Sixteenth Annual Pezcoller Symposium: Stem Cells and Epigenesis in Cancer

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Abstract

In the postgenomic era of cancer biology, it is becoming increasingly evident that epigenetic controls of gene expression play an important role in determining the phenotype of cancer cells, also indicating the possibility of restoring epigenetically a normal phenotype in cancer cells. Related to these mechanisms of control and their dynamic changes during carcinogenesis and tumor progression are the phenomena determining the relationships between stem cells and cancer cells. This symposium focused on epigenetic mechanisms affecting cancer development and possibly providing a basis for intervention. The basic biology of stem cells and the relationships between stem cells and cancer were discussed. Epigenetic control mechanisms affecting gene expression with emphasis on DNA methylation and histone function were considered. Therapeutic strategies stemming from the knowledge acquired in the basic topics discussed also were outlined.

Stem Cells: Basic Biology

George Daley indicated that bone marrow hematopoietic stem cells (HSCs) are widely used to manage genetic and malignant disease and are important targets for gene therapy. Harnessing embryonic stem (ES) cells as a source of HSCs would facilitate genetic modification of stem cell populations precisely by homologous recombination, enable basic investigation into genetic and epigenetic influences on hematopoietic cell function, and empower preclinical models for gene and cellular therapy. The question was asked whether an HSC could be identified clonally in differentiating cultures of ES cells. Because homeobox gene b4 (hoxb4) is expressed in bone marrow HSCs but not in yolk sac, hoxb4 was transiently activated in ES cells, cultured, transplanted into irradiated syngeneic mice and observed for long-term lymphoid-myeloid hematopoiesis in primary and secondary recipients, thereby showing definitive HSC production from ES cells. Together with Rudolf Jaenisch’s laboratory, ES cells were used to model therapeutic HSC transplation to manage genetic immunity deficiency by therapeutic cloning. Nuclear transfer from tail-tip fibroblasts of the recombination activating gene 2⁻/⁻ (rag2⁻/⁻) mouse was carried out to produce cloned embryos, and ES cell lines were harvested that were isogenic to the donor mouse (ntESrag2⁻/⁻). One of the two defective rag2 alleles was repaired by homologous recombination to generate the ntESrag2⁻/+ line. Partial restoration of the immune deficiency of rag2⁻/⁻ mice was achieved by transplantation of HSCs derived in vitro from the ntESrag2⁻/+ line. Recent work performed in collaboration with Leonard Zon’s group on the cdx4 homeobox gene, which acts upstream of hox genes to promote blood formation in the zebrafish and the mouse, showed that activation of the cdx4/hoxb4 pathway in murine ES cells enhances blood development, promotes high degrees of hematopoietic chimerism in irradiated animals, and shows stable patterns of lymphoid-myeloid reconstitution.

Gordon Keller discussed his studies aimed at clarifying the mechanisms of induction of mesoderm versus endoderm in culture. The green fluorescent protein (GFP) cDNA was targeted to the mesodermal gene, brachyury (bry). Using these ES cells (GFP-Bry), it was possible to track the formation of mesoderm and isolate mesodermal cells by sorting GFP⁺ cells from the differentiation cultures. It was shown that mesoderm that generates hematopoietic and vascular cells is distinct from mesoderm that gives rise to the cardiac lineage. This shows that cell fates are established early in development. Endoderm derivatives, including hepatocyte-like cells, lung cells, and gut tissue, also developed from a bry⁺ progenitor. It was shown that mesoderm and endoderm might develop from a common mesendoderm progenitor.

Austin Smith focused on the elucidation of the molecular machinery of stem cell self-renewal, the process whereby a stem cell suppresses differentiation during a given round of cell division but retains that potential for future divisions. This process is studied in pluripotent ES cells and in lineage-restricted neural stem (NS) cells that can form neurons or glia but not other germ layers. These two stem cell types have extensive multiplicative capacity in vitro. ES cell identity is governed by the specialized homeobox binding protein family (POU) transcription factor Octamer binding protein (Oct-4) and the divergent homeodomain protein pluripotency gene (nanog). Genetic deletion of either of these components results in a loss of pluripotent character and differentiation into extraembryonic fates. Overexpression of nanog but not Oct-4 is sufficient to sustain ES cell self-renewal. ES cells can readily be derived de novo from preimplantation embryos in the absence of serum using leukemia inhibiting factor (LIF) plus bone morphogenetic protein (BMP). Overexpression of Oct-4 has effects equivalent to those of LIF withdrawal, and nanog bypasses LIF requirements in the presence of serum. Thus, intrinsic determinants define and restrict lineage potential, and extrinsic signals are needed to actively stop differentiation.

Stem Cells and Cancer

Michael Clarke discussed the epigenetic regulation of self-renewal in normal and cancer stem cells, considering that emerging evidence suggests that similar molecular mechanisms regulate self-renewal in normal stem cells and their malignant counterparts. In the adult, the HSC population has two fundamental properties: HSCs need to self-renew to maintain the stem cell pool and the total number of HSCs is under strict genetic regulation, and HSCs must undergo differentiation to maintain a constant pool of mature cells in normal conditions. Differences in self-renewal pathways between cancer stem cells and normal stem cells that allow for the continuous expansion of self-renewing cells can be exploited to more effectively manage cancer; self-renewal is not synonymous with proliferation. Self-renewal is a cell division in which one or both of the daughter cells remain undifferentiated and retain the ability to give rise to another stem cell that has
the same capacity to proliferate as the parental cell. In contrast, proliferation does not require either daughter cell to be a stem cell or to retain the ability to give rise to a differentiated progeny. Normal stem cells share with at least some of the cancer cells within a tumor the ability to replicate without losing the capacity to proliferate. Some oncogenes function to promote stem cell self-renewal. Adult stem cells of the hematopoietic and neuronal tissues express the proto-oncogene bmi-1, a member of the polycomb family involved in the epigenetic repression of target genes. Tumorigenic and nontumorigenic subsets of cancer cells recently have been isolated from human breast cancers, providing, the first direct evidence for cancer stem cells in solid tumors. A xenograft model for human breast cancer was developed that allowed breast cancer tumors isolated directly from patients to be passaged reliably in vivo. In cancer cells isolated from most patients' tumors, tumorigenic cells could be distinguished from nontumorigenic cancer cells based on surface marker expression. Limiting-dilution assays showed that as few as 100 tumorigenic cancer cells were able to form tumors, whereas tens of thousands of the other populations of cancer cells failed to form tumors in nonobese diabetic/severe combined immunodeficient mice (NOD/SCID). Thus, tumorigenic breast cancer cells from most tumors appear to exhibit the properties of cancer stem cells, which may represent an important target for therapy.

Luis Parada discussed the cellular origin of Schwann cell tumor and glioblastoma in mice. Evidence was obtained that Schwann cell precursors develop benign tumors, which in turn develop malignant tumors: In this model, stem cell lines were identified as done by others in hematopoietic systems. A mouse glioblastoma was developed that is similar to human glioblastoma in its different stages. A molecular analysis of the mouse tumor confirmed the similarities between mouse and human tumors and revealed that ablation of P53 and Neurofiromin (NFI), a negative regulator of k-ras, is sufficient to induce glioblastoma. A sequence dependence of tumor formation on NFI and P53 ablation was detected, with greatest effect when P53 ablation preceded that of NFI. Through analysis of a variety of criteria, concrete evidence was obtained that stem cell could account for the origin of glioblastoma and that differential therapies might be developed.

John Dick discussed the role of stem cells in leukemogenesis. The concept that only a minor subpopulation of so-called cancer stem cells is responsible for maintenance of the neoplasm emerged ~50 years ago with the best evidence coming from the hematologic malignancies. With the advent of clonogenic assays for normal hematopoietic progenitors, it became possible to determine that the majority of acute myeloid leukemia (AML) blasts do not proliferate and that only a minor proportion (~1%) of human leukemic cells are clonogenic progenitors [AML-colony-forming units (AML-CFUs)]. Normal HSCs maintain the hematopoietic system throughout life, and stem cell regulation is a critical element in the control of normal hematopoiesis. Repopulation of immune-deficient mice was used to develop a quantitative assay for human stem cells that have been termed SCID repopulation. Repopulation of immune-deficient mice was used to develop a quantitative assay for human stem cells that have been termed SCID repopulation. SCID repopulation was developed that allowed breast cancer tumors isolated directly from patients to be passaged reliably in vivo. In cancer cells isolated from most patients' tumors, tumorigenic cells could be distinguished from nontumorigenic cancer cells based on surface marker expression. Limiting-dilution assays showed that as few as 100 tumorigenic cancer cells were able to form tumors, whereas tens of thousands of the other populations of cancer cells failed to form tumors in nonobese diabetic/severe combined immunodeficient mice (NOD/SCID). Thus, tumorigenic breast cancer cells from most tumors appear to exhibit the properties of cancer stem cells, which may represent an important target for therapy.

Epigenetic Control of Gene Expression

Maarten van Lohuizen outlined the role of Polycomb repressors in the control of stem cell fate. Repressive Polycomb-group (Pc-G) protein complexes and the counteracting Trithorax group (Trx-G) of nucleosome-remodeling factors are involved in the dynamic maintenance of proper gene expression patterns during development, acting at the level of chromatin structure. Developmental targets include the Hox gene clusters but also critical cell cycle regulatory genes, such as the Ink4a/Arf tumor-suppressor locus. Overexpression of the Polycomb gene Polycomb complex protein (Bmi1) promotes proliferation and induces leukemia in cooperation with c-myc and through repression of the Ink4a/Arf tumor-prevention fail-safe mechanism. Conversely, Bmi1 deficiency, as seen in bmi1<−/−> mice, leads to hematopoietic defects and severe progressive neurologic abnormalities. It was shown that in the brain, Bmi1 is essential for proliferation of granule precursor cells (CGNPs) and for maintenance of self-renewal of cortical neural stem cells. Deregulated proliferation of CGNPs, caused by mutations in the Shh signaling pathway in ±25% of cases, leads to medulloblastoma development. Bmi1 is critically required for CGNP proliferation and is a target of the Shh pathway. Gene bmi1 is highly overexpressed in the mouse and human cerebellum and in a majority of primary human medulloblastomas, which display aberrant constitutive-active Shh signaling. Using a conditional knockout approach, an essential role for Polycomb gene (Pc-G) silencing in maintenance of ES cell fate was shown. The Shh morphogen and development signaling pathway is linked to Pc-G regulation, suggesting a conserved role for epigenetic Pc-G repressive complexes acting in a cell-intrinsic manner to allow maintenance of stem cell fate by promoting renewal over differentiation.

Hugh Morgan and Svend Petersen-Mahrt discussed results from the Wolf Reik and Petersen-Mahrt Labs suggesting roles of DNA deamination and methylation in genetic reprogramming and cancer. On the basis of their results in vitro and in an Escherichia coli assay, they suggested that a coupled process of deamination and repair in these tissues could contribute to the wave of active demethylation that occurs in primordial germ cells (PGCs) and oocytes during epigenetic reprogramming. In vitro, they show that the DNA deamination by activation-induced cytidine deaminase (AID) occurs in a sequence-specific manner around the targeted methylycitosine. When mutations in adenomatous polyposis coli (APC) of sporadic tumors were analyzed, it was shown that this deaminase site preference was 25-fold overrepresented in the database. AID is present in several human tumors, but other deaminases occur in other tumors. This work shows an enzyme-catalyzed activity on methylycitosine that provokes the cell to think about a potential role for deaminases in genetic reprogramming and contribution to mutation leading to genetic diseases.

Genevieve Almouzni outlined the mechanisms of propagation of epigenetic states at the level of chromatin assembly. The ordered assembly of chromatin produces a nucleoprotein template capable of epigenetically regulating the expression and maintenance of the genome. Histone chaperones have been isolated from cell extracts that stimulate early steps in chromatin assembly in vitro and integrate histone metabolic pathways during the cell cycle and during development and through the life of the cell. The function of one such factor, chromatin assembly factor 1 (CAF-1), may extend beyond simply facilitating the progression through an individual nucleosome assembly reaction coupled with DNA synthesis; it also has active participation in a marking system of cell proliferation, and it is down-regulated in G0 cells. This marking system could be exploited at the crossroads of DNA replication and repair to monitor genome integrity and to define particular epigenetic states. Interrelationships occur with other assembly factors and their respective role in specific
assembly pathways: For example, histone regulation A (HIRA) is not
down-regulated in quiescent cells and facilitates nucleosome assembly
independently of DNA synthesis.

Rudolf Jaenisch discussed nuclear cloning as a tool to distinguish
between genetic and epigenetic alterations that restrict the develop-
mental potential of the genome. One of the most interesting issues of
nuclear cloning is the question of genomic reprogramming (i.e., the
question whether successful cloning requires the resetting of epige-
etic modifications that are characteristic of the adult donor nucleus).
Inappropriate expression of key developmental genes contributes to
lethality of cloned embryos. The presentation focused on using nu-
clear transplantation procedures to compare the potency of stem cells,
differentiated cells, and transformed cells with direct embryonic de-
velopment after nuclear transfer. Embryonic carcinoma cells and
somatic cancer cells, including defined leukemia cells and solid tu-
mors such as sarcoma and melanoma cells, were used as nuclear donors.
The results suggested that the genome of embryonic carci-
noma cells and some somatic cancer cells can be reprogrammed to
direct at least some embryonic development after transfer of the
nucleus into the oocyte. The similarities and differences between stem
cells and tumor cells also were evaluated. In ES cells, ~70 genes are
active, including Oct-3/4; the presence of activated Oct-4 gene in
donor nuclei increased the efficiency of the nuclear transfer, and it is
possible that ectopic activation of Oct-4 may increase the efficiency of
nuclear transfer. Although it is clear that genetic alterations accumu-
late during neoplasia, the importance of epigenetic alterations only
recently has become recognized.

Methylation and Cancer

Manel Esteller discussed cancer as an epigenetic disease with focus
on a disruption of DNA methylation and histone codes. DNA meth-
ylation is the main epigenetic modification in humans. Tumor cells
show aberrant methylation of several CpG islands but global dem-
ethylation versus the counterpart normal cells. Promoter hypermethy-
ation of particular genes has important consequences for the biology of
that particular tumor. For example, this is the case of the DNA
repair gene methyl-guanine methyl transferase (MGMT), whose
methylation-mediated silencing leads to transition mutations but at the
same time “marks” chemosensitivity. Chromatin immunoprecipitation
(ChIP) assays and restriction nuclease accessibility analysis show how
the majority of tumor-suppressor genes with CpG island promoter
hypermethylation-associated inactivation also present histone hy-
poacetylation and histone methylation. With tumor progression, there
is an increase in the number of genes whose promoter is methylated,
and there also is an increase in the expression of DNA methyltrans-
fersases. Overall, the data showed that human tumors have a profound,
but specific, disturbance in their DNA methylation and chromatin patterns.

Stephen Baylin outlined the dual role of DNA methylation and
histone modification in aberrant gene silencing in cancer. The pro-
gression of cancer, in addition to be driven by key genetic changes, is
mediated by numerous epigenetic abnormalities, the best character-
ized of which are heritable gene transcription–silencing events asso-
ciated with aberrant promoter region hypermethylation. Methylation
of lysine 9 of histone H3 (me-K9-H3) may be a critical signal that
helps to recruit DNA methylation to the promoters of silenced genes.
In turn, this mark, in association with deacetylation of K9-H3, is
integral to maintenance of the silencing, whereas the DNA methyla-
tion, once established, appears to act as a dominant “lock,” which
must be removed for reactivation of gene expression and reversal of
the aforementioned repressive histone modifications. Many epigeneti-
cally silenced genes are found that do not have mutations. Silencing
of such genes, as well as perhaps the majority of promoter hyperm-
ethylated genes in cancer, may be critically involved in the earliest
steps of tumor progression and may provide the precancerous cell
populations, which become the substrate for subsequent genetic
events that lead to the full progression to cancer. A role for the
hypermethylated genes in the inappropriate activation of pathways,
which are normally only active in stem cell–like cells but which
should be silent in mature cells, may be a key aspect of cancer
progression. The secreted frizzled related protein (SFRP) gene family,
which encodes for proteins that act as antagonists to the frizzled
proteins, is a key family of receptors that mediates Wnt pathway
signaling at the cell membrane. Epigenetic silencing of SFRPs pro-
vides an early, precancerous stage event that renders the Wnt pathway
abnormally active at the ligand level before downstream mutations in
the pathway, which also lead to Wnt pathway overactivity. This
facilitates transcriptional activation by the protein of growth-promot-
ging genes and inhibition of apoptosis signals to fully drive colon
癌 progression.

Therapeutic Strategies

Jean-Pierre Issa outlined hypomethylation-based therapies of can-
cer. 5-Azacytidine and 5-aza-2'-deoxycytidine (decitabine) have
shown efficacy in myeloid malignancies. In vitro, both drugs show
a narrow window of activity, with substantial cytotoxicity and loss of
hypomethylating activity at high doses. In a Phase I study in hema-
tologic malignancies, decitabine induced hypomethylation in a dose-
dependent way, according to a bell-shaped curve, with a plateau in
hypomethylation at an intravenous dose of 15 mg/m² daily for 10
days, which coincided with the optimal clinical dose (based on re-
sponses). In Phase III studies, both drugs had activity in patients
with myelodysplastic syndromes: The effect takes longer than it usually
does with cytotoxic agents and is greater at low drug doses, without
toxicity, than at high doses. At high doses, demethylation was greater
in nonresponders than in responders. Using methylation of repetitive
elements or total methylation measured by liquid chromatography–
mass spectroscopy (LC-MS), the degree of hypomethylation was
estimated to range between 0% and 20% 5 days after initiation of
therapy, depending on the dose. Remethylation begins shortly after
the drug is stopped and is invariably completed by 30 days. After
therapy, hypomethylomation of single copy genes has been observed,
including that of potential tumor-suppressor genes such as P15, but
there appears to be gene-specific factors that control the degree of
sensitivity to decitabine-induced hypomethylation, and the relation-
ship between gene-specifc demethylation and response remains un-
clear.

Paul Marks discussed the therapeutic use of histone deacetylase
(HDAC) inhibitors. There are three classes of human HDAC en-
zymes: class I, HDACs 1, 2, 3, 8, and 11, which have homology in the
catalytic sites with yeast HDAC (RPD3) deacetylase and are sensitive
to suberoylanilide hydroxamic acid (SAHA); class II, HDACs 4, 5, 6,
7, 9, and 10, which have homology in the catalytic sites to yeast Hda1
and are sensitive to trichostatin (TSA); and class III, NAD-dependent
HDAC (SIR-2) family of deacetylases, which have an absolute re-
quirement for NAD for activity and are sensitive to SAHA and TSA.
SAHA or TSA increase or decrease the expression of as few as 2% to
5% of expressed genes in transformed cells. Among the genes whose
expression frequency is increased are p21WAF1, TATA binding pro-
tein (TBP2), Bcl6, and cyclin E, and among the genes whose expres-
sion may be decreased are cyclin D1, ErbB-2, thymidylate synthetase,
cyclin A, and vascular endothelial growth factor. SAHA induces
growth arrest in W138 and its SV40-transformed counterpart (VA13).
VA13 cells undergo rapid apoptosis, whereas the W138 cells remain

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viable and on removal of SAHA proliferate normally. In Phase I and II clinical trials, SAHA administered either intravenously or orally causes accumulation of acetylated histone in peripheral mononuclear cells and in tumor cells. SAHA has induced responses (including stable decrease, partial responses, and complete responses) in hematologic and solid tumors, including cutaneous T-cell lymphoma, non-Hodgkin’s lymphoma, mesothelioma, laryngeal carcinoma, thyroid cancer, and others. In conclusion, HDAC inhibitors, such as SAHA, are promising new targeted anticancer agents.

Peter Jones outlined therapeutic approaches based on epigenetically switching genes on and maintaining them active. The methylation of cytosine residues in CpG islands located near the transcriptional start sites of human genes plays a major role in carcinogenesis. These alterations lead to the heritable silencing of genes. Unlike mutational changes, epigenetic alterations are acquired in a gradual process, which is associated with cellular division. Zebularine [1-(β-D-ribofuranosyl)-1,2-dihydroxypyrimidin-2-one] acts as an inhibitor of DNA methylation and exhibits chemical stability and minimal cytotoxicity in vitro and in vivo. Continuous application of zebularine to T24 cells induces and maintains p16 gene expression and sustains demethylation of the 5′ region for >40 days, preventing remethylation. Continuous zebularine treatment also effectively demethylated various hypermethylated regions, especially CpG-poor regions. The drug causes a complete depletion of extractable DNA methyltransferase 1 (DNMT1) and partial depletion of DNMT3a and DNMT3b3. Last, sequential treatment with 5-aza-2′-deoxycytidine, followed by zebularine, hinders the remethylation of the p16 5′ region and gene silencing, suggesting the possible combination use of both drugs as a potential anticancer regimen.

David Livingston concluded the symposium with a critical review of the information that was discussed in the preceding days. In comparing normal stem cells with cancer stem cells, one could conclude that both are multipotent, have self-renewing capacity, have the potential to develop into tumors, and require a microenvironment (“niche”) for function; normal stem cells do not appear to be immortal because one cannot transfer them indefinitely. Yet, in vivo, they can regenerate intestinal mucosa and bone marrow: Is this because of microenvironment requirements? Both require helper cells for function, but neither needs to be euploid for it; both undergo classical G0 to G1 transfer control. Many questions still remain to be answered: for example, whether cancer stem cells can give rise to differentiated progeny, whether they carry somatic cancer mutations, and whether they are relatively hyposensitive to DNA damage.

Perspectives

Although the importance of epigenetic alterations for cancer has been widely recognized during the past several years, the concept of cancer stem cells is a recent paradigm with potentially significant implications for mechanistic insights into tumor formation and therapy. Epigenetic mechanisms are known to be crucial for embryogenesis and cellular differentiation. Thus, one of the key issues for cancer research in the immediate future will be not only to define the genetic changes of the cancer cell genome but also to understand the epigenetic alterations that affect the differentiation potential of cancer stem cells.

Appendix

The program committee consisted of the cochairs: David Livingston, Dana-Farber Cancer Institute, Boston, MA; Frank Rauscher, The Wistar Institute, Philadelphia, PA; Bruno Amati, European Institute of Oncology, Milan, Italy; Alex Matter, Novartis Institute for Tropical Diseases, Singapore; and Marco Pierotti, Istituto Nazionale Tumori, Milan, Italy. In addition to the program committee members, invited participants included: Stephen B. Baylin, Johns Hopkins Comprehensive Cancer Center, Baltimore, MD; Michael F. Clarke, University of Michigan, Ann Arbor, MI; George Q. Daley, Children’s Hospital, Boston, MA; John E. Dick, Toronto General Research Institute, Toronto, Ontario, Canada; Manel Esteller, Spanish National Cancer Center, Madrid, Spain; Jean-Pierre Issa, M. D. Anderson Cancer Center, Houston, TX; Peter A. Jones, Norris Comprehensive Cancer Center, Los Angeles, CA; Gordon M. Keller, Mt. Sinai School of Medicine, New York, NY; Paul A. Marks, Memorial Sloan Kettering Cancer Center, New York, NY; Hugh D. Morgan, The Babraham Institute, Cambridge, United Kingdom; Luis F. Parada, University of Texas Southwestern Medical Center, Dallas, TX; Austin Smith, Institute for Stem Cell Research, Edinburgh, Scotland; and Maarten van Lohuizen, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

The posters were presented by M. E. Bianchi, San Raffaele Scientific Institute, Milan, Italy; M. A. Sabatino, Istituto Mario Negri, Milan, Italy; J. Giannios, Peripheral Hospital, Athens, Greece; R. Schneider-Stock, Otto-von-Guericke University, Magdeburg, Germany; R. Palumbo, San Raffaele Research Institute, Milan, Italy; B. Illi, Centro Cardiologico Fondazione I Monzino, Milan, Italy; S. Indraccolo, University of Padova, Padova, Italy; T. Rajkumar, Cancer Institute, Chennai, India; S. Petersen-Mahrt, Cancer Research United Kingdom, South Mimms, Herts, United Kingdom; W. Galagher, Conway Institute of Biomolecular and Biomedical Research, Dublin, Ireland; K. Baily, Roswell Park Cancer Institute, Buffalo, NY; S. M. Pollard, Institute for Stem Cell Research, Edinburgh, United Kingdom; I. Okamoto, Curie Institute, Paris, France; M. G. Catalano, University of Turin, Turin, Italy; A. Loyola, Institut Curie-Research, Paris cedex, France; G. Sotiropoulou, University of Patras, Patras, Greece; T. Dittmar, Institute of Immunology, Witten, Germany; M. Dijon, Institut Paoli-Calmettes, Marseille, France; T. Brabletz, University of Erlangen, Erlangen, Germany; D. Ponti, National Cancer Institute, Milan, Italy; I. Abdel Salam, National Cancer Institute, Cairo, Egypt; J.J.L.H. van Leenders, University Medical Center, Nijmegen, The Netherlands; M. F. Fraga, Spanish National Cancer Center, Madrid, Spain; C. Pepe, University of Pisa, Pisa, Italy; and G. Finocchiaro, Istituto Nazionale Neurologico Besta, Milan, Italy.
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