Review

Cancer Research

Tumor Dormancy and Relapse: From a Natural Byproduct of Evolution to a Disease State

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Abstract

Species evolve by mutations and epigenetic changes acting on individuals in a population; tumors evolve by similar mechanisms at a cellular level in a tissue. This article reviews growing evidence about tumor dormancy and suggests that (i) cellular malignancy is a natural byproduct of evolutionary mechanisms, such as gene mutations and epigenetic modifications, which is manifested in the form of tumor dormancy in healthy individuals as well as in cancer survivors; (ii) cancer metastasis could be an early dissemination event that could occur during malignant dormancy even before primary cancer is clinically detectable; and (iii) chronic inflammation is a key factor in awakening dormant malignant cells at the primary site, leading to primary cancer development, and at distant sites, leading to advanced stage diseases. On the basis of this evidence, it is reasonable to propose that we are all cancer survivors rather than cancer-free individuals because of harboring dormant malignant cells in our organs. A better understanding of local and metastatic tumor dormancy could lead to novel cancer therapeutics for the prevention of cancer. *Cancer Res; 77(10); 2564–9. ©2017 AACR.*

Malignancy Is a Byproduct of Evolutionary Mechanisms of Cell Survival

DNA is a dynamic and adaptable molecule that is constantly changing through the process of mutation and epigenetic modification. These are evolutionary mechanisms that allow survival of an individual against environmental insults. DNA mutation could spontaneously occur during DNA replication or could be accidental as a result of environmental exposure to certain chemicals, UV radiation, or other external factors that impact DNA replication. Spontaneous somatic mutations lead to genotypic and phenotypic heterogeneity within and between tissues, generating genetic mosaicism in the body and the risk of cancer that could arise from those mutations (1). Randomness of DNA mutations and epigenetic modifications during cell division results in different outcomes in the host. Spontaneous mutations could be harmless, beneficial, or deleterious to human cells, whereas accidental mutations are often harmful. Dynamics of DNA mutation and epigenetic modification mechanisms make cellular transformation an inevitable event.

Harmless somatic mutations have been reported in healthy hematopoietic stem cells of women with a constant mutation rate of four mutations per year or three mutations per cell division. These mutations were found in regions that were not evolutionarily conserved (2). Another example of harmless somatic mutations includes somatic mutations in the hypoxanthine-guanine phosphoribosyltransferase (hprt) gene in T cells of normal children. This is a V(D)J recombinase–mediated recombination event that is found in 30% to 35% of children under 5 years of age (3). The frequency of these specific changes is dramatically decreased in older children.

Beneficial somatic mutations constantly occur in cells of the immune system to maintain their effector function. For instance, somatic hypermutation in the variable regions of immunoglobulin genes is a major component of the process of affinity maturation, allowing diversification of B-cell receptors in recognizing numerous antigens and distinguishing self-antigens from foreign antigens (4). Lactose tolerance is also the result of beneficial mutations that create evolutionary polymorphism in lactase-phlorizin hydrolase, the enzyme responsible for hydrolysis of milk lactose into glucose and galactose. Lactose tolerance is found in around 35% of adults living in the world, mostly people with European ancestry (5). This enzyme is expressed during infancy, but after the weaning period is over, lactase production usually declines. However, 35% of human population continues to express lactase throughout adult life. Another beneficial mutation was reported in the *CCR5-delta32* gene, which can block the entry of human immunodeficiency virus (HIV) into $CD4^+$ T cells and protect the mutant carrier from AIDS (6). Beneficial mutations in a gene may progress to a harmful mutation. For instance, a point mutation in just one copy of the hemoglobin gene can protect the host from malaria (7), whereas two copies of the mutated hemoglobin gene cause sickle cell anemia. T-cell differentiation is also regulated through beneficial epigenetic modifications. Analysis of Th0, Th1, and Th2 cells indicated that the IFNγ and Th2 cytokine loci were not modified in Th0. In fact, active or repressive histone modifications in the cytokine locus determine Th1/Th2 differentiation (8).

Deleterious somatic mutations or epigenetic alterations result in cellular malignancy and cancer. Changes in methylation patterns or histone deacetylation are hallmarks of epigenetic modulation, which can alter gene expression. As methylation and

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histone deacetylation rates are faster than genetic mutation rates, epigenetic alterations could occur very quickly during the lifetime of an individual. DNA hypermethylation can inactivate the genes that are responsible for DNA damage response and repair, facilitating the establishment of cancer. It was reported that each environmental insult alters a specific checkpoint that it triggers and increases risk of certain cancers (9). For instance, bisphenol A, a plasticizer used for manufacturing polycarbonate plastics, can leach from plastics into food and water, disrupts mitotic progression, and increases risk of prostate and breast cancers (10, 11). Environmental insults often result in deleterious mutations, although subsequent induction of tumor suppressor genes inhibits growth of malignant cells and prevents cancer development. For instance, p53 is activated in response to DNA damage, hypoxia, and nucleotide deprivation. Activation of p53 leads to cell-cycle arrest, apoptosis, or DNA repair to restore the integrity of cells. However, loss of p53 function through mutations could lead to survival of malignant cells. Once the process of malignancy is completed, transformed cells cannot necessarily form cancer. Fortunately, metastasis suppressor genes could still limit invasiveness of malignant cells, and mutant protein antigens expressed by malignant cells can be specifically recognized and attacked by the immune system, resulting in the maintenance of malignant dormancy. However, tumor cells that arise from normal cells have adapted similar evolutionary mechanisms of survival that enable them to escape immune surveillance. These mechanisms have been well explained by the tumor immunoediting theory (12). In fact, humans have evolved two major mechanisms of survival from tumor-inducing environmental insults. These include (i) tumor-intrinsic mechanisms regulated by metastasis suppressor genes and cell-cycle checkpoint molecules, which could inhibit proliferation of malignant cells and establish tumor dormancy; and (ii) tumor-extrinsic mechanisms regulated by the immune surveillance, which could either eliminate or inhibit nascent transformed cells. Inhibition of transformed cells could, in turn, facilitate the establishment of immunogenic tumor dormancy. In fact, Th1 cells have been reported to inhibit HER2-positive tumor growth such that loss of anti-HER2 or anti-HER3 Th1 response was found to be associated with tumor recurrence (13, 14).

Cellular Dormancy Is an Evolutionary Conserved Mechanism of Survival

In a thorough review of the evidence of cancer dormancy, Aguirre-Ghiso suggested that cellular dormancy is an evolutionary conserved mechanism among organisms to help them adapt to stress and survive a hostile environment (15). In *Caenorhabditis elegans*, pathways that sense stress will induce cellular dormancy or growth arrest and result in resistance of larvae to nutritional deprivation (16). Mycobacterium tuberculosis and HIV survive in human cells by entering into a dormant, latent state (17, 18). Mammalian adult stem cells are also in a state of quiescent dormancy until they receive specific signals, such as tissue injury, to exit from dormancy and proliferate (19, 20). It was also reported that in the absence of antigen, memory T cells enter a state of dormancy associated with low energy utilization and proliferation to survive until they receive stimulatory signals during a subsequent infection (21). In fact, cellular dormancy is the mechanism by which memory T cells survive nearly throughout the lifetime to protect an individual from recall infections. Memory T cells could escape from dormancy during recall infection and generate effector T cells with the ability to proliferate (21). Although the mechanisms of cellular dormancy are not fully understood, stress-induced autophagy could lead to cellular dormancy. In T cells, macroautophagy is upregulated just before the contraction phase, when T cells stop dividing and the pathogen has been cleared (22). Autophagy-deficient $CD8^+$ T cells were found to be defective in generating memory phenotypes that are usually in the state of dormancy (22). Given that malignant cells arise from normal cells, it is reasonable to suggest that tumor dormancy recapitulates evolutionarily conserved mechanism of adaptation,that is, cellular dormancy to survive hostile microenvironment. This property facilitates the establishment of treatment-induced tumor dormancy following conventional cancer therapies or immunotherapy (23–25). In fact, IFNγ produced by tumor-reactive T cells induces tumor cell apoptosis as well as tumor cell dormancy, and relapse associated with tumor immunoediting, simultaneously (26, 27). Such a paradoxical response by tumor cells to the immune response was shown to be due to the inherent heterogeneity of mammary tumor cells for the expression of IFNγ Rα (28).

Local or Metastatic Tumor Dormancy Is Present Prior to Cancer

Patients with early-stage cancer do not die from primary cancer, which tends to be responsive to therapy, but rather as a result of distant recurrence of the tumor in the form of advanced stage diseases. Twenty percent to 45% of patients with breast or prostate cancer end up with distant recurrence of the disease years or decades after successful treatment of their primary cancer (29, 30). This phenomenon can be explained by cancer dormancy, a stage in which residual disease is present but remains asymptomatic, and most often, undetectable. Tumor dormancy is present in almost all cancers, particularly breast cancer. Emerging evidence suggests that local and metastatic tumor dormancy precede primary cancer and distant tumor metastasis, respectively.

Local tumor dormancy prior to establishment of primary cancer

The concept that local malignant dormancy precedes primary cancer is supported by the existence of "cancer without disease" (31), tissue-specific control of malignant dormancy (32), as well as clinical evidence in support of the existence of natural tumor dormancy in healthy individuals highlighted in the recent review articles (32, 33). For instance, postmortem examination of random sections of autopsied prostate tissues from men who did not have cancer revealed frequent "small carcinomata" in 14% of prostate specimens (34, 35). More recent studies revealed the presence of *in situ* carcinoma in 9%, 27%, and 34% of cancer-free men in their 20s, 30s, and 40s, respectively (35). Postmortem examination of women in their 40s showed a similar frequency (39%) of histologic breast cancers (36), although only 1% of women in this age range get breast cancer. Interestingly, all autopsied individuals ages 50 to 70 had *in situ* carcinomas in the thyroid gland (37), whereas the incidence of thyroid cancer in this age group is only 0.1% (31). Frequency of dormant lung cancer was lower, accounting for 1% of autopsied specimens from individuals who were cancer free (38). Pancreatic intraepithelial neoplasia being in a dormant state is remarkably common, particularly in cancer-free elderly (39). They contain mutations in the same genes that are mutated in invasive pancreatic cancer

(40, 41), suggesting the state of malignant dormancy. These data suggest that local tumor dormancy precedes primary cancer development and that tumor cells could remain dormant for the lifetime of an individual without ever causing cancer. Very recently, circulating tumor DNA carrying P53 mutations has been reported in healthy individuals (42), again suggesting that malignancy is present prior to the development of primary cancer.

Metastatic tumor dormancy prior to establishment of primary cancer

For the past century, it has been assumed that tumor metastasis follows a stepwise process from primary tumor to the regional lymph nodes and then distant organs. This classical understanding of tumor metastasis has guided removal of the draining lymph nodes during conventional therapies. Recent evidence from patients with solid malignancies indicates that metastasis is a very early event such that even small tumors (<5 mm) can establish metastasis long before they become detectable at the primary site. This phenomenon is defined as early dissemination but late metastasis, because metastatic cells could lie dormant for even a decade and then reemerge as metastatic disease (43, 44). More recently, the observations made in two groups of cancer patients have further challenged the classical view of tumor metastasis. The first group of patients comprises those with metastatic lesions either before the primary tumor became clinically detectable, or when harboring primary cancer at a very early stage without local invasion. For instance, patients with stage M0 breast cancer could relapse after complete resection of their primary tumor, and their metastatic tumor had significantly fewer genetic abnormalities than the primary tumor (45). Studies in melanoma model demonstrated that tumor cells were disseminated throughout the body even before primary tumor became clinically detectable (46). Mechanistic studies revealed that in early lesions prior to establishment of breast cancer, there was a subpopulation of early cancer cells that spread to distant organs. Further studies demonstrated that progesterone-induced signaling induces dissemination of malignant cells from early lesions shortly after HER2 activation and prior to breast cancer development (43). Another group of cancer patients comprises those with cancer of unknown primary. Up to 5% of all cancer diagnoses are classified as cancer of unknown primary (47). In these patients, primary cancer could not be identified after histopathologic review of biopsy material and CT scan, but full-body imaging identified metastatic lesions that were confirmed by biopsy. Even a postmortem examination of a small group of patients with cancer of unknown primary revealed only 55% to 85% of the primaries, which were very small asymptomatic tumors in the lung, gut, and kidney. The remaining were autopsy-negative primary sites with detectable metastatic lesions (48). Metastatic cancers of unknown primary were reported in cervical carcinoma, renal cancer, breast cancer, colorectal cancer, lung cancer, liver cancer, pancreatic cancer, and ovarian cancer. Cancer of unknown primary is a clinical puzzle for oncologists and could be explained by the notion that circulating tumor cells must be present very early during the process of malignancy and reside in distant organs in a dormant state prior to the establishment of primary tumor. These dormant cells can then establish metastatic cancer prior to the detection of primary cancer (cancer of unknown primary) or relapse at distant organs after successful treatment of the primary cancer. Perhaps, metastasis suppressor genes are involved in maintaining tumor dormancy at distant sites. Although both metastasis suppressor genes and tumor suppressor genes are tumor cell–intrinsic mechanisms of survival, the former is distinct from the latter in that metastasis suppressor genes maintain metastatic cells in a dormant state without affecting the growth of the primary tumor (49–52). On the other hand, tumor suppressor genes undergo mutation or epigenetic alterations during tumorigenesis or latency. Each cancer type appears to have distinct metastasis suppressor genes. For instance, *Nm23* and *BRMS1* are involved in breast cancer, *KAI1*, *MKK4*, *Rkip*, *RHOGDI2*, and *Drg-1* are involved in prostate cancer, and *TXNIP*, *CRSP3*, and *KISS1* are involved in melanoma (50). Failure of tumor cell–intrinsic mechanisms of survival, including metastasis suppressor genes, tumor suppressor genes, and cell-cycle checkpoint molecules, does not immediately result in cancer because cell-extrinsic mechanisms mediated by the immunosurveillance could still support tumor dormancy by inhibiting the growth of nascent transformed cells (12). This mechanism has been demonstrated by the equilibrium phase of tumor immunoediting (53). However, escape from immune-mediated tumor dormancy could lead to distant recurrence of cancer (33).

Chronic Inflammation Awakens Dormant Malignant Cells and Results in Cancer

A substantial body of evidence supports the role of chronic inflammation in cancer development. For instance, colon carcinoma is associated with inflammatory bowel disease, esophageal cancer is associated with acid reflux esophagitis, liver cancer is associated with fatty liver disease and hepatitis, bladder cancer is associated with cystitis and schistosomiasis, and stomach cancer is associated with chronic *Helicobacter* infection. It has long been thought that chronic inflammation facilitates cell transformation and malignancy by increasing free radicals. During inflammation, there are high levels of reactive oxygen and nitrogen species (RONS), which can induce mutagenic DNA lesions. RONS also induce DNA double-strand breaks, which can also be potently mutagenic if not accurately repaired. However, detection of malignant cells in postmortem autopsy specimens of individuals in the absence of any chronic inflammation outcasts a cause–effect relationship between chronic inflammation and cancer (31, 33, 39, 42). In addition, not all individuals with chronic inflammatory diseases end up with cancer. Tumorigenic manifestation of chronic inflammation could be due to its role in awakening dormant malignant cells rather than causing malignancy. To this end, the incidence and the type of cancer in individuals could be determined by the presence of malignant dormancy that each organ might carry to communicate with chronic inflammatory environment. In fact, chronic inflammation supports angiogenesis, which is an important factor in the promotion of growth of dormant micrometastasis (54). For instance, there is a strong correlation between inflammation and recurrence of endometrial cancer (55), oral cancer (56), breast cancer (57, 58), and tumor escape from dormancy induced by the inflammatory cytokine IFNγ (27, 28, 59, 60). In addition, data from patients with tumor recurrence after successful treatment of their primary cancer support this hypothesis. For instance, in a multisite study of 734 breast cancer survivors, high levels of circulating acute phase proteins (APP) were associated with distant recurrence of cancer (61). Therefore, posttreatment monitoring of serum inflammatory markers, such as APP, C-reactive

protein, and IL6, could be of prognostic value for predicting risk of breast cancer recurrence.

Escape from Cell-Intrinsic and Cell-Extrinsic Mechanisms of Tumor Dormancy Results in Distant Recurrence of Cancer

Like normal cells, malignant cells that lie dormant could evolve and escape from dormancy. Such evolutionary mechanisms could be facilitated by chronic inflammation that induces mutations and epigenetic alterations in metastasis suppressor genes. This, in turn, abolishes tumor cell–intrinsic mechanisms of metastatic dormancy, resulting in distant recurrence of the disease in the form of advanced stage cancer. Fortunately, mutant protein antigens expressed by malignant cells can be specifically recognized and attacked by the immune system, thereby providing tumor cell–extrinsic mechanisms for the maintenance of metastatic dormancy. In fact, immunogenic tumor dormancy has been suggested to be a key mechanism of tumor dormancy (33, 62). For instance, tumor cells that were disseminated prior to the formation of primary cancer were in the state of dormancy in the lung as a result of the cytostatic function of $CD8^+$ T cells (46). Depletion of $CD8^+$ T cells resulted in the outgrowth and relapse of metastatic dormant cells (46). Studies in an animal model of pancreatic cancer demonstrated that circulating pancreatic cells underwent epithelial-to-mesenchymal transition (EMT) and seeded the liver. EMT and invasiveness were most abundant at inflammatory sites such that treatment with the immunosuppressive drug, dexamethasone, abrogated tumor invasiveness. The authors suggested that inflammation enhances cancer progression in part by facilitating EMT (63). It was also reported that localized inflammation in the lungs triggers escape from dormancy, which develop into macroscopic metastases (64). However, dormant tumor cells that arise from normal cells possess similar evolutionary mechanisms of survival that could result in escaping from immunosurveillance. Thus far, two types of tumor dormancy have been reported; these include $Ki67^-$ quiescent dormancy and $Ki67^{low}$ indolent dormancy (27). The latter is maintained through a balance between sluggish cell proliferation and cell death. Interestingly, an indolent, but not a quiescent, type of tumor dormancy was found to be able to evolve through immunoediting and escape from the immune response. The inflammatory cytokine, IFNγ, was a key factor in facilitating tumor immunoediting (27). In fact, IFNγ-producing Th1 cells can induce apoptosis and HER2 loss in murine and human breast cancer (60). Immune escape mechanisms include, but are not limited to, tumor antigen loss, expression of PD-L1, loss or downregulation of MHC class I, and induction of MDSCs and/or Tregs. Therefore, distant recurrence of cancer in some but not all cancer survivors could depend on the state of dormancy, that is, quiescent or indolent.

In summary, (i) cellular transformation is unavoidable in biological systems; (ii) malignant cells often enter the state of dormancy to survive environmental insults; (iii) malignant dormant cells are best targets for the prevention of metastasis, as suggested in a recent review of by Ghajar (65); and (iv) malignant dormant cells could evolve, escape from the immune surveillance or other cancer therapies, and relapse. Therefore, attempts to destroy and eliminate cancer without any risk of relapse would be unfruitful. Rather, we need to develop new therapeutic strategies to control malignant cells through retaining them in the state of residual dormancy and preventing distant recurrence of the disease. This could be achieved by immunotherapeutic targeting of dormant cells, because all other currently available cancer therapies are toxic with off-target effects, whereas immune cells could establish memory against dormant tumor antigens such as mutated tumor antigens, and keep them dormant for the lifetime of an individual.

Disclosure of Potential Conflicts of Interest

M.H. Manjili is a consultant/advisory board member for Getting To Know Cancer.

Disclaimer

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Department of Defense.

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