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Radiation Resistance in Cancer Therapy: Meeting Summary and Research Opportunities

Report of an NCI Workshop held September 1–3, 2010

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INTRODUCTION

Radiation therapy is used to treat more than half of all cancer patients and remains the single most effective non-surgical modality for the cure of human cancers. Although advances in treatment delivery have enabled innovative dose escalation and hypofractionation approaches with promising results for some malignancies, resistance to therapeutic

doses of radiation remains a challenge. Key biological features such as tumor hypoxia, DNA damage response and checkpoint pathways, angiogenesis and vasculogenesis, cancer stem cells, tumor stroma, and immune response pathways all contribute to the complex dynamics governing tumor responses to radiation. A workshop entitled “Radiation Resistance in Cancer Therapy” (held in Bethesda, MD, September 1–3, 2010) was organized by the Divisions of Cancer Biology and the Radiation Research Program at the National Cancer Institute to identify research areas and directions that will advance understanding of radiation resistance in cancer and accelerate the development of strategies to overcome it. Over 3 days, experts in radiation biology and related fields met to identify and prioritize the key areas for future research. The overall consensus was that strategies are emerging to exploit DNA repair pathways, overcome tumor hypoxia, interfere with angiogenesis and vasculogenesis, and identify novel targets, but further basic and translational research and focused clinical trials are needed to identify optimal agents and strategies for therapeutic use. It was felt that improved models are needed to better study tumor stem cells and to elucidate tumor/stroma interactions, as well as to understand how radiation impacts the immune system and how immune responses can be manipulated for therapy with radiation. The chief objective of this publication is to communicate these research goals to the cancer biology community and encourage further work and investment of resources to move the field forward.

MEETING REPORT

Two keynote talks set the stage for the opening session by summarizing the current status of radiation resistance

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in cancer treatment. Simon Powell (Memorial Sloan Kettering Cancer Center, New York, NY) discussed strategies to exploit DNA damage response (DDR) defects in cancer cells to increase the effectiveness of chemo-radiation therapy. Defective DNA damage responses, which characterize cancer cells, are not found in corresponding normal cells, thereby allowing for the development of personalized oncology if the specific DNA repair/signaling pathways lost in the tumor can be elucidated and then targeted in a therapeutic setting. Ionizing radiation induces a spectrum of DNA damage, including both single-strand and double-strand breaks. Chemotherapy agents induce characteristic DNA injuries. The challenge is how to elucidate the specific inhibitor to optimize therapy. The combination of a poly(ADP-ribose) polymerase (PARP) inhibitor with radiation in homologous recombination repair-defective cells represents a potential model of synthetic lethality. However, heterogeneity exists even in the context of BRCA1- or BRCA2-deficient tumors, and the basis for diverse treatment responses is incompletely understood. Powell urged that studies to determine pathways be prioritized to characterize both increases and decreases and not just cell death. The goal is to develop rational combinations of DNA repair-targeting cytotoxics and biologics. In particular, new data were presented suggesting that RAD52 inhibition may be partially synthetic lethal with deficiencies in BRCA2, BRCA1, PALB2 and other members of the homology-dependent repair (HDR) pathway. Powell also suggested that CHK2 defects are epistatic with BRCA2 or BRCA1 mutations and highlighted the value of screening clinical samples for functional deficiencies in DNA repair. He concluded that the research challenge is to identify functionally relevant alterations in the DDR network to identify novel cancer-specific targets (1).

Martin Brown (Stanford University, Stanford, CA) discussed the role of the microenvironment on tumor radiosensitivity. While it is widely recognized that hypoxic cells are relatively resistant to radiation, they are heterogeneously expressed in tumors. It is increasingly evident that the responsiveness of tumors is influenced by the biology of the tumor stroma, including both vasculogenesis and angiogenesis. Brown presented data showing that vasculogenesis is activated by ionizing radiation by the induction of stromal cell-derived factor 1 (*SDF-1/CXCL12*) in a process where bone marrow-derived CD11b⁺ monocytes, which are pro-angiogenic and pro-inflammatory, restore the vasculature and contribute to tumor regrowth after irradiation. These monocytes are recruited into irradiated tumors where they differentiate into macrophages. Strategies to block recruitment of CD11b⁺ cells or endothelial cells by interfering with SDF-1/CXCR4 or SDF-1/CXCR7 interactions, respectively, appear highly promising to inhibit tumor regrowth in preclinical cancer models (2).

Studies are under way in patients with malignant brain tumors to determine if SDF-1 levels are elevated in the plasma of patients as they are in mice and rats after brain irradiation.

There were four speakers in the session on “DNA damage and signaling responses to therapeutic levels of ionizing radiation.” Thomas Helleday (Oxford University, United Kingdom) discussed the possibilities of targeting the DDR as an approach to improved cancer radiotherapy. He presented data on the analysis and patterns of synthetic lethal interactions determined in high-throughput screens where the goal is to define networks of synthetic lethal interactions (3). He emphasized that node removal (using an RNAi strategy, for example), is not the same, and may not have the same effects, as small-molecule inhibition, which is closer to current clinical applications. He presented data showing efficacy of a histone deacetylase (HDAC) inhibitor in radiation-resistant cells but noted that further *in vivo* models with careful studies of radiation fractionation and tumor kinetics are needed for increased translational significance.

Adriana Haimovitz-Friedman (Memorial Sloan Kettering Cancer Center, New York, NY) presented data showing that PKC α activation mediates downregulation of ATM, which radiosensitizes androgen-sensitive human prostate cancer cells *in vitro* and *in vivo*. Using TPA to activate PKC α , she noted that the resulting decrease in ATM levels and activation of ceramide synthase augments the apoptotic response to radiation.

David Chen (UT Southwestern, Dallas, TX) discussed the DNA-PK complex and its modulation of pathway choice in double-strand break (DSB) repair in S phase of the cell cycle. Specifically, he presented data showing that DNA binding by the DNA-PK subunit Ku plays a role in inhibiting DNA end resection. The result is a block of homologous recombination, which could be exploited to enhance radiosensitivity.

Cristina Furdul (Wake Forest University, Winston Salem, NC) discussed how new chemical probes, high-throughput technologies and computational methods can help dissect the mechanisms of radiation resistance in cancer. Using head and neck cancer (HNC) as a model, she presented results of redox proteomics and phosphoproteomics by mass spectrometry in the setting of EGF receptor stimulation or inhibition. Her results to date suggest that rewiring of signaling networks must be considered when identifying the protein targets most suitable for combination with radiation.

In the session on “Biomarkers and novel therapeutic targets for radiation therapy,” five speakers stressed the importance of the tumor microenvironment perspective, rather than an exclusive reliance on irradiation of cancer cell lines *in vitro*. Robert Bristow (University of Toronto, Canada) discussed the use of array CGH and copy number alterations as novel prognostic determinants of

prostate cancer outcome in the setting of radiation (4). He stressed the importance of developing well-defined clinical cohorts with paired high-quality material for genetic studies. His group has generated DNA, RNA and tissue microarrays on prostate cancer patients to search for biomarkers of prognosis and response to radiation. He noted that approximately 25% of patients have monoallelic losses in genes involved in DNA repair, but the functional significance of this is unknown.

James Larner (University of Virginia, Charlottesville, VA) introduced the concept of protein phosphatases as molecular targets for radiosensitization. Focusing on the PP2A family of phosphatases, he noted that PP6 is a well-conserved Ser/Thr phosphatase that acts on DNA-PK such that knockdown sensitizes cells to radiation. He presented two protein-protein interfaces important in phosphatase subunit assembly whose interaction could be targeted.

Thomas Helleday (Oxford University, UK) discussed siRNA screening for identification of radiosensitization targets within the DDR network. Using this methodology, DNA polymerase theta (PolQ), a low-fidelity polymerase, was identified. This polymerase is differentially expressed in cancers, where it could play a role in base excision repair (BER), and therefore may serve as a target. Studies to date suggest that PolQ expression is prognostic in cancer patients. Dr. Helleday also discussed tumor signaling inhibition by the protease inhibitor nelfinavir and its impact on the tumor microenvironment and radiosensitivity. He presented promising results from a phase I clinical trial of this approach in pancreatic cancer patients led by Dr. Thomas Brunner.

David Boothman (UT Southwestern, Dallas, TX) discussed the role of senescence and insulin-like growth factor-1-secretory clusterin (ATM-IGF-1-sCLU) expression as a consequence of ATM and TGF- β 1 activation in radioresistance *in vivo*. Secretory clusterin (sCLU) is an extracellular chaperone and potent anti-angiogenic factor. OGX-011 is an antisense inhibitor of sCLU and is currently in phase II/III clinical trials in combination with radiation.

Mircea Ivan (Indiana University, Indianapolis, IN) discussed the emerging roles of hypoxia-regulated microRNAs in cancer biology and therapy. Noting that both coding genes and noncoding RNAs are involved in radioresistance of hypoxic cells, he presented data on microRNAs (miR-210 among others) in preclinical models. One challenge is to determine whether to develop therapeutic strategies directed against the microRNA itself or its putative target(s).

Four speakers presented in the session on "Hypoxia as a confounding factor in radiation therapy." Peter Glazer (Yale University, New Haven, CT) reviewed the evidence showing that hypoxia promotes genetic instability via downregulation of MLH1 (via myc/max) and BRCA1 and RAD51 (via E2F4/p103 repressive complexes). Data

showing that hypoxia also promotes long-term silencing of the *BRCA1* promoter was presented, highlighting the frequent silencing of DNA repair/tumor suppressor genes in many sporadic tumors (5). Following the theme of synthetic lethality, Glazer showed that the polymerase beta inhibitor lithocholic acid is lethal to BRCA2-deficient cells and that this lethality is augmented by combined treatment with temozolomide, which engages the BER pathway via purine alkylation. Synthetic lethality was also demonstrated by the toxicity of PARP inhibitors to hypoxic cells, in which *BRCA1* and *RAD51* are downregulated. However, PARP inhibitors were also shown to suppress *BRCA1* and *RAD51* expression, and this downregulation was shown to account for much of the radiosensitization produced by PARP inhibition.

Ester Hammond (Oxford University, UK) reported that hypoxia does not cause detectable DNA damage by standard assays for strand breaks but does engage γ -H2AX phosphorylation. 53BP1 foci are not seen, but ATM is activated in a manner independent of the MRN complex and without clear focus formation, consistent with the absence of strand breaks. Using DNA fiber techniques, Hammond also demonstrated S-phase arrests and the inability to restart replication in S-phase cells after prolonged hypoxia, with loss of MRN proteins from chromatin. Importantly, Hammond showed that ribonucleotide reductase is oxygen dependent and that hypoxia leads to substantially reduced dNTP pools, accounting for the stalled replication. Interestingly, inhibiting CHK1 sensitizes cells to hypoxia, presumably by disrupting the protective cell cycle checkpoint, even though CHK1 levels are themselves suppressed by hypoxia. Hammond also demonstrated that hypoxia and PARP inhibitors are synthetically lethal.

Mark Dewhirst (Duke University, Durham, NC) focused on the importance of cycling hypoxia and its strong induction of HIF-1 α . Using a fluorescent analog of glucose (NBDG), he was able to show that cycling hypoxia increases glucose uptake and drives the Warburg effect and that HIF-1 knockdown compromises ability of tumors to make ATP. Dewhirst also showed that reoxygenation after hypoxia increases free radicals and thereby increases HIF-1. An SOD mimetic can inhibit the increase in HIF-1 after reoxygenation. It is clear that there is a need to distinguish chronic from cycling hypoxia, and the dominance of ROS and RNS suggests that they are potential targets for inhibition.

Dewhirst also emphasized the importance of drugs that will inhibit glucose consumption by hypoxic tumor cells. His work has shown that HIF-1 inhibition is very effective in accomplishing this. Also, inhibition of MCT1 can starve hypoxic tumor cells by forcing aerobic tumor cells to consume more glucose. In addition, hyperthermia is also a very effective means to improve

perfusion, drug delivery and reduce hypoxia. Hyperthermia increases HIF-1 and this upregulates PDK1, which moves cells toward a more glycolytic pathway. Hyperthermia also interferes with mitochondrial membrane potential, which further inhibits respiration. These effects will serve to increase tumor oxygenation.

Dewhirst further stressed that delivery is a real issue for drugs and that this is often ignored. He stressed that the problem includes what he terms longitudinal gradients in tumors with respect to oxygen delivery. This has to do with the path length of vasculature through a tumor and the overall vascular density. He has detected tumor microvessels that are perfused but that do not contain oxygen because they have traversed long distances through a tumor before exiting. The same thing will happen with drugs.

Denise Chan (University of California, San Francisco, CA) focused on proline hydroxylases. Hydroxylation of HIF-1 α is the key oxygen sensing step, and PHD2 is the key oxygen sensor. Chan reported that PHD2 mRNA is decreased in cancer compared to normal tissue, and silencing PHD2 increases tumor growth. She used shRNA to knock down PHD2 in HIF-1 $^{-/-}$ cells, but there was still increased tumor growth from PHD2 knockdown. PHD2 knockdown increases tumor angiogenesis as judged by CD31 staining. Evidence was presented that PHD2 knockdown promotes recruitment of bone marrow cells and yields increased vasculogenesis. Interestingly, PHD2-mediated tumor suppression was shown to be independent of hydroxylase function both by using a hydroxylase inhibitor and by using a rescue approach comparing wild-type and hydroxylase-deficient variants. The next question that needs to be addressed is what region or function of PHD2 is needed.

In the session on “Tumor microenvironment as a driver of radio-resistance,” four speakers presented several perspectives. Garth Powis (MD Anderson Cancer Center, Houston, TX) discussed the progress of small molecule inhibitors of HIF-1 in the clinic to date (6) and presented data on the role of hedgehog (Hh) signaling in desmoplasia and radiation resistance, providing evidence that Hh acts primarily on the stroma in solid tumors. Low Hh expression levels are associated with increased survival in pancreatic cancer patients where Hh inhibitors are currently in phase I clinical trials.

David Lyden (Cornell University, New York, NY) addressed the evolution of the metastatic niche. Bone marrow-derived cells are abundant at the invasive edge of the primary tumor and contribute to the formation of the premetastatic niche at distant sites. He introduced the concept of tumor exosomes, which fuse with bone marrow cells and may contribute to radioresistance.

Costas Koumenis (University of Pennsylvania, Philadelphia, PA) presented an *in vivo* mRNA and miRNA signature of hypoxia in solid tumors and discussed

implications for targeting the tumor microenvironment. He emphasized the need to directly identify targets for imaging and hypoxia response *in vivo*. Using the EF5 hypoxia tracer to localize hypoxic areas in tumors combined with laser-capture microdissection (LCM), he identified downregulation of genes associated with the immune response, raising the possibility that hypoxic areas are immune privileged. The EF5-LCM-MGEP strategy is feasible in human cancer patients and can be used to identify and associate hypoxic signatures with disease progression to elucidate targets.

James DeGregori (University of Colorado, Denver, CO) addressed ionizing radiation and cancer with a focus on altering the adaptive landscape and the implications for the evolution of cancer stem cells.

Focusing on the “Role of stem cells in radio-resistance,” three speakers discussed cancer stem cells and their potential contribution to therapeutic responses. Richard Hill (University of Toronto, Canada) raised the possibility that cancer stem cells do not arise from normal stem cells. At present, stem cells and cancer stem cells can be sorted on the basis of markers and are then injected into animals to assess their tumor-forming properties (7). The stability of cancer stem cells over time is unknown, as is the effect of radiation on the transit of stem cells.

Frank Pajonk (University of California-Los Angeles, Los Angeles, CA) discussed radiation-induced cancer stem cell plasticity. Focusing on breast cancer stem cells, he noted an increase after radiation and administration of exogenous erythropoietin. Radiation induces notch signaling, leading to cancer stem cell formation and setting the stage for the use of notch inhibitors to increase radiosensitivity.

Jeremy Rich (Cleveland Clinic, Cleveland, OH) presented an evolving view of cancer stem cells in cancer therapy. He discussed the limitations of the current models to study cancer stem cells and emphasized that it is difficult to study cancer stem cells in routine tissue culture since they reside in the perivascular microenvironment. Animal validation studies are essential. Radiation increases the population of CD133 $^{+}$ cells and ATM kinase activity is increased in CD133 $^{+}$ glioma cells. Radiation induces notch signaling, and notch antagonists sensitize cancer stem cells to radiation. He discussed implications for the role of HIF2 α , as CD133 and HIF2 α colocalize, and emphasized the importance of appreciating the hierarchy and plasticity of cancer stem cells in the tumor microenvironment.

The final session focused on the “Clinical aspects of radio-resistance and new translational possibilities.” Six investigators presented results from translational studies to date. Quynh-Thu Le (Stanford University, Stanford, CA) discussed predictive and prognostic markers for tirapazamine (TPZ) efficacy in HNC. She outlined the results of extensive clinical testing, including an international phase

TABLE 1
Key Biological Questions to be Addressed in Optimizing Radiation Therapy

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- What are the functionally and therapeutically relevant alterations in the DNA damage response (DDR) network in cancers?
 - How can we best exploit alterations in DDR pathways associated with genomic instability in cancer—the Achilles heel of cancer?
 - Is there a therapeutic index for repair inhibitors (ATM inhibitors, Ku inhibitors) and how can they be tumor specific?
 - Is homology-dependent repair the best target to achieve therapeutic gain?
 - HDAC, PARP and proteasome inhibitors all confer radiosensitization, but what is the mechanism of action and how can they best be exploited?
 - Apoptosis/necrosis/senescence—what are the key modes of cell death caused by radiation, and are they cancer specific?
 - What about the normal tissues in the radiation volume? How can these be modeled in culture?
 - microRNAs—is there a therapeutic ratio, and can they be used as therapeutics?
 - Is there a different biology to the large doses used in hypofractionation regimens?
 - Will giving large single doses resurrect old drugs like hypoxic cell sensitizers?
 - Irradiation of tumors may abrogate local angiogenesis, but what can we do about cells recruited to the tumors that mediate vasculogenesis?
 - Can the effects of hypoxia on DNA repair, and replication and the cell cycle be exploited? Are there possibilities for synthetic lethality?
 - What about acute versus chronic versus cycling hypoxia?
 - What about the effects of radiation on tumor stromal cells? Can this be exploited?
 - What are appropriate models for cancer stem cells, and how can they be targeted?
 - Are tumor stem cells truly more radioresistant? Do they differ in DNA repair capacity?
 - Do stem cell niches impact radiation response and can they be targeted?
 - How does radiation modulate the immune system and can this be exploited in therapy?
 - What are the systemic immune effects of localized radiation, and how can they be managed?
-

III trial comparing chemoradiation alone to chemoradiation plus TPZ in HNC patients (HeadSTART trial) (8). Although the addition of TPZ did not improve survival, ongoing assessment of biomarkers in tumor and surrogate tissue may be informative. Serum HGF levels appear to correlate with hypoxia imaging and outcomes in conventionally treated patients but not in the TPZ-treated group. Future studies may want to target patients with relatively poor prognosis, including HPV negative cancers.

Deric Wheeler (University of Wisconsin, Madison, WI) presented data on the role of nuclear EGFR as a therapeutic target whereby blocking nuclear translocation of EGFR may improve responses to radiation in combination with cetuximab in HNC. Both cetuximab and radiation induce EGFR nuclear translocation, which may contribute to radioresistance. He presented evidence that targeting Src family kinases may inhibit nuclear EGFR translocation and enhance responses.

William McBride (University of California-Los Angeles, Los Angeles, CA) expanded on the role of the immune system in radiation therapy for cancer. The tumor microenvironment is complex, with the immune system contributing to tumor development, anti-tumor responses and treatment resistance. It is not clear if radiation-induced damage generates antitumor immunity and/or enhances a tumor-sustaining wound-healing environment. He presented a rationale for immunotherapy in combination with radiation to stimulate a tumor-specific immune response.

Brian Czerniecki (University of Pennsylvania, Philadelphia, PA) discussed the tumor microenvironment as a target for radiation therapy in localized breast cancer and the possible synergy with the immune response. He presented opportunities to combine radiation with the toll-like receptor (TLR)-8 agonist (VentiRX) and/or vaccines to enhance the effects on tumor stroma. Using

immune conditioning with activated innate transfer, he reported very promising results with a neoadjuvant clinical trial in DCIS, Her2⁺ breast cancer patients.

Alec Vaezi (University of Pittsburgh, Pittsburgh, PA) discussed how to design therapy tailored to individual HNC biology based on DNA repair capacity. Specifically, he presented data implicating a role for XPF expression in tumors as a marker of response to radiation. In a clinical HNC cohort, XPF protein expression in HNC tumors and selected DNA polymorphisms may be correlated with clinical outcome, although the precise function of the SNPs is unknown. Assessment of XPF in a prospective cohort may facilitate treatment selection.

CONCLUSIONS OF THE WORKSHOP

The conclusions of the workshop were framed in the context of key questions to be addressed, as listed in Table 1. There was appreciation that recent advances in several areas have positioned the field for translation of novel approaches to the clinic but that additional basic science work and focused resource investment are needed. Strong preclinical data supporting the initiation of such trials will be essential. Highlights of the conference included synthetic lethal approaches to exploit DNA repair pathways, high-throughput methodologies to identify novel targets, new techniques to delineate biomarkers, insights into angiogenesis and vasculogenesis, further delineation of hypoxia biology, progress in understanding tumor stroma and cancer stem cells, and investigations of radiation/immune system interactions. There was also strong consensus that the time is ripe for well-designed clinical trials that test novel systemic agents in conjunction with radiation rather than trials in which such agents are tested in isolation.

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