor, a strong activator of ERK1/2 (16). Thus, it seems that different mechanisms may converge to regulate the ERK/p38 signaling ratio. Here we discuss the role of p38 signaling in controlling early breast cancer progression and early dissemination, and how the ERK/p38 signaling ratio can regulate reprogramming of aggressive tumor cells into quiescence.

The Pathway: Stress Signaling Through p38α/β

Mitogen activated protein kinases (MAPK) belong to a family of highly conserved intracellular kinases that transduce extracellular signals relayed by surface receptors or various types of damage (17). Three subfamilies exist in mammals and include ERK, JNK, and p38 kinases. Four isoforms (α, β, γ, and δ) constitute the p38 family. They were initially identified as modulators of inflammatory responses and shown to regulate the expression of different cytokines (17). Furthermore, they were found to play important roles in cell proliferation by activating G1/S and G2/M checkpoints (17). It is also known that p38 can suppress the transformation of normal epithelial cells (18–20) and activate anoikis, which prevents aberrant localization of epithelial cells (18). In addition, p38α can promote growth arrest by downregulating cyclin D1 (20) and by activating the p53 to p21 and/or p16 to Rb pathways (21, 22), among others (23). Further, p38α inhibits transformation by sensing oncogene-induced oxidative stress (24), inactivation of p38α facilitates Erbb2-induced mammary tumorigenesis in vivo (9, 21), and 18% of human primary breast carcinomas display Wip1/PPM1D (a p38 phosphatase) amplification (9, 21). Thus, Wip1 inhibitors (25) may be useful to restore p38α signaling in tumors. Activation of p38α can also cooperate with reduced ERK1/2 mitogenic signaling to induce quiescence of tumor cells (Fig. 1; ref. 15). Furthermore, as mentioned above, MSGs (i.e., MKK4) can act upstream or downstream of p38 activation (26). Despite these advances, it is still unclear how p38α signaling is spatiotemporally regulated during cancer progression to suppress early tumorigenesis and dissemination, or to prevent DTCs from becoming overt metastasis.

p38α/β Regulates Early Breast Cancer Progression and Dissemination

Activation of p38α/β is a barrier to mammary tumor progression (9). We recently pinpointed this function of p38α during mammary morphogenesis by demonstrating that it activates anoikis of centrally located luminal ductal cells during mammary acinar development (27). This work revealed that p38α inhibited ERK1/2, possibly by regulation of PP2A and MKP phosphatases (28), and activated ATF-2 to induce c-Jun. Then, jointly, these transcription factors (TF) along with reduced ERK1/2 activity induced the proapoptotic factor BimEL in cells devoid of integrin-mediated attachment (27). This triggered anoikis and lumen formation. Remarkably, this led to the formation of structures reminiscent of ductal carcinoma in situ (27). In MMTV-Neu mice, where dissemination occurs during premalignant...
Carrying this cell-signaling profile. In one scenario, when these cells reach a growth-permissive target tissue microenvironment (e.g., lung), a proliferative survival or proliferative programs might be activated. In primary expanding tumors, a proliferative scenario prevails, and tumor cells are able to disseminate and perhaps MSG expression, which restricts colonization of distant organs by contributing to clearance (via anoikis; ref. 18) or dormancy via quiescence (Fig. 1; ref. 15). Thus, maintaining p38 signaling in disseminated malignant cells might prevent clinical relapse.

**Dormancy Induced by an ERK<sub>low</sub>/p38<sub>high</sub> Signaling Ratio**

**Dormancy of a tumor mass versus dormancy of tumor cells**

The lack of proliferation markers in surviving DTCs in patients and data from experimental systems suggest that DTC dormancy may be controlled by mechanisms of quiescence (5), a reversible growth arrest that can be brought about by different signals (29). Further, specific TFs can prevent quiescent cells from entering differentiation or senescence (an irreversible growth arrest that can lead to cell death or clearing by phagocytic cells; ref. 29), 2 cellular end points that tumor cells can evade (30). Angiogenic dormancy or immune system-mediated tumor mass dormancy may also be important in certain contexts (31, 32). Of interest, antiangiogenesis and quiescence programs may be coupled, as there are many common regulated genes in angiogenic dormancy (31) and quiescence models.
Cancer and breast cancer, bone metastasis occurs at a
ment activates DTC dormancy (5). For example, in prostate
see below). Alternatively, the target organ microenviron-
quiescent tumor cells could be killed (refs. 40 and 41, and
using the GADD34-PP1c inhibitor salubrinal. Thus, even

tumor cells that survive bortezomib treatment enter quies-
cence due in part to activation of an UPR (40). Schewe and
other small numbers (<10⁸ cells) of DTCs in the BM, spleen, or liver. However, if
p38α/β is systemically inhibited, DTCs are detected and metastasis proceeds even in these growth-restrictive sites (our unpublished results; Fig. 1). This suggests that activation of p38 and/or other stress signals may curtail DTC expansion. In fact, DTCs recovered from the BM (but not lungs), when re-injected in vivo, remained dormant for at least 6 weeks, suggesting a reprogramming driven by the microenvironment. Unlike HeP3 DTCs derived from lungs, BM-derived DTCs displayed a low ERK/p38 signaling ratio and induction of BHLHB3/Sharp-1, NR2F1, and p33 (our unpublished results; Fig. 1). BHLHB3 was also found to function as a metastasis suppressor in MDA-MB-231 breast cancer cells when mutant p33 function was eliminated (49). In addition, studies on solitary dormant breast DTCs revealed that an enriched collagen-I microenvironment in the lung triggered intravenously delivered tumor cells to exit from dormancy (37). On the other hand, environments rich in fibrillar collagen-I were shown to induce quiescence of melanoma cells via activation of the discoidin domain receptor 2 and p15INK4b induction (11). These results imply that stress signaling induced either by therapies or by a restrictive tissue microenvironment (i.e., fibrotic or nonfibrotic target tissues, depending on the tumor type) can activate dormancy (or its interruption) in DTCs sustained in part by an ERKlow/p38high ratio even if they carry dominant mutations (i.e., B-Raf) as in melanoma cells.

Survival of Dormant Tumor Cells

The fact that quiescent DTCs survive for long periods suggests that survival mechanisms are uncoupled from proliferation signaling. It can be argued that analysis of quiescent tumor cells might provide leads about these survival signals. For instance, cell lines derived from breast cancer patient BM DTCs displayed, as reported for dormant D-HeP3 cells (refs. 5 and 48; Fig. 1), upregulation of UPR genes such as Grp78 and Grp94 (50), and Grp78 upregulation is usually a poor prognosis marker in carcinomas, including breast (51). The UPR attenuates protein synthesis

ECM and stress signaling regulation of dormancy

The seed and soil theory would support the idea that the interactions DTCs establish with the target organ ECM or stromal cells (34) can determine growth versus dormancy and dictate the distinct and predictable pattern of metastasis (5). For example, studies on breast cancer cell lines selected for growth in the bone showed that these cells selectively regulate gene expression programs that favor organ-specific colonization (35). In squamous carcinoma cells (HeP3), it was shown that reduced urokinase receptor expression inactivated α5β1-integrins and that made these cells incapable of binding efficiently to fibronectin (Fig. 1; ref. 36). This resulted in reduced FAK and EGFR signaling but also in p38 activation. Other groups have corroborated these findings, showing that loss of β1-integrin or FAK signaling in the mammary epithelium or in intravenously delivered mouse breast cancer cells can also induce dormancy, and that Src MLCK signaling can prevent the onset of dormancy (5, 37). It was also shown that activation of p38 by blockade of adhesion signaling resulted in further inhibition of ERK1/2 while also activating a stress adaptive response known as the unfolded protein response (UPR; refs. 15 and 38). Together, these signals favored survival and acquisition of a dormant phenotype by HeP3 (D-HeP3) cells (39) that was characterized by a deep G0-G1 arrest associated with p21, p27, p18, and p15 induction, and only observed in vivo (ref. 15 and unpublished results; Fig. 1). Activation of p38αβ induced at least 3 TFs, p53 (R213Qmut), BHLHB3/41/Sharp1, and NR2F1, and inhibited the expression of c-Jun and FOXM1, 2 G1-S transition TFs (15). Of importance, the R213Q mutation in p53 does not affect its ability to induce G0-G1 arrest, but it prevents the induction of senescence or apoptosis (ref. 15 and unpublished results). This combinatorial regulation of TFs is responsible for the quiescence program in dormant tumor cells in vivo (15). However, it remains to be determined whether these programs are activated in DTCs, and which signals elicit these quiescence and stress resistance programs.

Therapy- and microenvironment-induced dormancy

Residual tumor cells that survive chemotherapy may respond to this stress by entering quiescence. Modeling this phenomenon in multiple myeloma revealed that tumor cells that survive bortezomib treatment enter quiescence due in part to activation of an UPR (40). Schewe and Aguirre-Ghiso (40) eradicated bortezomib-induced quiescent MM cells by preventing eIF2α dephosphorylation using the GADD34-PP1c inhibitor salubrinal. Thus, even quiescent tumor cells could be killed (refs. 40 and 41, and see below). Alternatively, the target organ microenvironment activates DTC dormancy (5). For example, in prostate cancer and breast cancer, bone metastasis occurs at a frequency of 10% to 30% (42–44). However, detection of BM DTCs is much higher (>50% of patients; refs. 45 and 46), suggesting that not all DTCs are productive and that metastasis can be blocked or delayed. Furthermore, spontaneous metastases in mouse models (xenografts/xenotransplantation) also show organ-specific growth that does not always follow the presence of DTCs (Fig. 1; refs. 10 and 47). For example, in MMV-Neu transgenic mice, BM DTCs were readily detected but bone metastases never developed (10). However, if the mice were irradiated (10), the DTCs expanded in the BM (but not in other sites), suggesting that loss or gain of specific signals only after BM remodeling activated the DTCs to proliferate. Previous studies showed that HeP3 primary tumor cells spontaneously disseminated to lungs, LNs (47), liver, and BM (our unpublished results; Fig. 1). Although overt metastases develop in lung and LNs (47, 48), 10% to 40% of animals carry occult or small numbers (<10⁵ cells) of DTCs in the BM, spleen, or liver. However, if
and induces concomitant G2-M, growth arrest and survival via the upregulation of genes that promote adaptation to cellular stress (38). However, these cellular outcomes are not necessarily coupled (52).

Additional studies proposed that p38α/β upregulates the ER chaperone BiP/Grp78, which inhibits Bax activation and renders dormant HEP3 cells highly resistant to chemotherapy (53). Further analysis of p38α targets in the UPR pathway revealed that dormant tumor cells have a persistent activation of the UPR TF ATF6α (41). High expression levels of ATF6 correlated with poor prognosis in patients with head and neck squamous cell carcinomas (41), suggesting that dormant tumor cells overexpressing ATF6 may have a survival advantage. Of importance, we found that ATF6α transcriptionally induced the small GTPase Rheb to transduce survival signals (ref. 42 and unpublished results; Fig. 1). This small GTPase in turn activated mTOR and downstream S6K and S6RP phosphorylation, but this was independent of Akt activation (41). RNA interference to downregulate ATF6α or Rheb was sufficient to induce apoptosis of dormant D-HEP3 cells and eradicate them during their quiescent phase (41).

Thus, unlike BiP, ATF6α activates an alternative pathway to mTOR signaling that bypasses the need for growth factor and Akt signaling, and serves as a basal survival factor required for adaptation to in vivo microenvironments. Supporting the existence of quiescence-specific survival signals, the kinase Mirk/Dyrk1B protects quiescent pancreatic tumor cells from reactive oxygen species (54). The transcription factor HEVS-1, a target of Notch signaling, has also been implicated in repressing oncogene-induced senescence and differentiation programs while promoting quiescence (29). This suggests that growth-arrested tumor cells may activate quiescence-specific survival mechanisms that render them resistant to microenvironmental and genotoxic stress. Inhibition of these alternative survival pathways could be exploited to induce cell death in quiescent DTCs.

Clinical-Translational Advances

Our knowledge about how the biology and genetics of DTCs influence dormancy and progression is limited. Consequently, no dormancy-inducing or dormant-cell–killing drugs are currently available. Nevertheless, several translational and clinical applications can be envisioned, such as characterizing dormant DTCs to identify the mechanisms that drive dormancy and determining whether current therapies can be applied to maintain the dormancy of residual disease. In the first case, investigators must direct major basic and translational research efforts toward characterizing DTCs during asymptomatic periods both in the laboratory and in patients (55, 56). Furthermore, better preclinical models must be developed to reproduce the kinetics of disseminated residual disease in patients. Harnessing single-cell profiling technologies (7, 57) to study DTCs in an unbiased manner will also shed light on the genetics and epigenetics of DTC behavior and whether available targeted therapies can be applied to dormant tumor cells. An excellent review by Goss and Chambers (58) highlights the latter possibility. For example, in ER+/PR+ breast cancer, recurrences continue to develop after the initial 5 years of conventional antiestrogen treatment. Treatment with the aromatase inhibitor letrozole after a 5-year treatment with tamoxifen provided additional benefit by further delaying breast cancer recurrence with treatment schedules spanning >5 years (58).

Of interest, tamoxifen treatment can activate p38 signaling and quiescence (59), suggesting that these dormancy therapies may be able to tap into some of the mechanisms described here. This strategy could be considered a maintenance therapy that prevents DTCs from exiting a state of growth arrest (i.e., dormancy maintenance) or induces growth arrest (i.e., dormancy induction). However, such a strategy might select for ER−negative tumor cells (58). This is because, to induce a program of quiescence, simply inhibiting mitogenic signaling (i.e., RTK, Raf, or Mek1/2 inhibitors) may not be sufficient. Activation of stress signals, such as p38, downstream TFs, or others, may also be crucial to achieve a long-term, stable, dormant phenotype (15). In cutaneous and (most prominently) uveal melanoma, late recurrences have been described (11). Although the association between genetics and time to recurrence is not clear, a small study showed that longer disease-free survival periods were associated with B-Raf but not N-Ras mutations (11). Thus, it is possible that in certain patients, it may be able to keep B-Raf− residual melanoma cells dormant by treating the patients during asymptomatic conditions with B-Raf or Mek1/2 inhibitors. If this is the case, other small-molecule inhibitors such as lapatinib, sorafenib, or antibody-based therapies (i.e., herceptin) used to treat other cancers may be useful for maintaining residual disease dormancy by treating patients during asymptomatic periods. Although this approach might keep cells from interrupting dormancy, it will not eliminate the quiescent DTCs. Thus, a full molecular description of these cells may ultimately be required before we can specifically target dormant tumor cells. An important example of how analysis of DTCs might provide information different from that obtained from primary tumors comes from a study of DTCs in esophageal cancer (7). This work revealed that DTCs displayed frequent Her2/neu amplification and that this was significantly correlated with poor prognosis (7). This information could not be derived from primary tumor analysis, and it opens the possibility of treating disseminated disease in this type of cancer with therapies already available (i.e., herceptin and lapatinib) originally for breast cancer. The most successful clinical trial would involve testing a drug that targets dormant tumor cells while they are quiescent (5). Unfortunately, specific drugs to achieve this goal are currently unavailable, and they might be identified only after we understand how therapy and microenvironmental cues influence DTC quiescence and survival. The prevalence of p38 signaling as a negative regulator of cancer progression and an inducer of dormancy has additional significance.

Inhibitors of p38 (such
Table 1. Summary of some of the ongoing clinical trials in which small-molecule inhibitors of p38 are being used

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Phase</th>
</tr>
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<tbody>
<tr>
<td>Multiple myeloma</td>
<td>SCIO-469</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>Bone marrow diseases, myelodysplastic syndromes, hematologic diseases</td>
<td>SCIO-469</td>
<td>Phase Ia</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>RO4402257</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>PH-797804</td>
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<tr>
<td>Neuropathic pain</td>
<td>SB681323</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>Acute lung injury, acute respiratory distress syndrome</td>
<td>SB681323</td>
<td>Phase IIa</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>BMS-582949</td>
<td>Phase IIa</td>
</tr>
</tbody>
</table>

More information on these and other trials can be found at http://www.clinicaltrials.gov.

This study has been completed.

This study is currently recruiting participants.

as SCIO-469, RO4402257, PH-797804, SB681323, and BMS-582949) are currently in clinical trials for several neoplastic and nonneoplastic diseases (e.g., hematological malignancies, asthma, neuropathic pain, atherosclerosis, and rheumatoid arthritis; see http://www.clinicaltrials.gov and Table 1). Thus, understanding how p38 inhibitors might carry an inherent risk for a proportion of patients with cancer, with a predisposition to cancer, or with other diseases is of crucial importance because inhibition of this pathway may fuel cancer progression and metastasis in these patients.

It will be important to determine whether the genes that define growth versus dormancy in different experimental models (15, 31, 37, 40, 41) are present or absent in DTCs, and how this correlates with clinical progression in patients. For example, are the levels of P-ERK1/2 and P-p38 informative of patient prognosis when detected in DTCs? Detection of markers in CTCs might be informative because, similar to primary tumors, they might carry some prognostic information. However, DTCs after primary tumor removal are already in target organs, and their analysis might provide a more relevant tumor cell population to study because it would incorporate the cross-talk of these DTCs with the microenvironment. Patients with BM DTCs usually have a worse prognosis than those without DTCs, and their presence reports for metastasis development but not necessarily in the BM, suggesting that they can serve as a reporter population even for cancers that do not metastasize in bone (5). For those patients with BM DTCs, do the dormancy markers discriminate patients with different metastasis-free periods? Do DTCs detected at the time of surgery versus those detected during disease-free periods or after relapse differ in the expression of dormancy markers? The finding that lung fibrosis (37) interrupts the dormancy of DTCs also suggests that by monitoring the composition of the target organ in specific cancers, we may be able to predict relapse in certain patients. Thus, a short-term translational or clinical benefit from studying DTCs would be the identification of markers to classify patients with dormant (protractedly nonproductive; ref. 1) or active (productive) disseminated disease. These markers would be derived from the target organ microenvironment (i.e., collagen-I fibrotic tissues; ref. 37) and DTCs. Moreover, the combinatorial use of drugs that modify stromal cells in the target organ microenvironment, such as macrophages that might support metastatic growth (34), may add further advantages to the treatment. The challenges are great. Studying DTCs and dormant disease is a difficult task, but the benefits of these efforts should be of great importance for cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ERK1/2 and p38α/β Signaling in Tumor Cell Quiescence: Opportunities to Control Dormant Residual Disease

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