Dna Repair And Cancer From Bench To Clinic

The ?eld of cellular responses to DNA damage has attained widespread recognition and interest in recent years commensurate with its fundamental role in the ma- tenance of genomic stability. These responses, which are essential to preventing cellular death or malignant transformation, are organized into a sophisticated s- tem designated the "DNA damage response". This system operates in all living organisms to maintain genomic stability in the face of constant attacks on the DNA from a variety of endogenous by-products of normal metabolism, as well as exogenous agents such as radiation and toxic chemicals in the environment. The response repairs DNA damage via an intricate cellular signal transduction network that coordinates with various processes such as regulation of DNA replication, tr- scriptional responses, and temporary cell cycle arrest to allow the repair to take place. Defects in this system result in severe genetic disorders involving tissue degeneration, sensitivity to speci?c damaging agents, immunode?ciency, genomic instability, cancer predisposition and premature aging. The ?nding that many of the crucial players involved in DNA damage response are structurally and functionally conserved in different species spurred discoveries of new players through similar analyses in yeast and mammals. We now understand the chain of events that leads to instantaneous activation of the massive cellular responses to DNA lesions. This book summarizes several new concepts in this rapidly evolving ?eld, and the advances in our understanding of the complex network of processes that respond to DNA damage.

Chromatin and DNA Repair in Cancer, Volume 364 in the International Review of Cell and Molecular Biology series reviews and details current advances in cell and molecular biology. Chapters in this new release cover Genomic Instability and metabolism in cancer, Histones variants and Histones modifications in cancer and Aging, DNA Double-stranded breaks Repair in Cancer, Reactive oxygen species and DNA damage response in cancer, Transcription-Associated DNA Breaks and Cancer: A Matter of DNA Topology, Mechanisms of Base Excision Repair: Its Significance to Human Health, and more. The IRCMB series has a worldwide readership, maintaining a high standard by publishing invited articles on important and timely topics that are authored by prominent cell and molecular biologists. The articles published in IRCMB have a high impact and an average cited half-life of 9 years. This great resource ranks high amongst scientific journals dealing with cell biology. Publishes only invited review articles on selected topics Authored by established and active cell and molecular biologists, drawn from international sources Offers a wide range of perspectives on specific subjects

Continuing the tradition of presenting information on DNA damage and repair, this 3rd volume provides the latest reviews by leading researchers. They illuminate key aspects of DNA repair in mammalian systems and its relationship to human disease.

As a major defence against environmental damage to cells DNA repair

is present in all organisms including bacteria, yeast, drosophila, fish, amphibians, rodents and humans. DNA repair is involved in processes that minimise cell killing, mutations, replication errors, persistence of DNA damage and genomic instability. Abnormalities in these processes have been implicated in cancer and ageing. This book presents leading-edge research from around the world in this frontal field.

Cancer-Associated Defects in the DNA Damage Response: Drivers for Malignant Transformation and Potential Therapeutic Targets

Advances in DNA Repair in Cancer Therapy

DNA Repair and Cancer Research

New Research on DNA Repair

This book edition is intended to provide a concise summary for select topics in DNA repair, a field that is ever-expanding in complexity and biologic significance. The topics reviewed ranged from fundamental mechanisms of DNA repair to the interface between DNA repair and a spectrum on cellular process to the clinical relevance of DNA repair in oncologic paradigms. The information in this text should provide a foundation from which one can explore the various topics in depth. The book serve as a supplementary text in seminar courses with focus on DNA repair as well as a general reference for scholars with an interest in DNA repair.

Jac A. Nickoloff and Merl F. Hoekstra update and expand their two earlier acclaimed volumes (Vol. I: DNA Repair in Prokaryotes and Lower Eukaryotes and Vol. II: DNA Repair in Higher Eurkaryotes) with cutting-edge reviews by leading authorities of primary experimental findings about DNA repair processes in cancer biology. The reviews cover a wide range of topics from viruses and prokaryotes to higher eukaryotes, and include several new topics, among them the role of recombination in replication of damaged DNA, X-ray crystallographic analysis of DNA repair protein structures, DNA repair proteins and teleomere function, and the roles of BRCA1 and BRCA2 in DNA repair. Authoritative and up-to-date, DNA Damage and Repair, Vol. III: Advances from Phage to Humans surveys the rapidly moving research in DNA damage and repair, and explains the important functional relationships among different DNA repair pathways and the relationship between DNA repair pathways, cancer etiology, and cancer therapies.

DNA Repair and CancerFrom Bench to ClinicCRC Press

A comprehensive review of the recent developments in DNA repair research that have potential for translational applications. The book explains in detail the various biological mechanisms by which cancer cells can circumvent anticancer therapy and limits its usefulness in patients. They also review the impact of such novel inhibitors of DNA repair mechanisms as methylguanine-DNA-methyltransferase. Also examined are inhibitors of other DNA repair enzymes such as PARP and DNA-PK. The book captures-for both cancer researchers and oncologists dealing with hallmark "relapse" or "drug resistance" phenomena on a daily basis-the many exciting new uses of DNA repair inhibitors, either alone or in combination with anticancer therapies.

Inhibition of RAD52-based DNA Repair for Cancer Therapy

Volume 2

Proceedings of the International Symposia of the Princess Takamatsu Cancer Research Fund, Volume 13

Volume 2: DNA Repair in Higher Eukaryotes

Chromatin and Genomic Instability in Cancer

DNA Repair and Cancer Therapy: Molecular Targets and Clinical Applications, Second Edition provides a comprehensive and timely reference that focuses on the translational and clinical use of DNA repair as a target area for the development of diagnostic biomarkers and the enhancement of cancer treatment. Experts on DNA repair proteins from all areas of cancer biology

research take readers from bench research to new therapeutic approaches. This book provides a detailed discussion of combination therapies, in other words, how the inhibition of repair pathways can be coupled with chemotherapy, radiation, or DNA damaging drugs. Newer areas in this edition include the role of DNA repair in chemotherapy induced peripheral neuropathy, radiation DNA damage, Fanconi anemia cross-link repair, translesion DNA polymerases, BRCA1-BRCA2 pathway for HR and synthetic lethality, and mechanisms of resistance to clinical PARP inhibitors. Provides a comprehensive overview of the basic and translational research in DNA repair as a cancer therapeutic target Includes timely updates from the earlier edition, including Fanconi Anemia cross-link repair, translesion DNA polymerases, chemotherapy induced peripheral neuropathy, and many other new areas within DNA repair and cancer therapy Saves academic, medical, and pharma researchers time by allowing them to quickly access the very latest details on DNA repair and cancer therapy Assists researchers and research clinicians in understanding the importance of the breakthroughs that are contributing to advances in disease-specific research

For this eBook, and the associated Research Topic in Frontiers in Genetics, entitled: 'Cancer-associated defects in the DNA damage response: drivers for malignant transformation and potential therapeutic targets' we have selected 10 papers that each discusses important, yet distinct aspects of the response to DNA damage in normal cells and cancer cells. Using an evolutionary conserved signaling network called the 'DNA damage response (DDR)' cells maintain the integrity of their genome, and thus safeguard cellular functioning and the ability to create viably progeny. Initially, the DDR appeared to consist of few linear kinase-driven pathways. However, research over the past decades in model organisms, as well as in the human system has revealed that the DDR is a complex signaling network, wired by multiple parallel pathways and displaying extensive crosstalk. Besides phosphorylation, multiple other post-translational modifications, including ubiquitination and sumoylation, are involved to achieve chromatin remodeling and initiation of DNA repair. Also, rather than being a cell-intrinsic phenomenon, we increasingly appreciate that cell-cell communication is involved. The recognition and repair of DNA damage is essential to maintain normal physiology. Multiple pathological conditions have been attributed to defective DNA repair, most notably accelerated aging, neurodegeneration and cancer. In the context of cancer, through repair of DNA damage or elimination of irreparably damaged cells, the DDR clearly has a tumor-suppressive role. Indeed, many tumor cells show partially inactivated DDR signaling, which allows proliferation in the context of DNA damage-inducing oncogenes. Simultaneously, loss of specific DDR signaling nodes creates a specific dependence of tumor cells on their remaining DDR components, and thus creates therapeutic opportunities. Especially in the context of cancer treatment, numerous targeted agents are under

investigation, either to potentiate the cytotoxic effects of chemo-radiotherapy, or to induce synthetic lethality with cancer-specific alterations, with the treatment of BRCA1/2 mutant cancers with PARP1 inhibitors as a prototype example. We have selected four review articles that provide insight into the key components and the wiring of the DDR and DNA repair. Torgovnick and Schumacher review the involvement of DNA repair in the initiation and treatment of cancer, Brinkmann et al., describe the involvement of ubiquitination in DNA damage signaling and Jaiswal and Lindqvist discuss how cell-extrinsic signaling participates in communication of DNA damage to neighboring cells. In addition, Shatneyeva and colleagues review the connection between the cellular response to DNA damage and escape from immune surveillance. Concerning the therapeutic application of targeting the DDR and DNA repair, three articles were included. Krajewska and van Vugt review the wiring of homologous recombination and how this offers therapeutic opportunities. Additionally, Knittel and colleagues describe how genetic loss of the central DDR component ATM in chronic lymphocytic leukemia can be exploited therapeutically by targeting certain parallel DNA repair pathways. Syljuasen and colleagues report on how targeting of the DDR can be used as a therapeutic strategy in lung cancer. Finally, three chapters describe newly identified regulators of the cellular response to DNA damage. Von Morgen et al. describe the R2TP complex, Lezzi and Fanciluuli review the involvement of Che-1/AATF in the DDR, and Ohms and co-authors describe how retrotransposons are at the basis of increased genomic instability. Altogether, these articles describe how defective responses to DNA damage underlie disease - and especially in the context of cancer -can be exploited to better treat disease.

This book is based on the papers presented at the conference on "Mecha nisms of DNA Damage and Repair: Implications for Carcinogenesis and Risk Assessment," held at the National Bureau of Standards on June 2-7, 1985, This volume deals with mechanisms of DNA damage and repair at the molecular level; consequences of unrepaired or misrepaired damage, with major emphasis on carcinogenesis; drugs which bind selectively to altered and potentially damaging DNA sequences; and potential utilization of DNA damage as an endpoint for assessing risks of UV light, ionizing radiations, chemicals, drugs, and hazardous agents in foods. Because the induction of mutations by radiation and genotoxic chemicals has been observed to follow one-hit kinetics in some instances, it is generally assumed that any level of exposure to a DNA-damaging agent may increase the risk of genetic disease or cancer in an exposed population. At the same time, however, there is evidence that although the DNA of living cells is continually damaged by natural background radiation, free radicals, and other naturally occurring processes, most of the damage is normally repaired.

Proceedings of the 13th International Symposium of The Princess Takamatsu

Cancer Research Fund, held in Tokyo The proceedings deal with the potential relevance of ADP-ribosylation reactions in the genesis, prevention and treatment of cancer. These reactions were independently discovered in the laboratories of Paul Mandel, Osamu Hayaishi and Takashi Sugimura, all whom contribute to ADP-Ribosylation, DNA Repair and Cancer. Apart from these renowned scientists, many other outstanding researchers from the international research community have contributed chapters discussing their most recent research results.

Volume I: DNA Repair in Prokaryotes and Lower Eukaryotes

New Research Directions in DNA Repair

DNA Repair Mechanisms

Volume 1

System Biology Analysis of the Role of DNA Repair in Cancer Treatment Outcome

Written by research experts, this volume of Progress in Molecular Biology and Translational Science focuses on current science surrounding the mechanisms of DNA repair. Contributions from leading authorities Informs and updates on all the latest developments in the field

A comprehensive review of the recent developments in DNA repair that have potential for translational and clinical applications. The authors explain in detail the various mechanisms by which cancer cells can circumvent anticancer therapy and limits its usefulness in patients. They also review the clinical impact of such novel inhibitors of DNA repair mechanisms as methylguanine-DNA-methyltransferase. Also examined are inhibitors of other DNA repair enzymes such as PARP and DNA-PK, now under development and close to clinical trials. The book captures-for both cancer researchers and practicing oncologists dealing with hallmark "relapse" or "drug resistance" phenomena on a daily basis-the many exciting new uses of DNA repair inhibitors, either alone or in combination with anticancer therapies.

This book is intended for students and scientists working in the field of DNA repair. Select topics are presented here to illustrate novel concepts in DNA repair, the cross-talks between DNA repair and other fundamental cellular processes, and clinical translational efforts based on paradigms established in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

This book is a printed edition of the Special Issue " Chemically-Induced DNA Damage, Mutagenesis, and Cancer" that was published in IJMS
Cancer Therapeutics: Targeting DNA Repair Pathways
DNA Damage and Repair
Chemically-Induced DNA Damage, Mutagenesis, and Cancer
DNA Damage, DNA Repair and Cancer
DNA Repair and Mutagenesis

The DNA of all organisms is constantly being damaged by endogenous and exogenous sources. Oxygen metabolism generates reactive species that can damage DNA, proteins and other organic compounds in living cells. Exogenous sources include ionizing and ultraviolet radiations, carcinogenic compounds and environmental toxins among others. The discovery of multiple DNA lesions and DNA repair mechanisms showed the involvement of DNA damage and DNA repair in the pathogenesis of many human diseases, most notably cancer. These books provide a comprehensive overview of the interdisciplinary area of DNA damage and DNA repair, and their relevance to disease pathology. Edited by recognised leaders in the field, this two-volume set is an appealing resource to a variety of readers including chemists, chemical biologists, geneticists, cancer researchers and drug discovery scientists.

DNA Repair Mechanisms is an account of the proceedings at a major international conference on DNA Repair Mechanisms held at Keystone, Colorado on February 1978. The conference discusses through plenary sessions the overall standpoint of DNA repair. The papers presented and other important documents, such as short summaries by the workshop session conveners, comprise this book. The compilation describes the opposing views, those that agree and dispute about certain topic areas. This book, divided into 15 parts, is arranged according to the proceedings in the conference. The plenary sessions are grouped with the related workshop and poster manuscripts. The first two parts generally tackle repair in terms of its identification and quantification, as well as the models, systems, and perspectives it utilizes. The following parts discuss the various types of repair including base excision, nucleotide excision repair in bacteria, excision repair in mammalian cells, inducible/error-prone repair in prokaryotes, and strand break repair in mammalian cells among others. This reference material looks into the replicative bypass mechanisms in mammalian cells, viral probes, and hereditary repair defects. It explains repair deficiency and human disease, as well as mutagenesis and carcinogenesis. The last part of this book deals with the consequences and effects of DNA repair. This volume is a helpful source of reference for students, teachers, scientists, and researchers in the different fields of genetics, radiology, biochemistry, and environmental biology.

An essential resource for all scientists researching cellular responses to DNA damage. • Introduces important new material reflective of the major changes and developments that have occurred in the field over the last decade. • Discussed the field within a strong historical framework, and all aspects of biological responses to DNA damage are detailed. • Provides information on covering sources and consequences of DNA damage; correcting altered bases in DNA: DNA repair; DNA damage tolerance and mutagenesis; regulatory responses to DNA damage in eukaryotes; and disease states associated with defective biological responses to DNA damage.

Germline BRCA mutations underlay a significant risk for breast and ovarian cancer that increases in age. BRCA mutations are usually associated with the most aggressive subtypes of these cancers such as triple negative breast cancer and high-grade serous ovarian cancer. Conventional chemotherapeutic or hormonal therapies do not address the molecular deficiencies responsible for their resistance and there is a high rate of recurrence. Targeted therapy that can address the unique molecular features in these subtypes of cancer is the only way to cure the

disease or, at the very least, improve patients' quality of life. Homologous recombination repair is an accurate repair pathway that utilizes a copy of a homologous sequence to relay information to the break site. Cancer cells copy their DNA extensively meeting the principle demand for this high-fidelity repair pathway. Homologous recombination repair is utilized by cancer cells to cope with the most challenging forms of DNA damage such as DNA double strand breaks, stalled replication forks, adducts, and interstrand crosslinks. Among the key proteins in homologous recombination repair, RAD52 activity promotes cancer cells' tolerance and survival. Therefore, there is a therapeutic opportunity in inhibiting RAD52 activity to push DNA damage levels in homologous recombination repair-deficient tumors beyond the limits of viability. One of the early events in this repair is resection of the broken strand and generation of single strand DNA. Replication protein A cover and protect those strands and interact with key DNA repair proteins. RAD52 activity in DNA repair is dependent on its interaction with replication protein A. The hypothesis of this thesis is that it is possible to inhibit RAD52 activity by inhibiting its interaction with RPA and this inhibition will have therapeutic benefits for cancer patients. We explored the binding activity and affinity of the RAD52 interaction with RPA. Kinetic, and thermodynamic parameters dictating this protein:protein interaction were measured. The characterization of RAD52:RPA interaction data guided remapping of the RPA interaction domains on RAD52. To target RAD52 activity by inhibiting its interaction with RPA, we designed an in vitro fluorescent-based protein-protein interaction assay. This assay was further optimized for high throughput settings with a robust signal, minimal steps, statistical accuracy, and low cost. We screened over 100,000 compounds to look for small molecule inhibitors. Eleven hits were found and five were selected for their high EC50 values. Three of the five hits are FDA approved drugs and were selected for cytotoxicity tests in BRCA-deficient cell lines. The outcome of our characterization for these three candidate small molecule inhibitors may shed light on the variation of their efficacy and sensitivity among breast or ovarian cancer patients with BRCA-defective pathway versus those with none. Additionally, we present fluorescent-based protein-protein interaction assay as an affordable method to detect many protein:protein interactions in low-scale or high throughput settings applicable to finding small molecule inhibitors or aptamer modulators for protein:protein interactions.

Mechanisms of DNA Damage and Repair

From Bench to Clinic

Mechanisms of DNA Repair

Iowa Women's Health Study

Advances in DNA Repair

DNA repair is a rapidly advancing field in biology and these systems represent a major defense mechanism against environmental and intracellular damaging agents such as sunlight, ionizing radiation, and reactive oxygen species. With contributions from eminent researchers, this book explores the basics and current trends in this critical field. Topics include carcinogenesis as a predictive and/or prognostic biomarker for cancer therapy, nucleotide excision repair, and tumor genetics and personalized medicine. The contributions provide essential information to scientists, pharmaceutical investigators, and clinicians interested in cancer therapy.

DNA Damage, DNA Repair and Cancer.

The existence of 'cancer stem cells' (CSCs) has been a topic of heated debate for the last few years within the field of cancer biology. Their continuous characterization in a variety of solid tumors has lead to an abundance of evidence supporting their existence. CSCs are believed to be responsible for resistance against conventional treatment regimes of chemotherapy and radiation, ultimately, leading to metastasis and patient

demise. To help aid clinicians, pharmaceutical companies and academic labs investigating how to better kill these highly aggressive cells we have summarized the DNA repair mechanism(s) and their role in the maintenance and regulation of both normal and cancer stem cells. Our book represents a comprehensive investigation into the highly effective DNA repair mechanisms of CSCs and what we need to understand in order to develop more advanced therapies to eradicate them from patients. Currently, there are no other published works entirely on DNA repair and Cancer Stem Cells. In addition, our book provides a comprehensive overview of CSC isolation and characterization from a variety of solid tumor types.

DNA Repair and Replication brings together contributions from active researchers. The first part of this book covers most aspects of the DNA damage response, emphasizing the relationship to replication stress. The second part concentrates on the relevance of this to human disease, with particular focus on both the causes and treatments which make use of DNA Damage Repair (DDR) pathways. Key Selling Features: Chapters written by leading researchers Includes description of replication processes, causes of damage, and methods of repair

Mechanisms and Clinical Significance

Oncogene and Cancer

DNA-repair and Cancer

Molecular Biology of the Cell

DNA Damage and Repair in Human Tissues

Over the past decade a complex role for DNA damage response (DDR) in tumorigenesis has emerged. A proficient DDR has been shown to be a primary cause for cellular resistance to the very many DNA damaging drugs, and IR, that are widely used as standard-of-care across multiple cancer types. It has also been shown that defects in this network, predominantly within the ATM mediated signaling pathway, are commonly observed in cancers and may be a primary event during tumorigenesis. Such defects may promote a genomically unstable environment, facilitating the persistence of mutations, any of which may provide a growth or survival advantage to the developing tumor. In addition, these somatic defects provide opportunities to exploit a reliance on remaining repair pathways for survival, a process which has been termed synthetic lethality. As a result of all these observations there has been a great interest in targeting the DDR to provide anti-cancer agents that may have benefit as monotherapy in cancers with high background DNA damage levels or as a means to increase the efficacy of DNA damaging drugs and IR. In this book we will review a series of important topics that are of great interest to a broad range of academic, industrial and clinical researchers, including the basic science of the DDR, its role in tumorigenesis and in dictating response to DNA damaging drugs and IR. Additionally, we will focus on the several proteins that have been targeted in attempts to provide

drug candidates, each of which appear to have quite distinct profiles and could represent very different opportunities to provide patient benefit.

This book describes a course of cancer growth starting from normal cells to cancerous form and the genomic instability, the cancer treatment as well as its prevention in form of the invention of a vaccine. Some diseases are also discussed in detail, such as breast cancer, leucaemia, cervical cancer, and glioma. Understanding cancer through its molecular mechanism is needed to reduce the cancer incidence. How to treat cancer more effectively and the problems like drug resistance and metastasis are very clearly illustrated in this publication as well as some research result that could be used to treat the cancer patients in the very near future. The book was divided into six main sections: 1. HER2 Carcinogenesis: Etiology, Treatment and Prevention; 2. DNA Repair Mechanism and Cancer; 3. New Approach to Cancer Mechanism; 4. New Role of Oncogenes and Tumor Suppressor Genes; 5. Non Coding RNA and Micro RNA in Tumorigenesis; 6. Oncogenes for Transcription Factors

Cancer is one of the most lethal and hard to cure diseases. The common treatments for cancer include surgery, radiation therapy, chemotherapy, immunotherapy and hormone therapy. Ionizing radiation (IR) is one of the main clinical treatments for cancer and it works by inducing DNA double strand breaks (DSBs), which are the most toxic DNA lesions that lead to cell death. The effectiveness of IR treatment depends on the amount of induced damage and the DNA damage repair status of the cancer cells. DSBs are repaired by multiple DNA repair pathways and this repair reduces the effectiveness of the treatment leading to resistance to IR. It has been shown in the literature that by targeting the DNA repair pathways the treatment efficacy can be modulated.In this work, a systems biology approach is used to quantitatively study the role of DNA repair pathways in determining and improving the radiation treatment outcome. Specifically, the mathematical models of DNA repair pathways, non-homologous end joining (NHEJ) and homologous recombination (HR), are developed for analyzing the role of DNA repair in enhancing the treatment sensitivity for prostate cancer (PCa) when a combination of radiation and hormone deprivation therapies is used. DSBs are repaired by one of the two DNA repair pathways: NHEJ and homologous recombination (HR). NHEJ is the major pathway, whereas HR is restricted to S- or G2-phases of the cell cycle after DNA replication has been completed. The cell cycle specific contribution of the repair pathways are incorporated into the computational models. A comprehensive identifiability analysis is carried out to determine the

factors affecting parameter identifiability and strategies to increase identifiability are developed. In parallel to the NHEJ and HR models, a computational model of the base excision repair (BER) pathway is developed to analyze its role in response to chemotherapy under different treatment scenarios.Combination treatment strategies that aim to inhibit the functional DNA repair pathways for the cancer cells that are defective in other repair pathways achieve synthetic lethality. One such strategy is the use of PARP inhibitors (PARPi) in addition to the combination treatment with IR and ADT. The experimental data in the literature show that AR promotes both NHEJ and HR following IR, and inhibition of AR by ADT impairs both of these pathways in PCa cells leading to either increased radiosensitivity or sensitization to PARP inhibitors. The effect of using PARPi in this scenario has been computationally analyzed in this work by extending the modeling efforts to include the effect of PARP inhibitors on the treatment outcome. The inhibition of BER by PARPi is also quantitatively studied. The models and findings in this work can then be extended to other cancers, such as lung cancer and ovarian cancer that benefit from similar synthetic lethality.

Cutting edge reviews by leading researchers illuminate key aspects of DNA repair in mammalian systems and its relationship to human genetic disease and cancer. Major topics include UV and X-Ray repair, repair of chemical damage, recombinational repair, mismatch repair, transcription-repair coupling, and the role of DNA repair in disease prevention. Extensive up-to-date references and rigorous peer-review of each chapter make this volume definitive and bring it to the active frontiers of research.

DNA Repair and Replication

Proceedings of the International Symposia of the Princess Takamatsu Cancer Research Fund, Volume 13 ADP-Ribosylation, DNA Repair and Cancer

The DNA Damage Response: Implications on Cancer Formation and Treatment

Molecular Targets and Clinical Applications

DNA Damage, DNA Repair and Disease

As chemical exposures and cancer rates increase worldwide, there is a need for students, researchers, public health professionals, and physicians to understand the mechanisms connecting exposure with human cancer risk. This new book is an essential reference, as well as introduction to the field of chemical carcinogenesis, with particular focus on DNA damage as a critical link between exposure and disease, and emphasis on biomarkers associated with cancer risk in humans. In addition to

DNA damage, related topics covered include metabolism of selected chemical carcinogens, exposure-induced epigenetic changes, cancer-associated mutations and reduction of DNA damage and cancer risk by chemoprevention. The book is designed to be a comprehensive guide to basic principles, a teaching tool for academics, and a map for the development of protective mechanisms to reduce human cancer risk.

Prostate cancer (PCa) is the most frequently diagnosed tumor in men, accounting alone for 29% of incident cases. Radiotherapy, a front-line treatment regimen for PCa is administered in the clinic either as external beam radiotherapy or low dose-rate (LDR) brachytherapy, which is clinically more effective. Exposure to genotoxic agents, such as irradiation produces DNA damage, the toxicity of which is augmented when the DNA repair is impaired. The radiation response largely depends on the cells' ability to overcome the challenge by repairing the damage DNA. Non-homologous end joining (NHEJ) is the predominant pathway for repairing the radiation-induced damage to DNA. NHEJ is very rapid and involves several core factors: Ku70, DNA-PKcs, XRCC4, lig IV, and XLF. Poly (ADP-ribose) polymerase 1 (PARP-1) competes with Ku70 to bind to broken DNA ends to initiate repair. PARP inhibitors were found to be "synthetic lethal" in cells deficient in BRCA1 and BRCA2 that impair homologous recombination. However, since many tumors, including PCa rarely have such mutations, there is considerable interest in finding alternative determinants of PARP inhibitor sensitivity. This Dissertation demonstrates synergistic interactions of radiation with the PARP inhibitor, rucaparib that were largely paralleled by similar effects on senescence, thus implicating it as a major treatment outcome in PCa. Increased radio-sensitization was associated with persistent DSBs, as indicated by ionizing radiation (IR)-induced foci (IRIF). Rucaparib radiosensitized PCa cells, with a clear benefit of low dose-rate radiation (LDR) administered over a longer period of time that caused enhanced DNA damage. This combination was most effective in the presence of the TMPRSS2-ERG fusion, the most frequently observed translocation in PCa, and in the absence of PTEN, indicating clinical potential for brachytherapy in patients with intermediate and high risk PCa. The NHEJ repair is initiated by detection of DSBs by Ku70/80, processing of the damaged DNA ends to remove non-ligatable groups by DNA-PKcs, and finally ligation by the XRCC4-Ligase IV-XLF complex. DNA-PKcs is recruited on the chromatin by the KU70/80 heterodimer, then undergoes autophosphorylation, which triggers the conformational changes ultimately leading to the dissociation from DSBs. In this Dissertation the significance of NHEJ repair has been addsesses,

particularly by targeting DNA-PKcs following IR using two different molecular tools. Cells that express TMPRS22-ERG showed DNA damage foci constitutively and which were absent if the fusion gene was depleted by siRNA. Analyses of TMPRSS2-ERG fusion-expressing cell lines subjected to radiation reveals that TMPRSS2-ERG fusion gene interferes with DNA-PKcs function by interacting with it. The expression of TMPRSS2-ERG fusion gene inhibits the phosphorylation responsible for dissociation of DNA-PKcs. Similarly we provide evidence that the expression of p18CycE, a proteolytic cleaved form of CyclinE also perturbs NHEJ DNA repair by inhibiting DNA-PKcs. p18CycE-expressing cells showed diminished phosphorylation of DNA-PKcs, which in turn impairs DNA-PKcs kinase activity as well as its dissociation making the cells radiosensitive. Together, these two cell systems provide unique molecular tools to inhibit DNA-PKcs, which helps for a better understanding of the molecular mechanisms of NHEJ with the central focus on DNA-PKcs. Irradiation can also induce autophagy, a catabolic process involving the degradation of cellular organelles and proteins, in many tumors, including PCa, as a protective cellular response. Defective autophagy can mediate cell death as a consequence of the accumulation of toxic cellular content. However, in many tumor cells, autophagy has evolved to provide cells with their energy needs. In this Dissertation, the overall objective is to elucidate how to enhance the damage both to the DNA, by targeting DNA repair, and to the cellular content, by targeting autophagy and thus to provide effective, novel therapeutic approaches for PCa treatment. Clonogenic survival assays showed that autophagy had a protective role since inhibiting it by genetic knockdown of ATG7 sensitized PCa cells to IR-induced cell death. In autophagy-deficient cells, there was persistent DNA damage following IR, represented by [gamma]H2AX IRIFs. In contrast, there were no 53BP1 IRIFs in autophagy-deficient cells, reflecting its defective recruitment to chromatin. [gamma]H2AX undergoes ubiquitination by RNF168, that leads to recruitment of 53BP1. Indeed, autophagy-deficient cells showed also significantly reduced numbers of cells with RNF168 IRIFs. Diminished ubiquitination leading to failure to recruit p53BP1 could be caused by a hyperactive deubiquitinase (DUB). In autophagy deficient cells, treatment with a partially selective pharmacological DUB inhibitor WP-1130 restored 53BP1 IRIFs with IRIFs of [gamma]H2AX being reduced to the level in parental cells. We identified USP14 as the key DUB involved in [gamma]H2AX deubiquitination since PCa cells receiving a specific inhibitor of USP14, IU1 or shUSP14 restored kinetics of [gamma]H2AX IRIFs and 53BP1 to that of parental cells. These

observations suggest that autophagy inhibition interferes with DNA damage repair signaling by targeting ubiquitination of critical DNA repair molecules. Collectively, these findings suggest that the sensitivity to radio- and chemo-therapy is enhanced in PCa cells that have a defect in the repair of damaged DNA, which is caused by either harboring an ETS gene fusion (most commonly TMPRSS2-ERG) or to the cellular content (organelles and modified proteins, alone or in aggregates), when autophagy is impaired. This Dissertation has the potential to lead to the the development of innovative new treatments for advanced metastatic PCa that express ETS gene fusions, are impaired in DNA repair, and have augmented autophagy.

Physical and chemical agents in the environment damage the DNA of humans, and pose a major threat to human health today, and to the genetic integrity of human populations. Although studies on isolated DNA in vitro, on prokaryotes, on mammalian cells in culture, and on laboratory animals have provided essential background information, it is now possible to study DNA damage and repair in human tissues directly. New techniques of high sensitivity, especially those not requiring radioactive labeling have made possible quantitation of DNA damage and repair, as well as detection of residual, unrepaired DNA lesions . In recent years, several investigators have taken up the challenge of studying damage and repair responses in humans, and we have chosen that work as the special focus of this Symposium. Major advances in under standing damage and responses in human skin, in blood cells and in human internal organs indicate three major themes. First, DNA damage levels in human tissues depend not only on the initial exposures, but also on the capapacity of that tissue for repair of the specific lesion type. Second, repair in human tissues may differ quantitatively and qualitatively from that in human cells in culture.

DNA Repair Genes and Breast Cancer Risk

Advances from Phage to Humans

DNA Repair, Genetic Instability, and Cancer

Targeting the DNA Damage Response for Anti-Cancer Therapy

The Role of DNA Repair Pathways in Resistance to Chemotherapy and Radiotherapy in Cancer