Controversies in clinical cancer dormancy

Jonathan W. Uhr[a,1] and Klaus Pantel[b,1]

[a]Cancer Immunobiology Center, University of Texas Southwestern Medical Center, Dallas, TX 75093-8576; and [b]Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany

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Clinical cancer dormancy is defined as an unusually long time between removal of the primary tumor and subsequent relapse in a patient who has been clinically disease-free. The condition is frequently observed in certain carcinomas (e.g., breast cancer), B-cell lymphoma, and melanoma, with relapse occurring 5–25 y later. Clinical data suggest that a majority of breast cancer survivors have cancer cells for decades but can remain clinically cancer-free for their lifetime. Thus, there is a major effort to characterize the molecular mechanisms responsible for inducing tumor cell dormancy using experimental models or studying the early phases of cancer growth in humans. Many molecules and signaling pathways have been characterized and have led to concepts that dominate the field, such as the possible role of innate and adaptive immunity in immune surveillance and initiation and maintenance of dormancy. However, recent clinical data do not support many of these concepts. Several areas need further study to determine their relevance to clinical cancer dormancy. We suggest hypotheses that may contribute to elucidation of the mechanisms underlying the dormant state.

chronic cancer | organ size control | circulating tumor cell

Cancer dormancy, mentioned in 1864 (1) and described in 1959 (2), has been historically defined in clinical terms, namely recurrence of the cancer systemically or locally a long time after removal of the primary tumor in a patient who has been clinically disease-free. "A long time" has not been precisely defined, but is meant to exceed the time when recurrence is at a lower rate. The most exciting aspect of clinical cancer dormancy is that it approaches complete control of a chronic disease, that is, a persistent disease without symptoms or signs unless this balance is disturbed and a relapse occurs. In breast cancer, 20% of clinically disease-free patients relapse 7–25 y after mastectomy and, from 10 to 20 y, the rate of relapse is relatively steady at about 1.5%/y (3–5). Clinical cancer dormancy is also frequently observed in thyroid, renal, and prostate carcinomas as well as in B-cell lymphoma and melanoma, whereas late relapses are relatively rare in other common malignancies such as lung and colon cancer. Little attention was paid to this phenomenon until the last two decades, when new findings stimulated interest: (*i*) The Gompertzian model of tumor growth explained the kinetics of early tumor growth, and a period of tumor dormancy was hypothesized (5, 6), and (*ii*) a large portion of tumor cells in the bone marrow are in cell-cycle arrest both in hematopoietic malignancies (7) and carcinomas (8–10), and these nondividing cells have characteristics associated with so-called stem cells such as their immunophenotype, growth characteristics in vitro, resistance to radiation and chemotherapy, and ability to differentiate into more mature dividing tumor cells. These cells are currently considered to be the persisting, dormant ones (6, 9).

We discuss four aspects of cancer dormancy that we believe should be carefully reexamined: (*i*) the relationship of cellular dormancy early in disease to clinical cancer dormancy, (*ii*) the role of both adaptive and innate immunity in controlling cancer, (*iii*) the need for more effective anticancer immunizations, and (*iv*) hypotheses on the cellular population dynamics and control mechanisms underlying clinical cancer dormancy. We emphasize that data from humans are critical in interpreting data from model systems. Clinical cancer dormancy is a fascinating and mysterious phenomenon. Its understanding will undoubtedly lead to new insights into cancer biology and possibly improved treatment (11).

Relationship of Cellular Dormancy Early in Disease to Clinical Cancer Dormancy

Fig. 1 illustrates the current concept of clinical cancer dormancy. Numerous comprehensive reviews (12–14) have summarized all of the experimental models. Many studies involve the molecular mechanisms that induce tumor cells to become growth-arrested *early* in the growth of the tumor. The tumor cells in G_0/G_1 may be the precursors of the population of tumor cells underlying clinical cancer dormancy. Initially, this appeared to be a reasonable assumption, particularly because dormant tumor cells are the ones that are resistant to conventional therapy and persist (6, 8, 9, 12–17). However, studies on circulating tumor cells (CTCs) in breast cancer survivors 7–22 y after mastectomy and clinically disease-free challenge this notion (18). The short half-life of these CTCs (1–2 h) indicates that there must be a replicating population of tumor cells at secondary sites that replenishes the CTCs and keeps them at the same low level for many years (18). Therefore, the link between early dormant tumor cells and those replicating cells that underlie clinical cancer dormancy has not yet been made. Stem cells, or a subpopulation of them, or another cell type may give rise to the replicating tumor cell population underlying clinical cancer dormancy. It may be possible to answer this question if cancer cells in the bone marrow can be characterized and compared with CTCs isolated from such patients 7 or more years after mastectomy.

Adaptive and Innate Immunity to Cancer Cells

The role of immunity in controlling cancer, including the maintenance of dormancy, represents a major effort in the field. The hypotheses of immune surveillance by Thomas (19) and Burnet (20) were that the immune system could constantly inhibit the emergence of neoplastic clones and thereby act as a major protector from the development of cancer. Only modest attention was paid to this hypothesis until the discovery of innate immunity. Since then, a large number of impressive experiments have been performed primarily in mice (21–23) that support the existence of immune surveillance and adaptive immunity to cancers, whether spontaneous or induced. Elegant studies at a molecular level have led to considerable insight and many conclusions regarding "immune surveillance," "immunoediting," "sculpting cancer," the relationship of adaptive to innate immunity, and claims of successful immunization to various malignant murine tumors (24, 25).

The conclusions from these extensive experiments would be expected to be confirmed by experiments in humans. However, there are insufficient data to determine whether the innate immune response plays a role in maintaining clinical cancer dor-

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[1]To whom correspondence may be addressed. E-mail: jonathan.uhr@utsouthwestern.edu or pantel@uke.uni-hamburg.de.

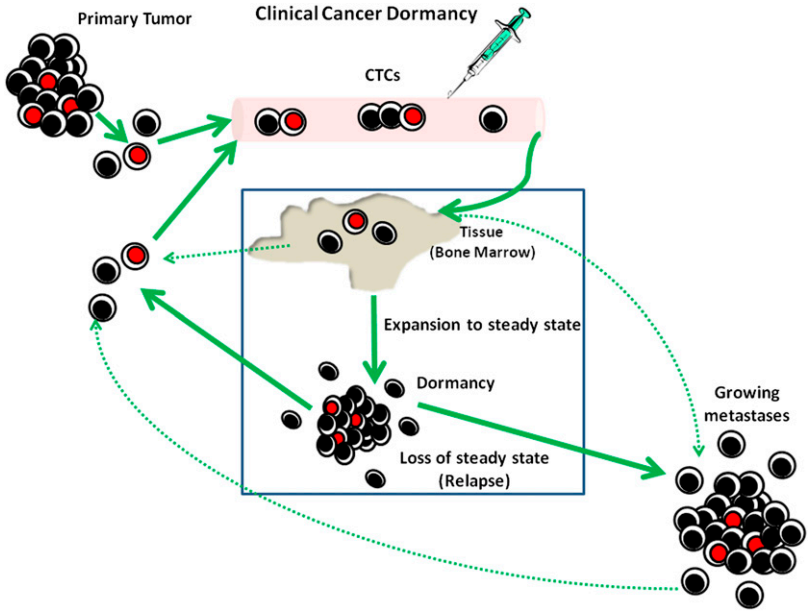

Fig. 1. Diagram of clinical cancer dormancy. Cells from the primary tumor are shed into the circulation (CTCs) and a small percentage lodge in tissue including bone marrow. A portion of the CTCs are in cell-cycle arrest and are chemo- and radio-resistant, that is, stem-like cells. These are colored red. Later, these initial cells, a differentiated subset of them, or a different cell type proliferate and establish micrometastases in tissue. There is a steady-state balance between cell proliferation and cell death. Some of the cells that are destined to die are shed into the blood (CTCs). In some patients, the balance changes and metastatic growth occurs (relapse). Solid lines represent dormancy pathways; dotted lines represent pathways for conventional metastatic growth.

mancy (26–28). There are extensive clinical data on the occurrence rate of new cancers in patients who have undergone organ transplantation and resultant immunosuppression. The experimental data and models predict that such patients should have a markedly elevated rate of occurrence of all of the typical kinds of cancers if innate and adaptive immunity act as tumor surveillance. However, this is not the case. In the approximately 29,000 patients studied in the New Zealand-Australia databank (26), there are several types of nonviral carcinomas that may have been elevated by a factor of two. This is relatively weak evidence for an immune surveillance mechanism. That paper also stated that "there is no elevation in the rate of spontaneous carcinomas in breast and prostate cancer," the two major types of human cancer. In the 12,900 renal-transplanted patients studied by Penn, there were *no* elevated rates of occurrences in the common carcinomas, namely lung, breast, prostate, and colon (27). Rather, such studies (26) show a marked elevation of viral-associated cancers in immunosuppressed patients. There is almost a 100-fold elevation in nonmelanoma skin cancers, and this could be related to human papillomavirus (HPV) infection.

A puzzling feature is that renal carcinoma, in contrast to the other common carcinomas and not thought to be associated with viral infection, shows a marked elevation in incidence in transplanted patients (26). However, an important control group, rarely considered in the above comparison, consists of patients with advanced renal disease on the waiting list for transplantation but who have not received one. In one such study of 832,000 patients, there was a major elevation in the incidence of renal cancer compared with the common carcinomas. Their kidneys have marked pathological alterations resulting in major changes in host physiology that undoubtedly contribute to the increased incidence of renal malignancy (29, 30). In summary, the evidence supporting innate and adaptive immunity as major factors underlying spontaneous immunity to cancer in humans is not convincing.

Cancer in Immunodeficient Mice

There are a number of immunodeficient mouse strains that have been studied for spontaneous tumors (for a review, see ref. 31). SCID mice, with markedly reduced adaptive immune responsiveness, have no increased incidence of the common types of cancers of humans (32). Activation of oncogenes that cause cancer in mice is apparently concomitant with the development of tumor antigen-specific tolerance. Thus, highly malignant sporadic tumors are unable to induce functional cytotoxic T cells, arguing against a major role for immune surveillance (33). $Rag2^{-/-}$ mice develop intestinal adenomas (50%), adenocarcinomas of the intestine (35%), and lung tumors (15%) (34). After 1 y of age, $Rag2^{-/-}$/$Stat1^{-/-}$ mice develop methylcholanthrene (MCA)-induced sarcomas and spontaneous intestinal and mammary cancers and $Rag1^{-/-}$ mice develop MCA-induced sarcomas (34); IL-12R$\beta2^{-/-}$ mice develop plasmacytomas and lung carcinomas or both (35). All these strains are particularly susceptible to infections both viral and bacterial (36). In some of these strains, antibiotic administration prevents or at least delays tumor onset (37, 38). However, there are others, such as $Rag2^{-/-}$ and $Rag^{-/-}$+$Stat1^{-/-}$ mice maintained on the same antibiotics and housed under strict pathogen-free conditions, that still display abnormal heightened tumor incidence (34). The above mouse strains present evidence that suppression of the adaptive or innate immune system can result in a marked increase in the incidence of malignant tumors. However, each strain appears to have this tendency in only one or two tumor types (i.e., organs of origin of the tumor). For example, IL-1R$\beta2^{-/-}$ mice develop only two malignancies (lung carcinoma and plasmacytomas as mentioned above). This raises the possibility that there are specific causes such as viral or bacterial infections or genetic changes for these murine strain-specific tumors, rather than a general mechanism such as failure of immune surveillance. Therefore, these results do not buttress the concept of immune surveillance of cancer.

Immunization to Cancer

None of the above arguments exclude the possibility that deliberate immunization may stimulate an adaptive immune response that could control or destroy existing cancers. Many approaches to the development of vaccines have been tried, in-

cluding immunization with tumor cells or their antigens and peptides, combined with different adjuvants (39, 40). However, despite decades of such efforts, the results are modest. One example of a human malignancy that can respond to immunization is B-cell lymphoma (41). The pioneering studies of Levy's group indicate that the unique Ig produced by each malignant B-cell clone can be recognized by the immune system and used as a therapeutic vaccine. One result of such a response is the development of clinical cancer dormancy (41). Similar results in a murine B-cell lymphoma (BcL1) were also obtained by vigorous immunization to the idiotype of the B-cell Ig (42, 43). Such mice developed clinical dormancy despite 10^6 tumor cells in their spleen. Unexpectedly, the antibody acted as an agonist to the tumor cells, and together with a T-cell response caused the tumor cells to die at the same rate as they were dividing (44, 45). There are reports that infiltration of various types of T cells into many human cancers is associated with a more favorable outcome, for example, in colorectal tumors (46). In mice, transfer of tumor-infiltrating lymphocytes or tumor antigen-reactive CTLs generated in vitro can result in significant tumor regression of melanoma cells (25). In human clinical trials, tumor-infiltrating lymphocytes expanded ex vivo and then adoptively transferred to melanoma patients resulted in objective responses in 34% of melanoma patients (24). However, $CD8^+$ T cells with melanoma specificity that circulate in the blood and display robust inflammatory and cytotoxic functions contrast with those that reside in tumor lesions which are functionally tolerant (47). This is evidence that the tumor itself and its environment can blunt T-cell effector functions and offers an explanation for the failure of many tumor-specific responses to counter tumor progression (48). Recent phase 3 clinical studies using complex antigen–adjuvant cell combinations have shown extension of life span in advanced prostate adenocarcinoma (49) and melanoma (50). Genetically induced changes in cancer antigens have led to rapid tumor eradication in a murine model of lung carcinoma (51). It will be important eventually to use these novel types of immunogens in patients with early cancers. In summary, more clinical data are needed to determine whether immunization to cancer will become a major form of treatment.

It is also important to develop more relevant experimental models of clinical cancer, especially with respect to the issue of cancer dormancy. For example, painting the skin of mice with a carcinogenic agent results in sarcomas that are controlled by an immune response, which is not observed if $RAG1^{-/-}$ mice are used (22). The analogy of this model to human clinical dormancy falls short, however, because the tumor is not spontaneous and is not one of the common epithelial tumors. Indeed, most of the carcinogen-induced murine models of tumor development result in sarcomas (31), a relatively rare type of tumor in humans (excluding those associated with known viruses). Why sarcomas and not carcinomas in mice? Mucosal cells are highly proliferative. This disparity has not been adequately addressed in the literature.

Recently, Almog et al. (52) developed models in which human tumors remain dormant for a prolonged period (greater than 120 d) until they switch to rapid growth and become strongly angiogenic. A genome-wide screen has identified several dormancy-associated candidate genes in this model.

Tissue Homeostatic Control Mechanisms That May Underlie Clinical Cancer Dormancy

Many hypotheses have been advanced to explain the cellular population dynamics in clinical cancer dormancy. These include the earlier prediction of Folkman of insufficient angiogenesis (53), a small number of micrometastases or solitary cancer cells (54, 55), aging disseminated cells that have developed a reduced division rate (17), an effective immune response that keeps the carcinoma population stable (22), a parallel gene evolution of disseminated cells in distant organs that results in a new population of cancer cells which may be the "drivers" of clinical dormancy (56, 57), hormonal changes (58, 59), the influence of diet (60), and cross-talk between several cell types and their secretions in a metastatic niche which initiates signaling pathways that include G_0/G_1 arrest (61, 62).

There appears to be a precise balance between life and death of the persisting tumor cells. Therefore, we are adding two hypotheses for this balance. The first is a simple one: Persisting tumor cells divide asymmetrically, giving rise to one similar daughter cell that divides and continues the line. The second daughter cell is different; it divides rapidly, but dies at a particular point in its development and is expelled into the blood as well as dying in situ.

Another possibility is that the size of the persisting human tumor cell population is kept constant by some of the same mechanisms that control the size of organs and subsets of cells (63). Evolution has given mammals and other species the regulatory equipment to keep organs at a precise size and to restore that size if the organ is altered in size (63–65). Thus, each cell type in the blood is kept at a relatively constant level, barring disease. The same is true for solid organs; for example, if half the liver is removed, liver cells begin to divide and stop dividing only when the liver has reached normal size (66). Organisms from *Drosophila* to mammals have evolved elaborate mechanisms to coordinate cell proliferation and cell death, thereby preventing inappropriate proliferation of somatic cells. Many molecules and signaling pathways have been studied to explain organ size in *Drosophila*, and there is considerable conservation of the signaling molecules between *Drosophila* and humans. For example, the *Drosophila* insulin growth factor (IGF1) and its receptor (the homologs in humans are IGF1 and AKT/PKB, respectively) coordinate cell growth (67). There are numerous reports that implicate serum IGF levels in increasing risk of developing many of the common malignancies (68–70). More convincingly, IGF can inhibit the beneficial effect of trastuzumab on human breast cancer cells in culture (71). Resistance to trastuzumab was abolished by adding IGF-binding protein 3, which decreased IGF-1R signaling (71). Cotargeting HER-2 and IGF1 receptors causes synergistic inhibition of growth in HER-2-overexpressing breast cancer cells (72). IGF-1R causes massive apoptosis in vivo in human ovarian cancer cells in nude mice (73). Prostatic involution caused by finasteride is associated with elevated levels of IGF-binding proteins (74). IGF-II receptor reduces organ size mediated by IGF-II or other mechanisms (75). These experiments suggest that there are significant clinical implications of the IGF1 interactions on cancer therapy. In addition, there are other human homologs that control cell and organ size in *Drosophila*, such as IRS1-4 (76) and TSC1 and TSC2 (77).

Many of the above genes have been implicated in an emerging and exciting pathway, the Hippo (Hpo) signaling pathway. It controls organ size by both restricting cell growth and proliferation and promoting cell death (78). This pathway has been implicated in regulating cell contact inhibition, organ size, and tumorigenesis. Central to the Hpo pathway is a kinase cascade consisting of Hpo, Salvador, Warts, and Mats (79). Mutations in any of these genes resulted in overgrowth of adult appendages including eye and wing. Hpo is a *Drosophila* homolog of mammalian Ste20 family kinases Mst1 and Mst2 (79). YAP is the primary effector of the mammalian Hpo pathway. YAP in humans is a candidate oncogene that is amplified in several types of tumors (80). As in *Drosophila*, the TEAD family of transcription factors mediates the function of Yap and Taz in mammalian cells. In the mammalian Hippo pathway, Mst1 and Mst2 are required for size control of some organs and tumor suppression in mice (80). The Hpo pathway thereby provides a robust mechanism to quickly stop organ growth at the appropriate time in development, acting like an on/off switch. Admittedly, we know

very little about the mechanisms of this extraordinary balance, but it is possible that some of its mechanisms contribute to the constancy of the size of the persisting pool of dormant breast cancer cells. This in no way excludes other mechanisms (e.g., growth factors, genetic changes, availability of nutrients, etc.) that may act in combination with organ size control pathways to initiate and then stabilize the dormant state.

Conclusions and Future Directions

It is possible that all "survivors" of breast cancer have a small number of tumor cells somewhere in their body, the growth of which is controlled usually for the lifetime of the host. If the mechanisms underlying tumor dormancy and relapse were understood, it is possible that appropriate targeting drugs could be developed which could eliminate or control these persistent tumor cells and thereby prevent their occasional transformation into growing metastases. If this could be achieved, the control of this chronic disease could be considered an "operational cure," as first suggested by Folkman (53). This is different from the current paradigm of "cure" (meaning elimination of all cancer cells). These arguments in no way diminish efforts to rid the body of all cancer cells, but they indicate that there is an alternative goal.

Therefore, it is essential to fully characterize circulating tumor cells in breast cancer survivors without clinical evidence of disease many years after mastectomy. The bone marrow may contain these dormant cancer cells, and the assessment of the environment that shapes the "metastatic niche" in the bone marrow might be even more informative. Such data would add information and insights into the biology of clinical cancer dormancy. In addition, experimental models mimicking clinical cancer dormancy are urgently needed. Such models might be helpful in identifying novel dormancy-associated mechanisms and additional biomarkers for dormant cells.

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