Tumor Dormancy, Quiescence, and Senescence
Volume 1

Tumor Dormancy and Cellular Quiescence and Senescence
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Tumor Dormancy, Quiescence, and Senescence
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Tumor Dormancy, Quiescence, and Senescence

Aging, Cancer, and Noncancer Pathologies

Edited by

M.A. Hayat
Distinguished Professor
Department of Biological Sciences
Kean University, Union, NJ, USA

Springer

Editor
M.A. Hayat
Department of Biological Sciences
Kean University
Room 213, Library building
Morris Avenue 1000
Union, NJ 07083, USA

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"Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena."

Richard J. Reed, MD

One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test, may revert to normal cells. Tumor shrinkage, regression, dormancy, senescence, reversal, or stabilization is not impossible. Can prosenescence therapy be an efficient alternative strategy to standard therapies for cancer prevention and treatment?

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guinet al. 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al. 2008). These and other studies justify the "wait and see" strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless *MYCN* gene is amplified. Infants with nonamplified *MYCN* and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without *MYCN* have excellent survival with minimal or no treatment. Another example of spontaneous shrinkage and loss of tumors without any treatment is an intradurallipoma (Endoh et al. 1998).

Although cancers grow progressively, various lesions such as cysts and thyroid adenomas show self-limiting growth. Probably, cellular senescence occurs in many organ types following initial mutations. Cellular senescence, the growth arrest seen in normal mammalian cells after a limited number of divisions, is controlled by tumor suppressors, including p53 and p16, and so this phenomenon is believed to be a crucial barrier to tumor development. It is well-established that cell proliferation and transformation induced by oncogene activation are restrained by cellular senescence.

Metastasis is the main cause of death from cancer. Fortunately, metastasis is an inefficient process. Only a few of the many cancer cells detached from the primary tumor succeed in forming secondary tumors. Metastatic inefficiency varies depending on the location within an organ, but the malignancy may continue to grow preferentially in a specific tissue environment. Some of the cancer cells shed from the primary tumor are lost in the circulation due to hemodynamic forces or the immune system, macrophages, and natural killer cells.

Periodic rejection of a drug by FDA, which was previously approved by the FDA, is not uncommon. Most recently, the FDA ruled that Avastin should not be used to treat advanced breast cancer, although it remains on the market to treat other cancers, including colon and lung malignancies. Side-effects of Avastin include high blood pressure, massive bleeding, heart attack, and damage to the stomach and intestines.

Unwanted side effects of some drug excipients (e.g., propylene glycol, menthol) may also pose safety concerns in some patients. Excipients are defined as the constituents of the pharmaceutical formulation used to guarantee stability, and physicochemical, organoleptic and biopharmaceutical properties. Excipients frequently make up the majority of the volume of oral and parenteral drugs. Not all excipients are inert from the biological point of view. Although adverse drug reactions caused by the excipients are a minority of all adverse effects of medicinal products, the lack of awareness of the possible risk from excipients should be a concern for regulatory agencies, physicians, and patients (Ursinoet al. 2011). Knowledge of the potential side effects of excipients is important in clinical practice.

It is known that chemotherapy can cause very serious side-effects. One most recent example of such side-effects was reported by Rubsam et al. (2011). Advanced hepatocellular carcinoma (HCC) induced by hepatitis C virus was treated with Sorafenib. It is an oral multikinase inhibitor that interferes with the serine/threonine kinases RAF-1 and B-Raf and the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the platelet-derived growth factor receptor-beta. Although Sorafenib is effective in regressing HCC, it shows serious side-effects including increasingly pruritic and painful skin changes (cutaneous eruption).

An example of unnecessary surgery is the removal of all the armpit lymph nodes after a biopsy when a sentinel node shows early stage breast cancer; removal of only the sentinel node may be needed. Limiting the surgery to the sentinel node avoids painful surgery of the armpit lymph nodes, which can have complications such as swelling and infection (such limited surgery is already being practiced at the Memorial Sloan-Kettering Cancer Research Center). Radiation-induced second cerebral tumors constitute a significant risk for persons undergoing radiotherapy for the management of cerebral neoplasms. High-grade gliomas are the most common radiation-induced tumors in children (Pettorini et al. 2008). The actual incidence of this complication is not known, although it is thought to be generally low.

Medical Radiation

Chromosome aberrations induced by ionizing radiation are well-known. Medical radiation-induced tumors are well-documented. For example, several types of tumors (sarcomas, meningiomas) can develop in the CNS after irradiation of the head and neck region (Parent 1990). Tumorigenic mechanisms underlying the radiation therapy of the CNS are discussed by Amirjamshidi and Abbassioun (2000) (see below).

Radiation therapy is commonly used to treat, for example, patients with primary and secondary brain tumors. Unfortunately, ionizing radiation has limited tissue specificity, and tends to damage both neoplastic and normal brain tissues. Radiation-induced brain injury, in fact, is a potential, insidious later cerebral side-effect of radiotherapy. Most commonly it consists of damage in small arteries and capillaries, resulting in secondary processes of ischemia.

After radiation therapy, imaging techniques (CT, MRI, SPECT) can be used to assess treatment response and detect radiation-induced lesions and recurrent tumors. Optical spectroscopy has also been used for detecting radiation damage (Lin et al. 2005). The F_{500}nm spectral peak allows accurate selection of tissues for biopsy in evaluating patients with new, contrast enhancing lesions in the setting of previous irradiation. This peak is highly correlated with a histological pattern of radiation injury. Deep lesions require a stereotactic biopsy to be conclusive. Also, much of the radiation effect is mediated by acute and chronic inflammatory cellular reactions. Biopsy samples supplement pathological differentiation of radiation effect from tumor progression. It should be noted that most of the biopsies show radionecrosis as well as scattered tumor cells.

Women treated with therapeutic chest radiation may develop cancer. This possibility becomes exceedingly serious considering that 50,000–55,000 women in the United States have been treated with moderate to high-dose chest radiation (~20 Gy). This possibility is much more serious for pediatric or young adult cancer patients, because these women are at a significantly increased risk of breast cancer and breast cancer mortality following cure of their primary malignancy (Martens et al. 2008). A recent study also indicates that such young women develop breast cancer at a young age, which does not appear to plateau (Henderson et al. 2010). In this high risk population, ironically there is a benefit associated with early detection. In other words, young women with early stage breast cancer following chest radiation have a high likelihood for favorable outcome, although life-long surveillance is needed.

Presently, although approximately 80% of the children with cancer are cured, the curative therapy could damage a child's developing organ system; for example, cognitive deficits following cranial radiotherapy are well known. Childhood survivors of malignant diseases are also at an increased risk of primary thyroid cancer (Sigurdson et al. 2005). The risk of this cancer increases with radiation doses up to 20–29 Gy. In fact, exposure to radiation therapy is the most important risk factor for the development of a new CNS tumor in survivors of childhood cancer, including leukemia and brain tumors. The higher risk of subsequent glioma in children subjected to medical radiation

at a very young age reflects greater susceptibility of the developing brain to radiation. The details of the dose-response relationships, the expression of excess risk over time, and the modifying effects of other host and treatment factors have not been well defined (Neglia et al. 2006).

A recent study indicates that childhood brain tumor survivors are at an increased risk of late endocrine effects, particularly the patients treated with cranial radiation and diagnosed at a younger age (Shalitin et al. 2011). Among children with cancer, the application of radiotherapy, therefore, should not be taken lightly, and it should be administered only when absolutely necessary to successfully treat the primary tumor. When radiotherapy is administered, use of the minimum effective dose tends to minimize the risk of second CNS neoplasms (late effect). Prolonged follow-up of childhood cancer survivors (particularly those treated with radiation) is necessary because of the long period between treatment and the development of malignancy. This practice should be a part of the effective therapy of the primary disease.

It is well established that radiation doses are related to risk for subsequent malignant neoplasms in children with Hodgkin's disease. It has been reported that increasing radiation dose was associated with increasing standardized incidence ratio ($p=0.0085$) in survivors of childhood Hodgkin's disease (Constine et al. 2008). Approximately, 75% of subsequent malignancies occurred within the radiation field. Although subsequent malignancies occur, for example, in breast cancer survivors in the absence of radiotherapy, the rise increases with radiation dose.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, chemotherapy or hormonal therapy or a combination of these therapies? Although the conventional belief is that cancer represents an "arrow that advances unidirectionally", it is becoming clear that for cancer to progress, it requires cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression, and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Prostate Cancer

There were an estimated 217,730 new cases of prostate cancer in the United States in 2010 with 32,050 deaths, making it the second leading cause of cancer deaths in men. Currently, there are more than 2,000,000 men in the United States who have had radical or partial prostate surgery performed. Considering this huge number of prostate surgeries and the absence of a cumulative outcome data, it seems appropriate to carefully examine the benefits of radical surgery, especially in younger men.

Clinical prostate cancer is very rare in men of the ages younger than 40 years. In this age group the frequency of prostate malignancy is one in 10,000 individuals. Unfortunately, the incidence of malignancy increases over the ensuing decades, that is, the chance of prostate malignancy may reach to one in seven in men between the ages of 60 and 79 years. Reactive or aging-related

alterations in the tumor microenvironment provide sufficient influence, promoting tumor cell invasion and metastasis. It has been shown that nontumorigenic prostate epithelial cells can become tumorigenic when cocultured with fibroblasts obtained from regions near tumors (Olumi et al. 1999).

Prostate cancer treatment is one of the worst examples of overtreatment. Serum prostate specific antigen (PSA) testing for the early detection of prostate cancer is in wide use. However, the benefit of this testing has become controversial. The normal cut-off for serum levels of PSA is 4 ng/ml, so a man presenting with a PSA above this level is likely to require a rectal biopsy, but only in 25% of men with serum levels of PSA between 4 and 10 ng/ml have cancer (Masters 2007). The PSA threshold currently being used for biopsy ranges between 2.5 and 3.4 ng/ml. Up to 50% of men presenting with prostate cancer have PSA levels within the normal range. It is apparent that screening of prostate cancer using PSA has a low specificity, resulting in many unnecessary biopsies, particularly for gray zone values (4–10 ng/ml). According to one point of view, the risks of prostate cancer overdetection are substantial. In this context, overdetection means treating a cancer that otherwise would not progress to clinically significant disease during the lifetime of the individual. Overdetection results in overtreatment. The advantages and limitations of PSA test in diagnosing prostate cancer were reviewed by Hayat (2005, 2008).

Androgen deprivation therapy (ADT) is an important treatment for patients with advanced stage prostate cancer. This therapy is carried out by blocking androgen receptor or medical or surgical castration. Although ADT is initially very effective, treated tumors inevitably progress to androgen-independent prostate cancer (AIPC); which is incurable. One possible mechanism responsible for the development of AIPC is modulation of the tissue microenvironment by neuroendocrine-like cancer cells, which emerge after ADT (Nelson et al. 2007).

Recently, Pernicova et al. (2011) have further clarified the role of androgen deprivation in promoting the clonal expansion of androgen-independent prostate cancer. They reported a novel linkage between the inhibition of the androgen receptor activity, down-regulation of S-phase kinase-associated protein 2, and the formation of secretory, senescent cells in prostate tumor cells. It is known that several components of the SASP secretome, such as IL-6, IL-8, KGH, and epidermal growth factor, are capable of transactivating androgen receptor under androgen-depleted conditions (Seaton et al. 2008). It needs to be pointed out that androgen deprivation therapy, used in high-risk patients with prostate cancer, may cause reduced libido, erectile dysfunction, fatigue, and muscle loss; osteoporosis is also a late complication. Therefore, periodic bone density scanning needs to be considered.

Recently, the FDA cleared the use of NADiA (nucleic acid detection immunoassay) ProsVue prognostic cancer test. This proprietary nucleic acid detection immunoassay technology identifies extremely low concentrations of proteins that have not been routinely used as a diagnostic or prognostic aid. It is an in vitro diagnostic assay for determining the rate of change of serum total PSA over a period of time. The assay can quantitate PSA at levels <1 ng/ml. This technique can be used as a prognostic marker, in conjunction with clinical

evaluation, to help identify patients at reduced risk for recurrence of prostate cancer for years following prostatectomy. It targets the early detection of proteins associated with cancer and infectious diseases. This technique combines immunoassay and real-time PCR methodologies with the potential to detect proteins with femtogram/ml sensitivity (10–15 g/ml). Additional clinical information is needed regarding its usefulness in predicting the recurrence.

A significant decrease in the risk of prostate cancer-specific mortality is observed in men with few or no comorbidities. Indeed, active surveillance in lieu of immediate treatment (surgery or radiation, or both) is gaining acceptance. Most men with prostate cancer, even those with high-risk disease, ultimately die as a result of other causes (Lu-Yao et al. 2009). Debate on this controversy is welcome, but narrow opinions and facile guidelines will not lead to facts and new information; men worldwide deserve it (Carroll et al. 2011). Automatic linking of positive diagnosis with treatment, unfortunately, is a common clinical practice. Unfortunately, even men who are excellent candidates for active surveillance in the United States often undergo some treatment. Deferment of treatment is advised in men with low-risk disease, especially of a younger age.

Active surveillance is proposed for patients with low-risk prostate cancer in order to reduce the undesirable effects of overdiagnosis. Prostate specific antigen serum level lower than 10 ng/L and Gleason score lower than 7 are the main criteria to select patients for active surveillance. The correct use of these two criteria is essential to differentiate between aggressive and nonaggressive prostate cancer. Autopsy studies indicate that approximately one out of three men older than 50 years show histological evidence of prostate cancer (Klotz 2008). Thus, a large proportion of prostate cancers are latent, never destined to progress, or affect the life of the patient. It is estimated that the percentage of low-risk prostate cancer is between 50 and 60% of newly diagnosed cases. A large number of patients die having prostate cancer, but not because of this cancer (Filella et al. 2011).

First whole genome sequences of prostate tumors were recently published online in *Nature* journal (vol. 470: 214–220, 2011). This study revealed that rather than single spelling errors, the tumor has long "paragraphs" of DNA that seem to have broken off and moved to another part of the genome (rearrangement of genes), where they are most active. These portions of DNA contain genes that help drive cancer progression. The mutated genes involved include *PTEN*, *CADM2*, *MAG12*, *SPOP*, and *SPTA1*. This information may lead to the development of more efficient, less invasive ways to diagnose and treat this cancer. Such information, in addition, should lead to personalized therapeutics according to sequencing results of different gene mutations or chromosomal rearrangements. The urgent need of such studies becomes apparent considering the huge number of new cases of prostate problems reported every year.

In contrast to prostate cancer, cardiovascular disorders take the heavier toll of life. In other words, the risk of death for men in the United States between the ages of 55 and 74 years due to cardiovascular disease surpasses that of prostate cancer. Cardiovascular disease is the most common of the chronic non-communicable diseases that impact global mortality. Approximately,

30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by cardiovascular disease alone.

In conclusion, initial treatment with standard surgery, irradiation, chemotherapy, or hormonal therapy, or combination of these protocols can result in both local and systemic sequelae. Therefore, surveillance for late recurrence and secondary primary malignancies is recommended for most cancer patients. Patients with breast, lung, prostate, colorectal, and head and neck cancers constitute the largest groups requiring long-term monitoring and follow-up care.

Eric Hayat

References

Amirjamshidi A, Abbassioun K (2000) Radiation-induced tumors of the central nervous system occurring in childhood and adolescence. Childs Nerv Syst 16:390–397

Carroll PR, Whitson JH, Cooperberg MR (2011) Serum prostate-specific antigen for the early detection of prostate cancer; always, never, or only sometimes? J Clin Oncol 29:345–346

Constine LS, Tarbell N, Hudson MM et al. (2008) Subsequent malignancies in children treated for Hodgkin's disease; associations with gender and radiation dose. Int J Rad Oncol Biol Physol 72:24–33

Endoh M, Iwasaki Y, Koyanagi I, Hida K, Abe H (1998) Spontaneous shrinkage of Iumbosacrallipoma in conjunction with a general decrease in body fat: case report. Neurosurgery 43(1):150–151; discussion 151–152

Filella X, Alcover J, Molina R. (2011) Active surveillance in prostate cancer: the need to standardize. Tumor Biol 32:839–843

Guin P, Gilbert E, Jones B (1969) Incidental neuroblastoma in infants. Am J Clin Pathol 51:126–136

Hayat MA (2005) Prostate carcinoma: an introduction. In: Immunohistochemistry and in situ hybridization of human carcinomas, vol 2. Elsevier, San Francisco, pp 279–297

Hayat MA (2008) Prostate carcinoma. In: Methods of cancer diagnosis, therapy, and prognosis, vol 2. Springer, New York, pp 391–396

Henderson TO, Amsterdam A et al. (2010) Surveillance for breast cancer in women treated with chest radiation for a childhood, adolescent or young adult cancer: a report from Children's Oncology Group. Ann Intern Med 152:1–22

Hero S, Simon T, Spitz R, Ernestus K, Gnekow A, Scheel-Walter H, Schwabe D, Schilling F, Benz-Bohm G, Berthold F (2008) Localized infant neuroblastomas often show spontaneuous regression: results of the prospective trials NB95-S and NB 97. J Clin Oncol 26:1504–1510

Klotz L (2008) Low-risk prostate cancer can and should often be managed with active surveillance and selective delayed intervention. Nat Clin Pract Urol 5:2–3

Lin W-C, Mahadevan-Jansen A, Johnson MD, Weil R, Toms SA (2005) In vivo optical spectroscopy detects radiation damage in brain tissue. Neurosurgery 57:518–525

Lu-Yao GL, Albertsen PC, Moore DF et al (2009) Outcomes of localized prostate cancer following conservative management. JAMA 302:1202–1209

Masters JR (2007) Clinical applications of expression profiling and proteomics in prostate cancer. Anticancer Res 27:1273–1276

Mertens AC, Liu Q, Neglia JP et al (2008) Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 100:1368–1379

Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ et al (2006) New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst 98:1528–1537

Nelson EC, Cambio AJ, Ok JH, Lara PN Jr, Evans CP (2007) Clinical implications of nueroendocrine differentiation in prostate cancer. Prostate Cancer Prostatic Dis 10:6–14

Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR (1999) Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Res 59:5002–5011

Parent AD (1990) Late complications of radiation-induced neoplasms. Neurosurgery 26:1090–1091

Pernicova Z, Slabakova E, Kharaishvill G, Bouchal J, Kral M, Kunicka Z, Machalam M, Kozubik A, Soucek K (2011) Androgen depletion induces senescence in prostate cancer cells through down-regulation of SKp2. Neoplasia 13:526–536

Pettorini BL, Park Y-S, Caldarelli M, Massimi L, Tamburrini G, DiRocco C (2008) Radiation induced brain tumors after central nervous system irradiation in childhood: a review. Child's Nerv Syst 24:793–805

Rubsam K, Flaig MJ, Ruzicka T, Prinz JC (2011) Erythema marginatumhemorrhagicum: a unique cutaneous side effect of sorafenib. J Am Acad Dermatol 64:1194–1196

Seaton A, Scullin P, Maxwell PJ, Wilson C, Pettigrew J, Gallagher R, O'Sullivan JM, Johnston PG, Waugh DJ (2008) Interleukin-8 signaling promotes androgen-independent proliferation of prostate cancer cells via induction of androgen receptor expression and activation. Carcinogenesis 6:1148–1156

Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Philip M (2011) Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr 76:113–122

Sigurdson AJ, Ronckers CM, Mertens AC et al (2005) Primary thyroid cancer after a first tumor in childhood (the childhood cancer survivor study): a nested case-control study. Lancet 365:2014–2023

Ursino MG, Poluzzi E, Caramella C, DePonti F (2011) Excipients in medicinal products used in gastroenterology as a possible cause of side effects. Regul Toxicol 60:93–105

Preface

Little is known regarding the factors that regulate entry of residual cancer into a dormant state or the subsequent reinitiation of growth. The prognostic factors present in the primary tumor are imprecise in predicting which patients will be cured by local treatment and which patients will have metastatic recurrence.

Although much progress has been made in identifying many of the genetic factors that contribute to cancer development, much remains to be learned about genetic and epigenetic factors that influence both tumor dormancy and the growth of metastasis. A majority of us have in situ tumors that may remain dormant or may progress into a lethal form of cancer; the former are prevented from recruiting their own blood supply.

This is volume 1 of the multivolume series discussing Tumor Dormancy, Quiescence, and Cellular Senescence. The role of tumor dormancy in a number of diseases, including breast cancer, melanoma, prostate cancer, liver cancer, and lung cancer is discussed. It is also pointed out that quiescent state regulates hematopoietic stem cells and muscle stem cells. The mediation of reversible quiescent state in a subset of ovarian, pancreatic, and colon cancers by the kinase is detailed. Molecular mechanisms underlying stress-induced cellular senescence and accumulation of reactive oxygen species and induction of premature senescence are presented. The importance of the role of microRNASE in oxidative stress-induced apoptosis and senescence and the effect of microRNA as a modulator of cell proliferation in lung cancer are detailed. Suppression of cellular senescence in glioblastoma brain tumor is also explained.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against a terrible human diseases and injuries. It is difficult for a single author to discuss effectively the complexity of diagnosis, therapy, including tissue regeneration. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of cancer cure and tissue regeneration. I hope these goals will be fulfilled in this and other volumes of the series. This volume was written by 60 contributors representing 11 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the readers in these important areas of disease and injury. I respect and appreciate the hard work

and exceptional insight into the role of dormancy, quiescence, and cellular senescence in various diseases and stem cell functions provided by these contributors. The contents of the volume are divided into three subheadings: Dormancy, Quiescence, and Cellular Senescence for the convenience of the readers.

It is my hope that subsequent volumes of the series will join this volume in assisting in the more complete understanding of the major human diseases and their treatments. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure and hopefully prevention. In the light of existing cancer calamity, government funding must give priority to eradicating deadly malignancies over military superiority.

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M.A. Hayat

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Contributors

Ana Banito Cell Proliferation Group, MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College, London, UK

Kevin Blighe Cancer Studies and Molecular Medicine, Robert Kilpatrick CSB (Room 305), Leicester Royal Infirmary, Leicester, UK

Molly L. Bristol Department of Pathology, Virginia Commonwealth University, Richmond, VA, USA

Maurizio C. Capogrossi Laboratorio di Patologia Vascolare, Instituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy

Ann F. Chambers Department of Microbiology and Immunology, University of Western Ontario, London, ON, Canada

R. Charles Coombes Cancer Research UK Laboratories, Department of Oncology, Imperial College, London, UK

Anabelle Decottignies Genetic and Epigenetic Alterations of Genomes, de Duve Institute, Catholic University of Louvain, Brussels, Belgium

Renate Eckel Munich Cancer Registry, Clinic Grosshadern, Ludwig-Maximilians-University, Munich, Germany

Lynne W. Elmore Department of Pathology, Virginia Commonwealth University, Richmond, VA, USA

Rebecca Emeny Munich Cancer Registry (MCR), Clinic Grosshadern, Ludwig-Maximilians-University (LMU), Munich, Germany

Jutta Engel Munich Cancer Registry (MCR), Clinic Grosshadern, Ludwig-Maximilians-University (LMU), Munich, Germany

Emanuela Felley-Bosco Laboratory of Molecular Oncology, Clinic of Oncology, Zurich University Hospital, Zurich, Switzerland

Eileen Friedman Pathology Department, Upstate Medical University, Syracuse, NY, USA

So-ichiro Fukada Laboratory of Molecular and Cellular Physiology, Pharmaceutical Sciences, Osaka University, Suita City, Osaka, Japan

Sayuri Fukui Laboratory for Molecular Developmental Biology, Department of Life Sciences, Meiji University, Kanagawa, Japan

Jesús Gil Cell Proliferation Group, MRC Clinical Sciences Centre, Faculty of Medicine, Imperial College, London, UK

David Guttery Department of Cancer Studies and Molecular Medicine, Infirmary Close, Leicester Royal Infirmary, University of Leicester, Leicester, UK

M.A. Hayat Biology Department, Kean University, Union, NJ, USA

Trang Hoang University of Montreal, Montreal, Canada

Dieter Hölzel Munich Cancer Registry (MCR), Clinic Grosshadern, Ludwig-Maximilians-University (LMU), Munich, Germany

Peter J. Hornsby Department of Physiology and Sam and Ann Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center, San Antonio, TX, USA

Ji-Won Jung Division of Intractable Diseases, Center for Biomedical Sciences, Korea National Institute of Health, Yeonje-ri, Gangoe-myeon, Chungbuk, South Korea

Kyung-Sun Kang Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, Seoul, South Korea

Ekkehard Kasper Department of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Hiroshi Kondoh Department of Geriatric Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Valery Krizhanovsky Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

Seunghee Lee Adult Stem Cell Research Center, College of Veterinary Medicine, Seoul National University, Seoul, South Korea

Matilde E. LLeonart Department of Geriatric Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Michael M. Lizardo Department of Medical Biophysics, University of Western Ontario, London, ON, Canada

Ian C. MacDonald Department of Medical Biophysics, University of Western Ontario, London, ON, Canada

Salvador Macip Department of Biochemistry, University of Leicester, Leicester, UK

Alessandra Magenta Laboratorio di PatologiaVascolare, Instituto Dermopatico dell'Immacolata, IRCCS, Rome, Italy

Ionica Masgras Department of Biochemistry, University of Leicester, Leicester, UK

Takumi Mikawa Department of Geriatric Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Kenichi Miyata Laboratory for Molecular Developmental Biology, Department of Life Sciences, Meiji University, Kanagawa, Japan

Vincent L. Morris Department of Microbiology and Immunology, University of Western Ontario, London, ON, Canada

George R. Nahas New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

Hiroaki Ohdaira Laboratory for Molecular Developmental Biology, Department of Life Sciences, Meiji University, Kanagawa, Japan

Karen Page Cancer Studies and Molecular Medicine, Robert Kilpatrick CSB (Room 305), Leicester Royal Infirmary, Leicester, UK

Jacqueline M. Park New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

Dean B. Percy Department of Medical Biophysics, University of Western Ontario, London, ON, Canada

Zuzana Pernicová Department of Cytokinetics, Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

Center of Biomolecular and Cellular Engineering, International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic

Department of Experimental Biology, Faculty of Sciences, Masaryk University, Brno, Czech Republic

Tamer Rabie School of Life Sciences, University of Hertfordshire, Hatfield, UK

Pranela Rameshwar New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA

Pradip Raychaudhuri Department of Biochemistry and Molecular Genetics, Cancer Center, University of Illinois, Chicago, IL, USA

Nilotpal Roy Department of Biochemistry and Molecular Genetics, Cancer Center, University of Illinois, Chicago, IL, USA

Shanti Rojas-Sutterlin University of Montreal, Montreal, Canada

Masaki Sekiguchi Laboratory for Molecular Developmental Biology, Department of Life Sciences, Meiji University, Kanagawa, Japan

Jacqui Shaw Cancer Studies and Molecular Medicine, Robert Kilpatrick CSB (Room 305), Leicester Royal Infirmary, Leicester, UK

Karel Souček Department of Cytokinetics, Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

Center of Biomolecular and Cellular Engineering, International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic

Rolf A. Stahel Laboratory of Molecular Oncology, Clinic of Oncology, Zurich University Hospital, Zurich, Switzerland

Justin Stebbing Cancer Studies and Molecular Medicine, Leicester Royal Infirmary, Leicester, UK

Lisa-Marie Sturla Department of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Thierry Tchénio LBPA, UMR8113 ENSC-CNRS, Ecole Normale Superieure de Cachan, Cachan, Cedex, France

Petr Vaňhara Department of Cytokinetics, Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Kirsten H. Walen Viral and Rickettsial Disease Laboratory, California Department of Health Services, Richmond, CA, USA

Uwe Wollina Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany

Masahiko Yamaguchi Laboratory of Molecular and Cellular Physiology, Pharmaceutical Sciences, Osaka University, Suita City, Osaka, Japan

Kenichi Yoshida Laboratory for Molecular Developmental Biology, Department of Life Sciences, Meiji University, Kanagawa, Japan

Pascal Zinn Department of Neurosurgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Part I

Tumor Dormancy

Dormancy, Quiescence, and Cellular Senescence

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M.A. Hayat

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Keywords

Dormancy • Quiescence • Cellular senescence • Hibernation

Dormancy (Hibernation)

Dormant tumors are defined as microscopic (diameter of ~1 mm) human cancers, either primary, recurrent or metastatic, and can remain in an asymptomatic, non-detectable, and occult form for a long period of time. In other words, this phenomenon of long-term persistence of cancer cells that do not grow is called tumor dormancy (hibernation). Patients can carry cancer cells for a very long time, in some cases indefinitely without relapsing. Based on tumor type and stage, the dormancy period may range from years to even decades between the initial therapy and the occurrence of relapsed tumors or recurrent metastatic disease. As seen in autopsies of adults who have died from non-cancer causes, tumors can be dormant as long as a lifetime without ever becoming clinically evident. Dormant tumors represent the earliest stages in tumor development and are highly prevalent in humans. This phenomenon occurs early in tumor development, indicating that tumor growth is not continuous, and may pass through a long period of subclinical equilibrium. Dormant tumors have been identified in many organs, including thyroid, breast, and prostate, and are being described as cancer without disease.

M.A. Hayat (✉)
Biology Department, Kean University,
Union, NJ 07083, USA
e-mail: ehayat@kean.edu

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Therefore, clinical relevancy of tumor dormancy is important.

Tumor dormancy is attributed to the long latency periods frequently observed in cancer patients between the primary diagnosis and treatment and the potential clinical evidence of local recurrence or distinct metastasis. It may happen after treatment in the form of minimal residual disease. Late relapse after treatment is well-documented in breast cancer patients, and dormancy is a common phenomenon in these patients. These dormant micrometastases escape the treatment and can lead to late relapse.

It is possible to induce tumor dormancy in immunoincompetent hosts by prior immunization against tumor cells. Equilibrium between immune response and tumor cells leads to a long-term tumor dormancy. This equilibrium is also observed early in tumor development, and adaptive immunity may help contain tumor outgrowth. However, after variable times, tumor dormancy ends with the disease progress. The presence of immunoescape mechanisms in tumor cells from relapsing patients also suggests that the immune equilibrium which maintained dormancy has broken down. Identification of such mechanisms would offer new leads to favor the immune balance, and thus clear minimal residual disease from patients.

Although the clinical implication of tumor dormancy in prevention and treatment of tumors has intrigued the medical community for years, there is a paucity of molecular markers and mechanistic understanding. A critical limitation confronting the field of tumor dormancy is the lack of suitable experimental models as well as consistent and abundant sources of dormant tumor cells. It is still unclear what keeps these tumors in a microscopic size, preventing their expansion, and what triggers their proliferation. Genetic and epigenetic factors responsible for these two phases will be explained in the proposed four volumes of Tumor Dormancy and Cellular Quiescence.

Tumor dormancy is the result of angiogenesis suppression and some other environmentally imposed limitations to growth. Dormant tumors can become malignant and aggressive after undergoing an angiogenic switch, receiving appropriate molecular signals, and overcoming genetic and environmental constraints to tumor progression. Understanding how to prevent conversion of such lesions from harmless dormant nodules into malignant tumors may lead to the development of improved cancer treatments. Preventing the development of metastases is perhaps achievable more readily than curing patients with overt metastases. It is estimated that two out of three humans never develop cancer.

As stated above, angiogenesis plays a major role in the growth promotion of dormant micrometastasis because blood vessels deliver oxygen and nutrients into the tumor microenvironment. However, it is accepted that human tumors can arise in the absence of angiogenic activity and exist in a microscopic dormant stage for months to years without neovascularization. The disease stage of cancer, therefore, seems to be a late event in tumor development.

Cellular Quiescence

Hematopoietic stem cells are responsible for blood cell production throughout the lifespan of an organism. Millions of blood cells are used every second in humans, and hematopoietic cells must replenish these cells. The properties of these cells include relative quiescence, self-renewal capacity, and the ability to differentiate into multiple lineages. In fact, adult hematopoietic stem cells exist in a relatively quiescent state in the bone marrow microenvironment to fulfill long-term self-renewal and multilineage differential functions, an event that is tightly regulated by extrinsic and intrinsic cues. In general, hematopoietic stem cells either stay in quiescence or proliferate toward differentiation for the production of mature blood cells or toward self-renewal for giving rise to themselves. In other words, the state of quiescence in hematopoietic stem cells is reversible and differs from quiescence associated with senescence, differentiation, or growth factor deprivation.

In order to both maintain a supply of mature blood cells and not to exhaust themselves throughout the lifetime of an individual, under steady state, most hematopoietic stem cells remain quiescent, and only a small number enters the cell cycle. However, in response to hematopoietic stress, such as blood loss, these cells exit quiescence and rapidly expand and differentiate to repopulate the peripheral hematopoietic compartments. When quiescence is disrupted, hematopoietic stem cells display defective maintenance in G_0 phase of cell cycle, leading to premature exhaustion of the stem cell pool under conditions of hematopoietic stress, impaired self-renewal, and loss of competitive repopulating capacity. This eventually causes hematological failure. Quiescence of hematopoietic stem cells is critical not only for protecting the stem cell compartment and sustaining stem cell pool during late periods, but also for protecting stem cells by minimizing their accumulation of replication-associated mutations.

As stated above, understanding the regulation of hematopoietic stem cells quiescence is of great importance not only for undertaking the physiological functions of these cells, but also pathological origins of many related disorders. Under standing quiescence regulation in hematopoietic cells will also enable directed manipulation of the function of these cells, which will improve the efficiency of bone marrow transplantation and treatment of various hematopoietic disorders. The current advances in quiescence regulators and related pathways for hematopoietic stem cells will be discussed.

Relative quiescence is a defining characteristic of hematopoietic stem cells, while their progeny has dramatic proliferative ability and inexorable progress toward terminal differentiation. The balance between quiescence and proliferation is tightly controlled by both hematopoietic stem cell intrinsic mechanisms and the interaction of these cells with their specific microenvironments (known as stem cell niches). This control is carried out through cell-cell, cell-extracellular matrix, and receptor-ligand interactions, and involves both positive and negative regulators. This information increases the efficiency of both bone marrow transplantation and treatment for hemato-deficiency and hematopoietic cancers.

Despite the enormous proliferative capacity of hematopoietic stem cells, most of these cells reside in a non-cycling quiescent state at any given time point. This ensures lifelong-hematopoiesis and protection of hematopoietic stem cell pool from myelotoxic insult and premature exhaustion under conditions of hematopoietic stress. The naturally quiescent state of hematopoietic stem cells is controlled by negative regulators of cell proliferation. For example, endogenous levels of the cyclin-dependent kinase inhibitor p21 is crucial in order to maintain quiescence of hematopoietic stem cells and to protect stem cell pool from exhaustion during stressed conditions. In the absence of p21, increased cell cycling leads to stem cell exhaustion and hematopoietic failure. Under conditions of stress, restricted cell cycling is crucial to prevent premature stem cell depletion and hematopoietic death.

Is Tumor Dormancy Clinically Relevant?

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Dieter Hölzel, Renate Eckel, Rebecca Emeny, and Jutta Engel

Contents

Abstract

Late progressions can be observed with all solid cancers. With the term dormancy a potential cause is offered for these observations. In this article we present a point of view from a cancer registry and analyze clinical data about metastasis (MET)-free survival, post-MET survival, and overall survival to quantify late progressions. If dormancy is a characteristic of the MET process then all types of MET, including local recurrences, regional MET in the lymph nodes, or distant MET in organs, must be considered. First, it can be deduced from clinical data that the initiation of secondary foci is a temporally sequential process, which can begin years, or days, before a R0-resection. Second, the growth time of these different MET can be estimated from the survival time and generally takes years. Third, remarkable growth differences of these secondary foci must be considered which already can be correlated, in part, with molecular subgroups. Within these subgroups, growth is quite homogeneous. These three factors of MET growth largely explain the variability of observed relapse-free survival times. In contrast, the term dormancy is vague. It is an appealing metaphor with strong analogies such as circulating tumor cells of hematological neoplasms or dormant tumor cells in transplanted organs. But late MET can be the result of a number of very different causes. Where a disseminated tumor cell

D. Hölzel (✉) • R. Eckel • R. Emeny • J. Engel
Munich Cancer Registry (MCR), Clinic Grosshadern, Ludwig-Maximilians-University (LMU), D-81377 Munich, Germany
e-mail: hoe@ibe.med.uni-muenchen.de

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lodges, in niches or in specific organs, how long a tumor cell circulates before settling and establishing a focus, or whether the tumor cell has differential growth or even cell quiescence phases, determined by a dynamic equilibrium of divisions and apoptosis, could all contribute to the differential occurrence of MET. MET detection may also be delayed by adjuvant treatment, and all causal variants can be functionally equivalent, delay MET diagnosis, and appear as a slow growing tumor. But time of initiation and the growth of tiny foci are inaccessible and impossible to measure in humans. Therefore, the term tumor dormancy conceals our ignorance of the multi-step MET process. Because it is such a cloudy and elusive term it cannot be clinically relevant. It is a hypothetical construct that fails to offer new research perspectives, additional prognostic factors or an opportunity for novel therapy.

Keywords
Tumor dormancy • Model • Breast cancer • Colorectal cancer • Metastasization • Long-term survial

Introduction

Tumor progression after an above-average, long, metastasis-free survival can be observed in all solid tumors. In many publications frequencies, characteristics, and survival of intact or fragmented tumor cells (TC) in blood, bone marrow, lymph nodes (LN) and organs are described. These facts are correlated with progressions and should show the relevance of dormant TC for late metastases (MET) (Meng et al. 2004; Naumov et al. 2002; Uhr and Pantel 2011; Weinberg 2008). The observation of a bimodal distribution of the MET-free survival time in breast cancer (BC) in one cohort study was already interpreted in 1990 as a result of a rest period of disseminated TC before growing up to a detectable MET (Demicheli et al. 2010). Since then, longer MET-free survival times for BC, e.g. beyond 5 years, are connected today with the term "TC dormancy" (Aguirre-Ghiso 2007).

In the following pages we describe, with the results of experimental and clinical studies, and with data from a cancer registry, the growth of secondary foci with MET-free, post-MET and overall survival. The Munich Cancer Registry (MCR) collects data about local, regional and distant relapses during the course of disease as important outcome criteria (Munich Cancer Registry). We present population-based data from patients who were registered from 1988 to 2009, did not have earlier or synchronous second malignancies and were followed-up during this period. It is important to note that the data about the courses of disease are not complete and therefore the percentage of primary MET of all cancer-related death is slightly overestimated. Additionally, MET is diagnosed during the course of disease if symptoms require clarification or a palliative chance exists. Therefore, any MET pattern is a selected perspective. Nevertheless, population-based data can add generally valuable aspects to the alternative view of heavily selected study cohorts.

Correlations of MET relapses with prognostic factors of the primary tumor (PT) reveal growth differences and an order of late progressions. Well known survival curves with adjuvant treatments describe further aspects of the MET process. Nonetheless, such a registry-based viewpoint does not contribute new results. Only additional facts can be considered and supplemental questions arise with our attempt to align known clinical outcomes with the hypothesis of dormant TC. But we have not been able to achieve this: therefore the current clinical relevance of the term tumor dormancy has to be questioned.

Basic Characteristics of the MET Process

Generally, MET is a secondary focus established by a disseminated TC of the PT. MET foci can arise locally, near the PT, regionally in the LN, or in distant organs. They are the result of a complex multistep process (Talmadge and Fidler 2010; Valastyan and Weinberg 2011). Three characteristics of the MET-process will be distinguished for the sake of reasoning (Hölzel et al. 2010); the temporally sequential initiation of MET, the